

Further Developments and Applications of Oxazoline-Containing Ligands in Asymmetric Catalysis

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Cite This: *Chem. Rev.* 2021, 121, 6373–6521

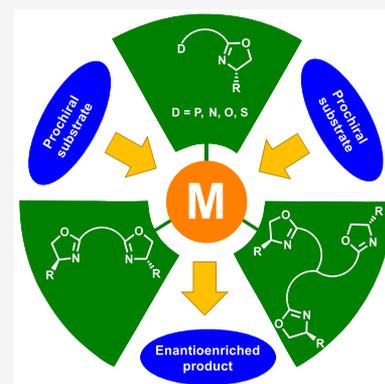
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ABSTRACT: The chiral oxazoline motif is present in many ligands that have been extensively applied in a series of important metal-catalyzed enantioselective reactions. This Review aims to provide a comprehensive overview of the most significant applications of oxazoline-containing ligands reported in the literature starting from 2009 until the end of 2018. The ligands are classified not by the reaction to which their metal complexes have been applied but by the nature of the denticity, chirality, and donor atoms involved. As a result, the continued development of ligand architectural design from mono(oxazolines), to bis(oxazolines), to tris(oxazolines) and tetra(oxazolines) and variations thereof can be more easily monitored by the reader. In addition, the key transition states of selected asymmetric transformations will be given to illustrate the features that give rise to high levels of asymmetric induction. As a further aid to the reader, we summarize the majority of schemes with representative examples that highlight the variation in % yields and % *ees* for carefully selected substrates. This Review should be of particular interest to the experts in the field but also serve as a useful starting point to new researchers in this area. It is hoped that this Review will stimulate both the development/design of new ligands and their applications in novel metal-catalyzed asymmetric transformations.



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Received: August 10, 2020

Published: May 21, 2021



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1. INTRODUCTION

Ligands containing a chiral oxazoline are some of the most successful, versatile, and commonly used ligand classes in asymmetric catalysis due to their ready accessibility, modular nature, and applicability in a wide range of metal-catalyzed transformations.

The vast majority of these ligands are formed in short, high yielding synthesis from readily available chiral β -amino alcohols. Therefore, the stereocenter controlling the enantioselectivity of the metal-catalyzed process resides α - to the oxazolinyl nitrogen donor and, as a result, is in close proximity to the metal active site to directly influence the asymmetry induced in the reaction.

Since the first report of chiral oxazoline-based ligands in asymmetric catalysis in 1986, an enormous range of ligands containing one, two, three or four oxazolines incorporating various heteroatoms, additional chiral elements and other specific structural features have been subsequently developed with great success in a significant range of asymmetric reactions. SciFinder data for the years 2009 to 2019 confirm

the significance of research related to the term “oxazoline” (Figure 1).

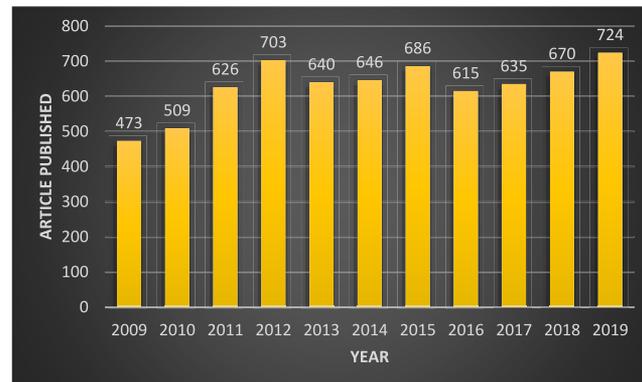


Figure 1. SciFinder data on oxazoline-related research for the years 2009 to 2019.

This review reports on the use of such ligands in homogeneous metal-catalyzed asymmetric synthesis since 2009, when the area was last reviewed by us.¹ This review does not cover the application of such ligands in heterogeneous systems or in the synthesis of polymers. We cover, in our view, the most significant applications of oxazoline-containing ligands reported in the literature until the end of 2018. This review will be structured in the same manner as our 2004² and 2009 reviews as we classify ligands, not by the reaction to which their metal complexes have been applied, but by the nature of the denticity, chirality and donor atoms involved. As a result, the continued development of ligand architectural design can be more easily monitored. In addition, the key transition states of selected asymmetric transformations employing metal complexes of oxazoline ligands will be given to illustrate the features that give rise to high levels of asymmetric induction. As a further aid to the reader, we summarize the majority of schemes with representative examples which highlight the variation in % yields and % *ees* for carefully selected substrates.

2. MONO(OXAZOLINE) LIGANDS

2.1. Mono(oxazoline) *P,N*-Ligands (Phosphinooxazoline)

2.1.1. Phosphinooxazoline Ligands with One Stereocenter. Phosphinooxazoline (PHOX) is a popular class of bidentate ligand in which the chiral oxazoline moiety is solely responsible for asymmetric induction in product formation (Figure 2).^{3–6} In this section, various PHOX ligands (1–17) and their applications in a broad range of asymmetric transformations will be discussed. This section is further divided into subsections based on the type of reactions the metal complexes of PHOX ligands have been used for.

2.1.1.1. Applications of PHOX in Asymmetric Allylation. In late 2004, Stoltz and Trost independently developed a Pd-catalyzed decarboxylative asymmetric allylic alkylation (DAAA) reaction using *t*Bu-PHOX (1) and Trost-type ligands, respectively (Scheme 1).^{7,8} The generally accepted mechanism of the DAAA involves the coordination of the Pd(0) complex to the allyl moiety leading to oxidative addition, followed by the loss of CO₂ to generate the Pd enolate 18-Y, which then attacks the intermediate allyl group to form the enantio-enriched product 19 and regenerate the Pd(0) catalyst.⁹

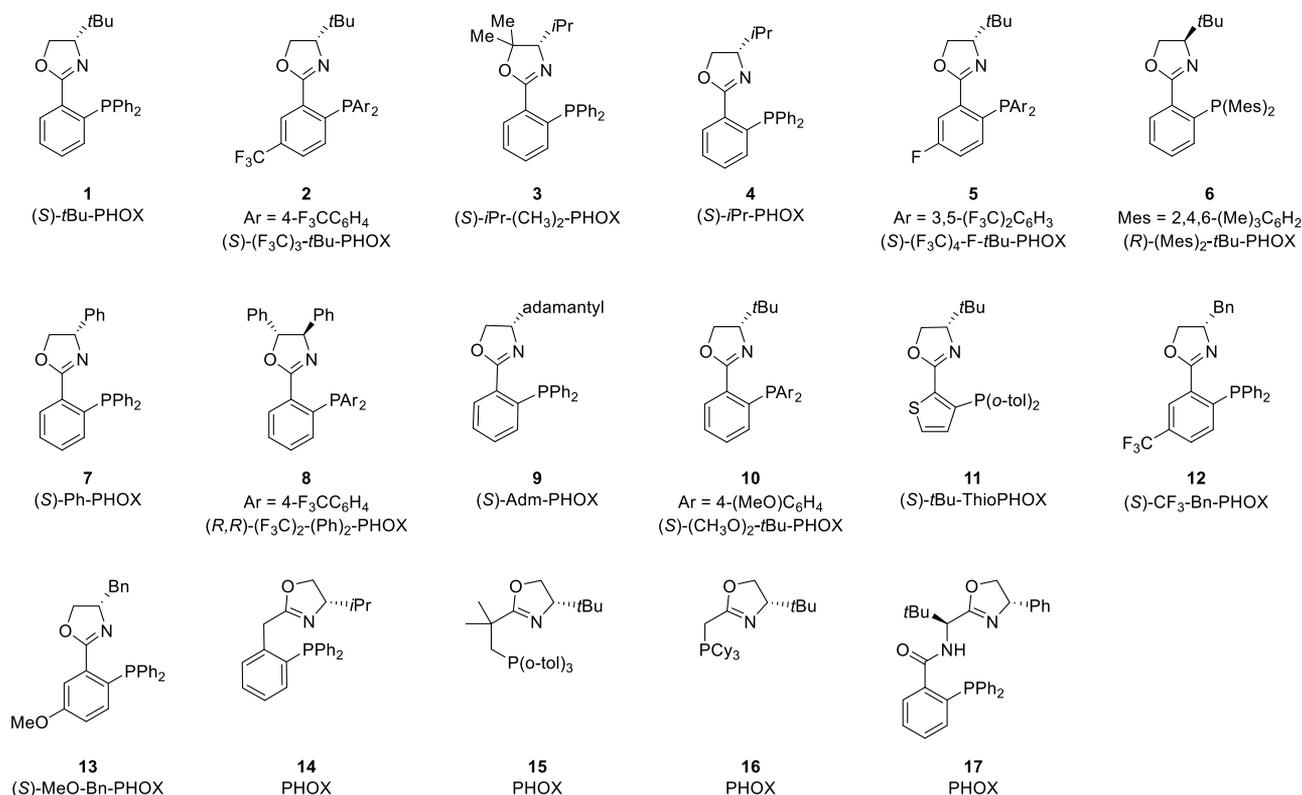
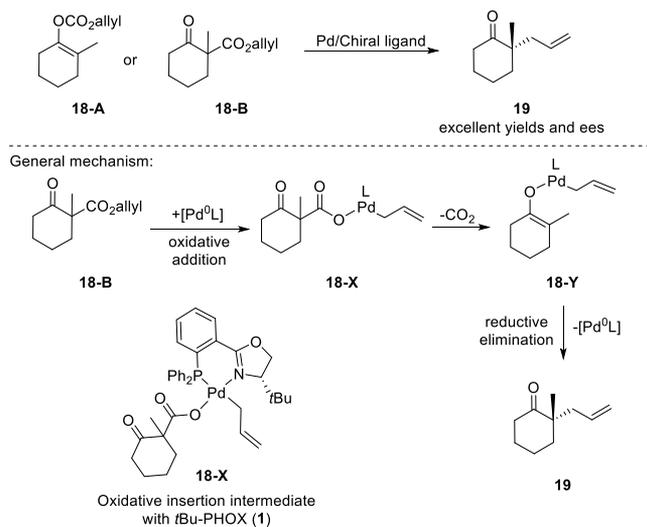


Figure 2. Various phosphinooxazoline (PHOX) ligands

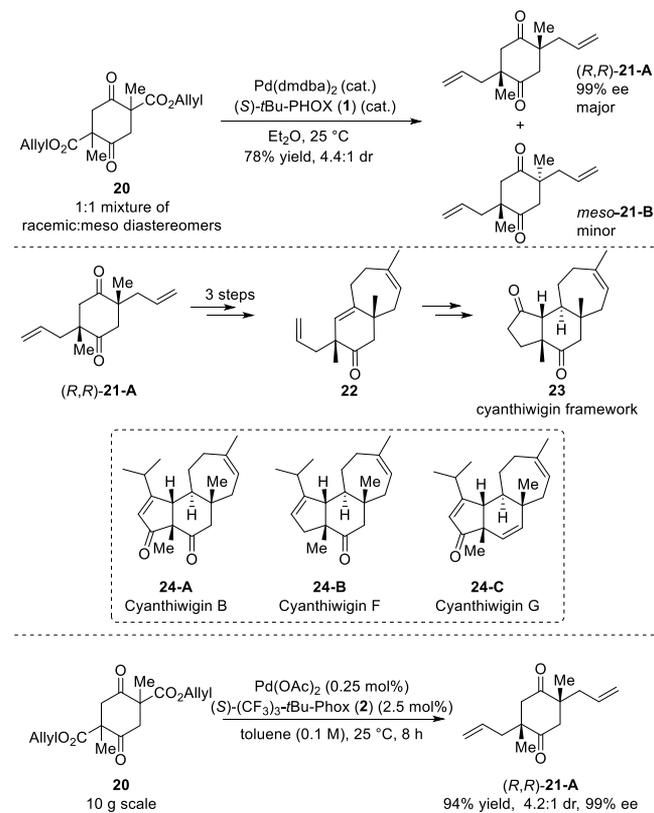
Scheme 1. Decarboxylative Asymmetric Allylic Alkylation (DAAA)



Since the seminal report from Stoltz, the scope and application of PHOX ligand in DAAA has been expanded to different substrate classes and also in natural products synthesis.

In 2008, Stoltz described a concise and versatile strategy for the preparation of the natural products, cyanthiwigin B, F and G by using a key double stereoablative decarboxylative asymmetric allylic alkylation of bis(β -keto ester) **20** (Scheme 2).^{10,11} Their strategy involved the synthesis of the central six-membered ring, cyclohexadione **21**, with a special emphasis on the early installation of two of the most critical stereocenters of the cyanthiwigin framework in good yield with a high level of

Scheme 2. Catalytic Asymmetric Synthesis of Tricyclic Cyanthiwigin Framework



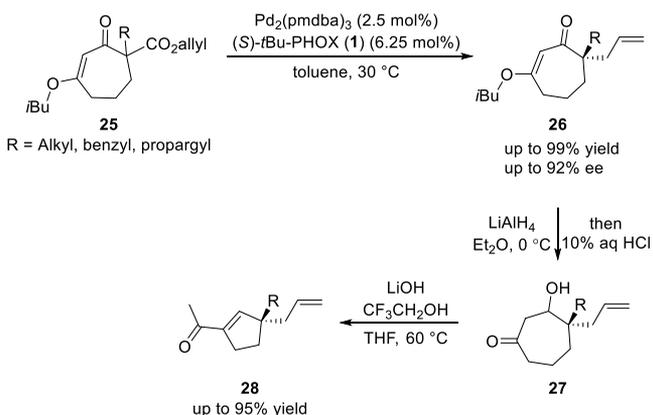
stereoselectivity (4.4:1 dr and 99% *ee*). The major diastereomer of cyclohexadione (*R,R*)-**21-A** was subsequently

converted for the efficient synthesis of cyanthiwigin B (**24-A**), F (**24-B**), and G (**24-C**). It is worthwhile noting that the observed selectivity in the double decarboxylative allylation with the (*S*)-*t*Bu-PHOX (**1**) ligand was excellent given the fact that the reaction begins with a complicated mixture of racemic and *meso*-diastereomers which leads to several possible stereochemical outcomes, and pathways.

The key double catalytic enantioselective alkylation was troublesome on a large scale due to the poor solubility of the catalyst which required low reaction concentrations (0.01 M). This problem was improved significantly in their subsequent report wherein the enantioselective alkylation was carried out on a 10 g scale furnishing the desired diketone (*R,R*)-**21-A** in 94% yield, 4.2:1 dr and 99% *ee*.¹²

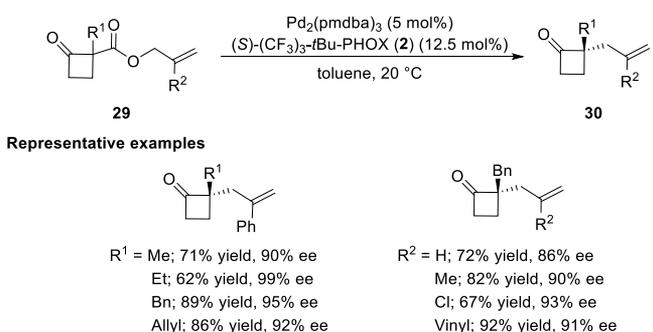
Stoltz extended DAAA to seven membered cyclic β -keto-allyl ester (**25**) to generate allylated products (**26**), which were further employed in the asymmetric synthesis of densely functionalized acylcyclopentenes (**28**), valuable intermediates for the synthesis of natural products, in excellent yields (up to 99%) and high enantioselectivities (up to 92% *ee*) (Scheme 3).¹³ The synthesis of **28** from **25** involves a Pd-catalyzed decarboxylative asymmetric allylic alkylation followed by a two-carbon ring contraction.

Scheme 3. Asymmetric Synthesis of Densely Functionalized Acylcyclopentenes



Later in 2013, Stoltz reported a Pd-catalyzed enantioselective α -alkylation to cyclobutanones (**30**). The palladium complex of an electron-deficient (*S*)-(CF₃)₃-*t*Bu-PHOX (**2**) ligand demonstrated excellent catalytic activity to afford α -quaternary cyclobutanones in good to excellent yields and enantioselectivities (Scheme 4).¹⁴ A wide variety of substituents were compatible at both the α -keto and 2-allyl

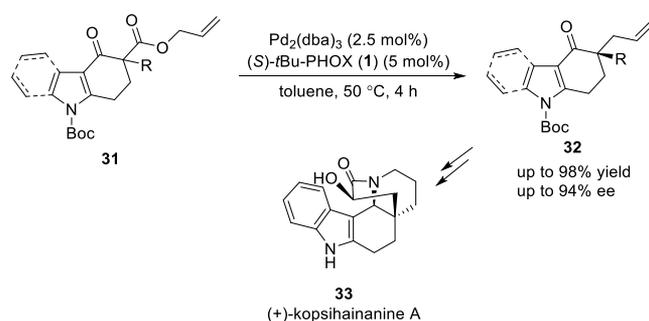
Scheme 4. Enantioselective α -Alkylation of Cyclobutanones



positions especially considering the presence of highly electrophilic cyclobutanones. Furthermore, chiral cyclobutanones were converted into dialkyl γ -lactams, dialkyl γ -lactones, α -quaternary cyclopentanones, and quaternary [4.5]-spiro-cycles.

In 2013, Lupton reported a Pd-catalyzed decarboxylative asymmetric allylation for the enantioselective synthesis of carbazolone and indolone heterocycles (**32**) (Scheme 5).¹⁵ A

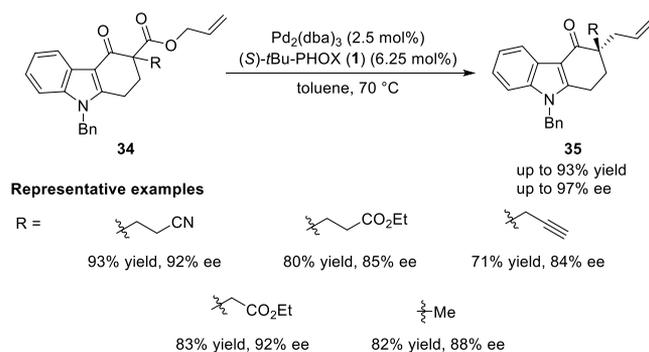
Scheme 5. Catalytic Decarboxylative Asymmetric Allylation of Carbazolones and Indolones



variety of carbazolones and indolones containing a quaternary carbon center were synthesized in excellent yields (up to 98%) and enantioselectivities (up to 94% *ee*). Moreover, the application of this methodology was shown in the synthesis of (+)-kopsihainanine (**33**).

In 2013, Shao reported the Pd-catalyzed enantioselective decarboxylative allylic alkylation of carbazolone heterocycles (**34**) (Scheme 6).¹⁶ A variety of highly functionalized chiral

Scheme 6. Catalytic Decarboxylative Asymmetric Allylation of Carbazolones

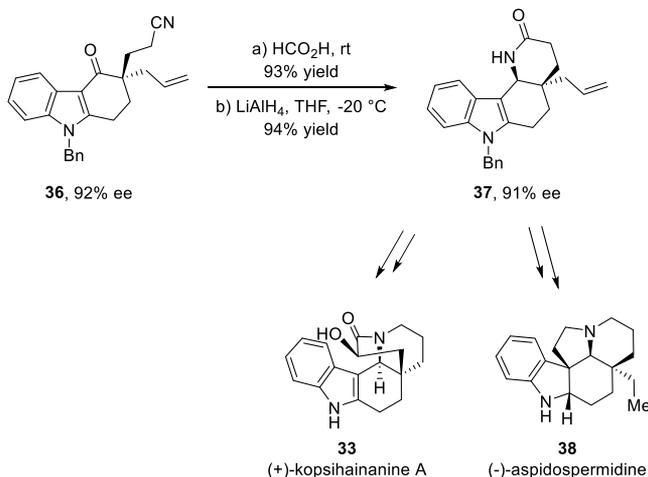


carbazolones (**35**) featuring an α -quaternary carbon center were synthesized in good yields (up to 93%) with high levels of enantioselectivity (up to 97% *ee*).

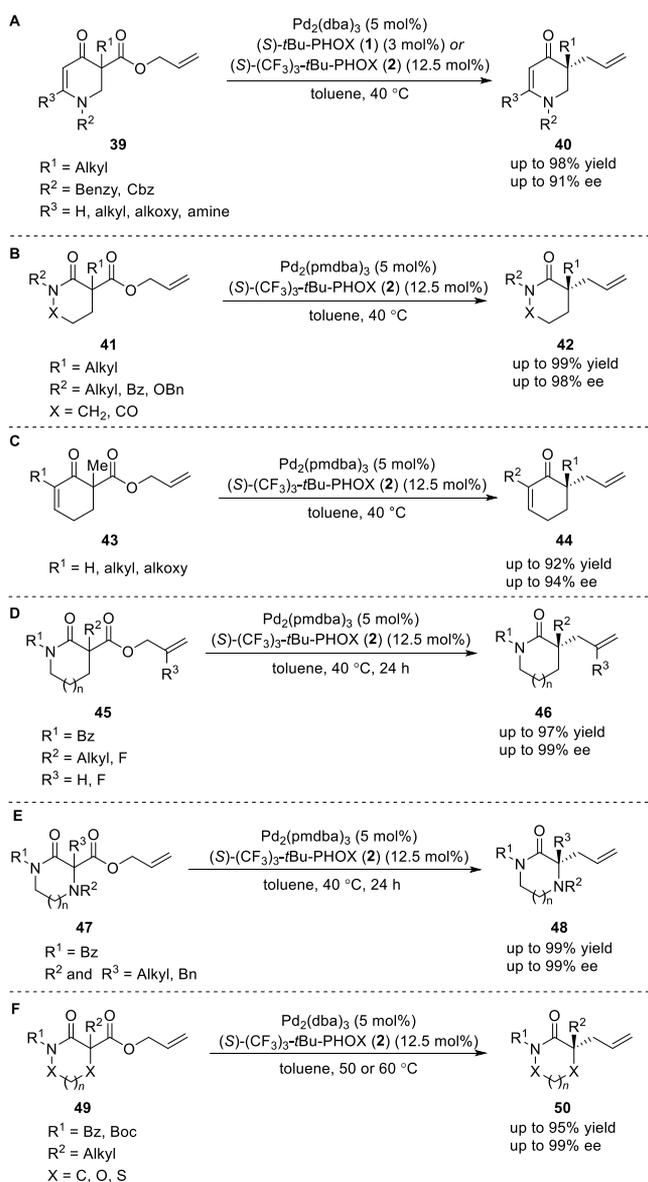
Using this methodology, a catalytic asymmetric strategy for the synthesis of (+)-kopsihainanine A (**33**) and (–)-aspidospermidine (**38**) was accomplished from a common intermediate (Scheme 7).

Stoltz in 2013 reported a Pd-catalyzed decarboxylative allylic alkylation of novel allyl ester substrates (**39**, **41**, and **43**) to probe the influence of enolate electronics and the role of α -functionality on the selectivity (Scheme 8A–C).¹⁷ It was observed that the high enantioselectivities obtained with imides and lactams are due to both electronic and steric effects associated with the α -substituent, and the enolate

Scheme 7. Catalytic Asymmetric Synthesis of (–)-Aspidospermidine and (+)-Kopsihainanine A



Scheme 8. Decarboxylative Asymmetric Allylic Alkylation



electronics alone contribute comparatively less to the stereochemical outcome of the reaction.

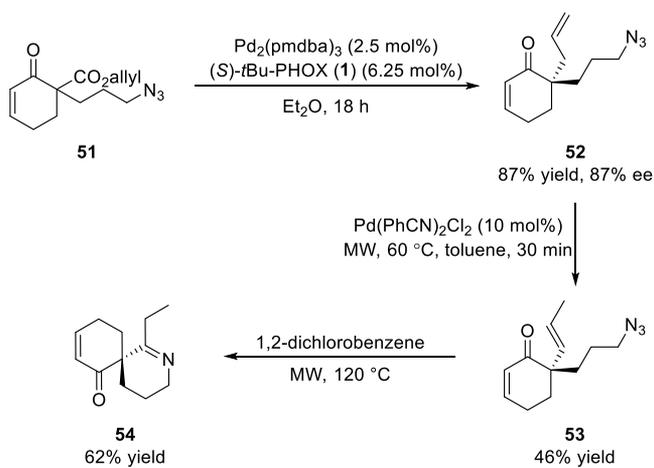
In 2012, Stoltz reported the highly enantioselective Pd-catalyzed decarboxylative allylic alkylation of readily available lactams (45) to form 3,3-disubstituted pyrrolidinones, piperidinones, caprolactams and structurally related lactams (46) (Scheme 8D).¹⁸ This method was employed for the catalytic asymmetric synthesis of key intermediates previously used for the construction of *Aspidosperma* alkaloids quebrachamine and rhazinilam.

In 2015, Stoltz reported the synthesis of α -tertiary piperazin-2-ones (48) by a Pd-catalyzed decarboxylative allylic alkylation (Scheme 8E).¹⁹ This method employed a more electron-rich Pd catalyst, $[\text{Pd}_2(\text{pmdba})_3]$ and an electron-deficient PHOX ligand to afford products in good to excellent yields and enantioselectivities. Additionally, this method also allows for the synthesis of α -secondary piperazin-2-ones in modest to excellent yields and good to excellent enantioselectivities. A variety of substituents at nitrogen and also at the stereocenter were tolerated under the reaction conditions employed.

In 2015, Stoltz developed a method to synthesize α,α -disubstituted *N*-heterocyclic carbonyl compounds (50), by using the well-established DAAA reaction (Scheme 8F).²⁰ Various heterocycles including morpholinone, thiomorpholinone, oxazolidin-4-one, 1,2-oxazepan-3-one, and 1,3-oxazin-4-one performed well to furnish carbonyl products with fully a substituted stereocenter at the α -position. The presence of an electron-deficient *N*-substituent was required for high reactivity and enantioselectivity.

Guillou reported a method to access enantioenriched spiroimines (54) using Pd-catalyzed decarboxylative allylic alkylation (Scheme 9).²¹ A variety of cyclic ketones (52)

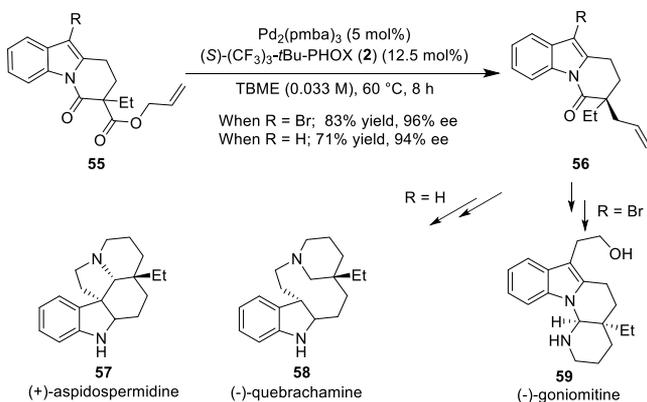
Scheme 9. Enantioselective Synthesis of Spiroimines



having α -allyl, propyl or butyl azido groups were synthesized in moderate to good enantioselectivity which, upon isomerization of the allyl group followed by a [3 + 2]-cycloaddition of the azidoalkene, afforded a variety of chiral spiroimines.

In 2016, Stoltz reported the first catalytic asymmetric total synthesis of (–)-goniomitine (59) starting from indole in 11 steps with an 8% overall yield (Scheme 10).²² The important step during this synthesis involves the Pd-catalyzed decarboxylative allylic alkylation of rationally designed heteroaryl bromide 55 furnishing product in 83% yield and 96% ee.

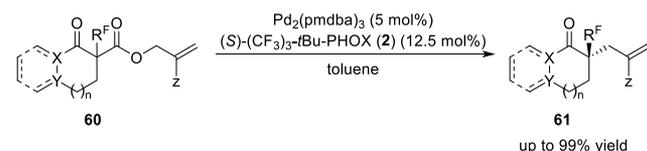
Scheme 10. Catalytic Asymmetric Total Synthesis of (–)-Goniomitine, (+)-Aspidospermidine, and (–)-Quebrachamine



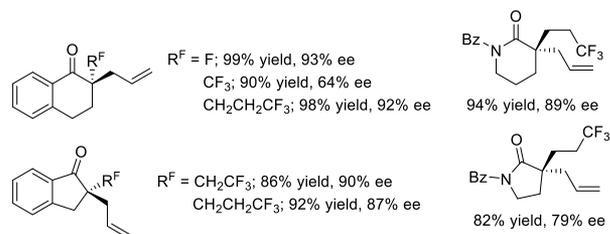
Additionally, the formal synthesis of (+)-aspidospermidine (57) and (–)-quebrachamine (58) was also demonstrated.

In 2018, Stoltz reported a strategy to construct fluorine-containing tetra-substituted stereocenters by the enantioselective Pd-catalyzed decarboxylative allylic alkylation of various carbonyl compounds (60) (Scheme 11).²³ An electron-

Scheme 11. Enantioselective Synthesis of Fluorine-Containing Tetra-Substituted Stereocenters



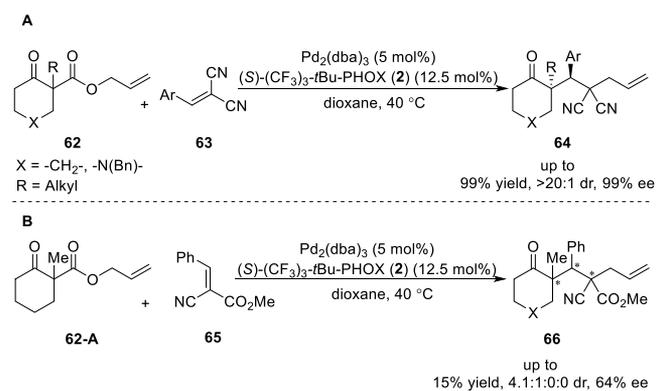
Representative examples



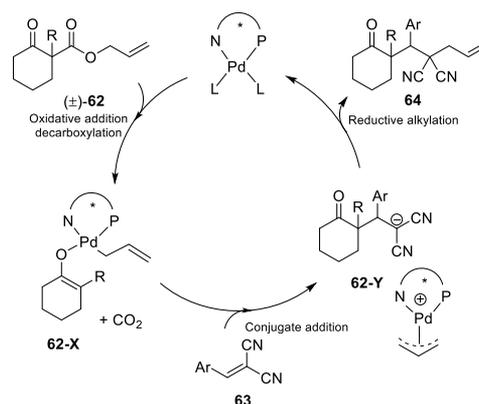
deficient (S)-(CF₃)₃-tBu-PHOX (2) ligand was optimal and this reaction showed significant substituent tolerance as a variety of five- and six-membered ketones and lactams (60) afforded the corresponding products with good yields and enantioselectivities.

In 2010, Stoltz devised a Pd-catalyzed highly enantio- and diastereoselective α -alkylation cascade protocol (Scheme 12A).²⁴ This method allowed for the installation of vicinal quaternary and tertiary stereocenters in a single step. Cyclohexanone based β -keto-allyl esters **62** and arylidene malononitrile **63** were suitable substrates and the desired products **64** were formed in up to 99% ee and with *a* > 20:1 dr. Small alkyl groups (R) were tolerated best in the reaction, although the use of electron-donating substituents on the arylidene malononitrile gave rise to lower yields. The installation of three stereocenters was also attempted by employing α -nitrile esters **65** (Scheme 12B). However, using a palladium complex of the chiral ligand (CF₃)₃-tBu-PHOX (2) in the reaction gave a poor yield of 15% and 64% ee. The reaction proceeds via the decarboxylation of β -keto-allyl ester

Scheme 12. Enantioselective Decarboxylative Enolate Alkylation Cascade



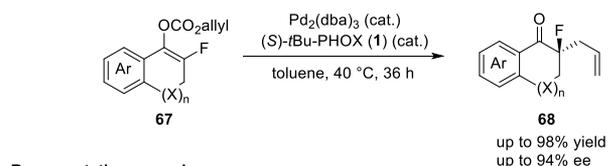
C: Mechanism



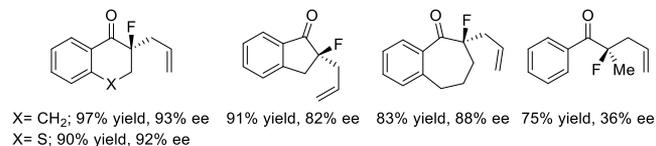
(62) to generate a Pd-enolate of cyclohexanone (62-X), followed by a conjugate addition to a prochiral activated Michael acceptor which generates densely functionalized molecules (64) that possess a quaternary stereocenter next to a tertiary center (Scheme 12C).

In 2008, Paquin detailed a Pd-catalyzed enantioselective decarboxylative allylic alkylation of fluorinated allyl enol carbonates (67) (Scheme 13).²⁵ They discovered an important

Scheme 13. Enantioselective Decarboxylative α -Alkylation of Fluorinated Allyl Enol Carbonates



Representative examples

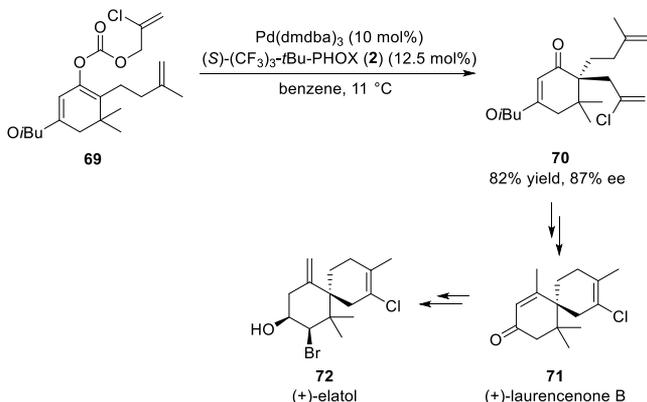


and unusual effect of the L/Pd ratio on the enantioselectivity, whereby a L/Pd ratio of 1:1.67 (and as low as 1:4) is required to afford the α -fluoroketones (68) in high enantioselectivity (up to 94% ee).

In 2008, Stoltz devised a concise enantioselective strategy for the syntheses of elatol (72) and (+)-laurencenone B (71) (Scheme 14).²⁶ The key Pd-catalyzed decarboxylative

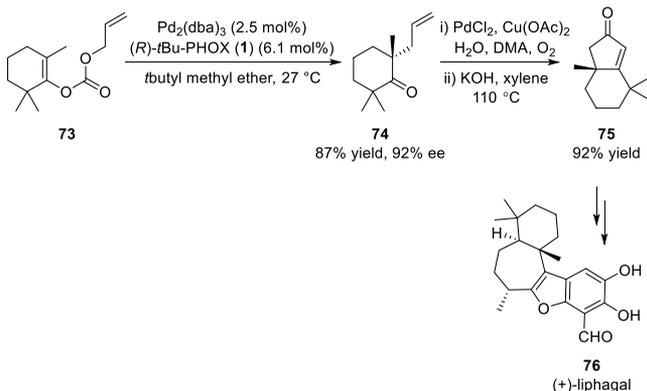
enantioselective alkylation was employed to access sterically encumbered enantioenriched vinylogous esters.

Scheme 14. Enantioselective Synthesis of Elatol and (+)-Laurenconone B



In 2011, Stoltz completed the catalytic enantioselective total synthesis of (+)-liphagal (**76**) in 19 overall steps from commercially available starting materials (Scheme 15).²⁷ The

Scheme 15. Catalytic Enantioselective Total Synthesis of (+)-Liphagal



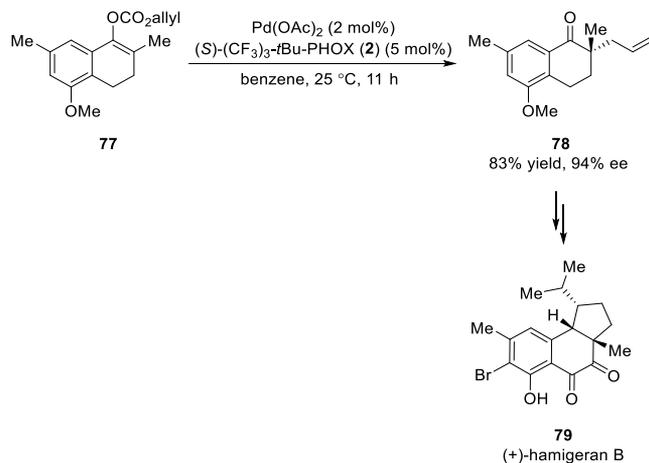
key step involves a Pd-catalyzed decarboxylative allylic alkylation of enol carbonate **73** to furnish tetra-substituted ketone **74** in 87% yield and 92% ee. This intermediate was elaborated to bicycle **75** in a two-step sequence which was further used for the completion of the first total synthesis of (+)-liphagal.

In 2011, Stoltz developed a formal synthesis of (+)-hamigeran B (**79**) starting from tetralone **77** using a key Pd-catalyzed enantioselective decarboxylative allylic alkylation (Scheme 16).²⁸ The other key reaction involves a Ru-mediated cross-metathesis with methyl vinyl ketones and a CuH-mediated domino conjugate reduction-cyclization.

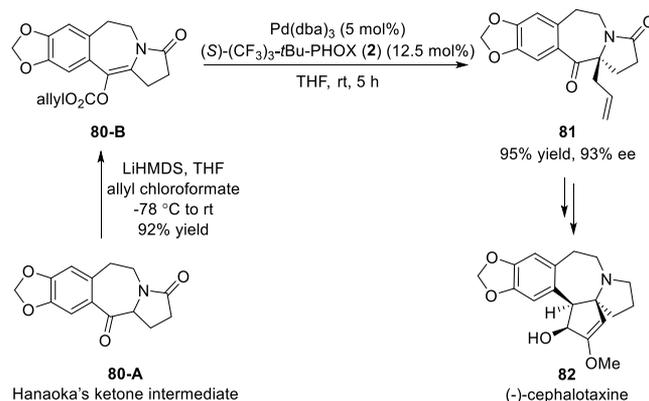
In 2018, Zhang reported a catalytic asymmetric synthesis of (–)-cephalotaxine **82** using a Pd-catalyzed Tsuji allylation (Scheme 17).²⁹ The synthesis involved 15 steps starting from homopiperonylamine with a 6.2% overall yield. The key allyl enol carbonate precursor **80-B** was prepared from the classic Hanaoka's pyrrolobenzazepine intermediate (**80-A**).

In 2012, Hanessian reported a new approach for the synthesis of tekturma (**85**), a drug used in the treatment of hypertension. This approach involves a modified Stoltz Pd-

Scheme 16. Formal Synthesis of (+)-Hamigeran B

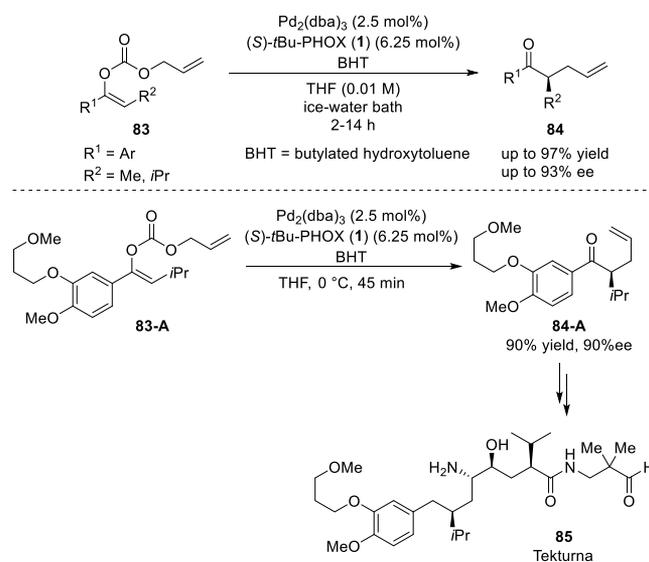


Scheme 17. Catalytic Asymmetric Synthesis of (–)-Cephalotaxine



catalyzed decarboxylative asymmetric allylation (Scheme 18).³⁰ A remarkable effect of BHT (2,6-di-*t*Bu-*p*-cresol) as a protic additive on the reaction time and enantioselectivity was discovered. The alkyl aryl enol carbonate (**83-A**) was converted into intermediate, (*R*)- α -isopropyl allyl aryl ketone

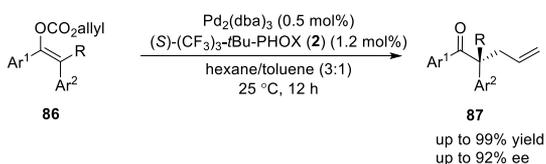
Scheme 18. Application of DAAA for Synthesis of Tekturma



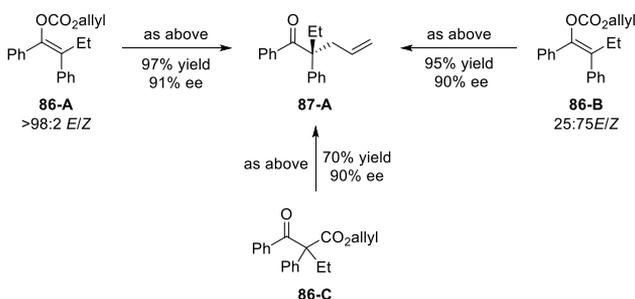
(**84-A**) in 90% yield and 90% *ee* which was used for the synthesis of tekturna **85**.

In 2018, Stoltz reported the first enantioselective Pd-catalyzed decarboxylative allylic alkylation of fully substituted acyclic enol carbonates (**86**) providing linear α -quaternary ketones (**87**) (Scheme 19).³¹ High yields and enantiomeric

Scheme 19. DAAA of Fully Substituted Acyclic Enol Carbonates



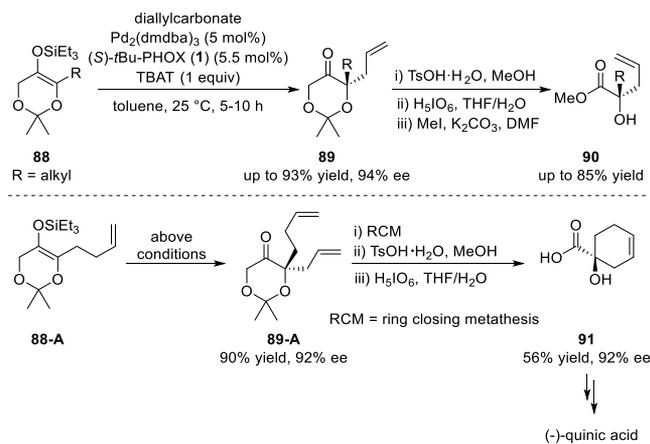
Importance of enolate geometry



excesses of the product were achieved using the electron-deficient ligand, (*S*)-(CF₃)₃-*t*Bu-PHOX (**2**). Previous reports in Pd-catalyzed allylic alkylation suggested differing selectivities with different enolate geometries but here it was found that the enolate geometry of the starting material has no adverse effect as the same enantiomer of the product was obtained with the same level of selectivity regardless of the starting ratio of enolates. It was postulated that a dynamic kinetic resolution of the two enolate geometries occurs in the reaction possibly due to facile equilibration between O-bound and C-bound Pd enolates in the presence of the electron-deficient PHOX ligand.

In 2008, Stoltz developed a Pd/(*S*)-*t*Bu-PHOX-catalyzed asymmetric alkylation of simple dioxanone derivatives (**88**) to obtain enantioenriched tetra-substituted dioxanone **89** possessing allyl group at α -position (Scheme 20).³² The enantioenriched tetra-substituted dioxanone subsequently was

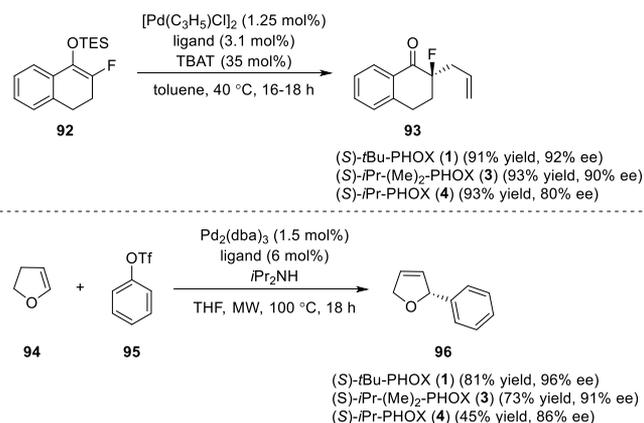
Scheme 20. DAAA of Dioxanone Derivatives



transformed into the enantioenriched α -hydroxyketones, acids, and esters via a three-step sequence which involved acetonide cleavage catalyzed by *p*-toluenesulfonic acid (TsOH·H₂O), oxidative cleavage with periodic acid (HIO₄) and finally methylation of the acid moiety. Additionally, this procedure allowed a catalytic enantioselective formal synthesis of (–)-quinic acid, a useful chiral building block.

Paquin reported a new member of the PHOX family, 5,5-(dimethyl)-*i*Pr-PHOX (**3**), having parallel reactivity to (*S*)-(CF₃)₃-*t*Bu-PHOX (**2**) with the key advantage of being easily accessible as both enantiomers (Scheme 21).³³ The application

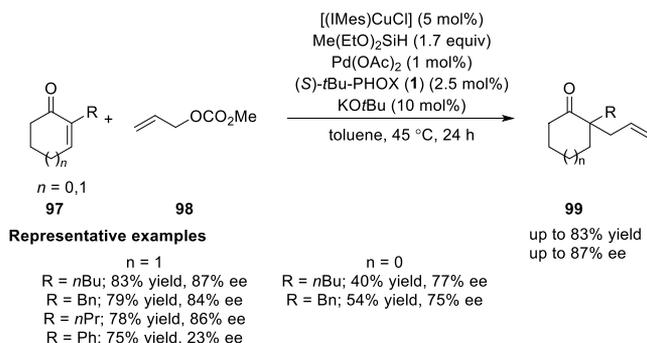
Scheme 21. Enantioselective Allylation of Fluorinated Silyl Enol Ether and Heck Reaction



of ligand was carried out in the enantioselective allylation of fluorinated silyl enol ether (**92**) and the enantioselective Heck reaction between 2,3-dihydrofuran (**94**) and phenyl triflate (**95**). It was observed that the new ligand's reactivity was as good as (*S*)-*t*Bu-PHOX (**1**) and better than the (*S*)-*i*Pr-PHOX (**4**), which lacks the *gem*-dimethyl at C-5, thus demonstrating the beneficial effect of the substituents at C-5.

Riant reported a cooperative dual catalysis based on a Pd(0)/Cu(I) system to generate quaternary carbon stereocenters (Scheme 22).³⁴ In this domino process, the first

Scheme 22. Asymmetric Cooperative Dual Catalysis of α -Substituted Cyclic Enones

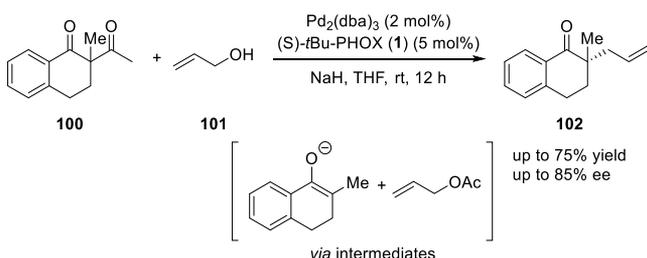


reaction involves a 1,4 reduction of cyclic enones using Cu(I) hydride to generate the Cu enolate species *in situ* which further reacts with the π -allyl-Pd complex to form the desired allylation product in an asymmetric fashion. The role of KOtBu as an additive was crucial to increase the enantioselectivity. This method showed tolerance toward alkyl and benzyl groups at the α -position of enones furnishing

products in comparable yields and enantioselectivities. The presence of the phenyl group at the α -position of enones was also tolerated to give the expected products in good yield, but unfortunately with low levels of enantioselectivity.

Tunge reported a method for the asymmetric allylic alkylation of α -tetralones via deacylative allylation using Pd(0) and (*S*)-*t*Bu-PHOX (**1**) ligand (Scheme 23).³⁵ This

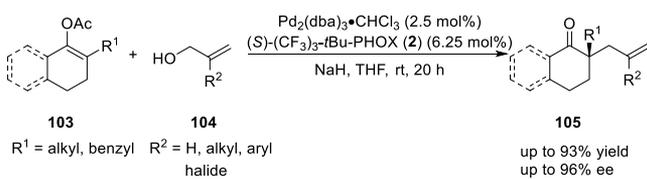
Scheme 23. Asymmetric Deacylative Allylation



method uses a readily available cyclic ketone pro-nucleophile (**100**) and allylic alcohol (**101**) as the allyl source. The reaction involves a retro-Claisen cleavage which results in the formation of both reactive intermediates, the active nucleophile (alkoxide) and electrophile (π -allyl). It was observed that the starting acetyl tetralone (**100**) must be used in slight excess (1.05 equiv) compared to the alkoxide as it had a detrimental effect on *ee*. The possible explanation for this is that excess alkoxide competes with the enolate for coordination to Pd which interferes with the inner sphere mechanism for allylation as reported by Stoltz.³⁶

After Tunge's initial report, Aponick extended this intermolecular Tsuji allylation to enol acetates (Scheme 24).³⁷ The enol acetate substrate (**103**) is advantageous over

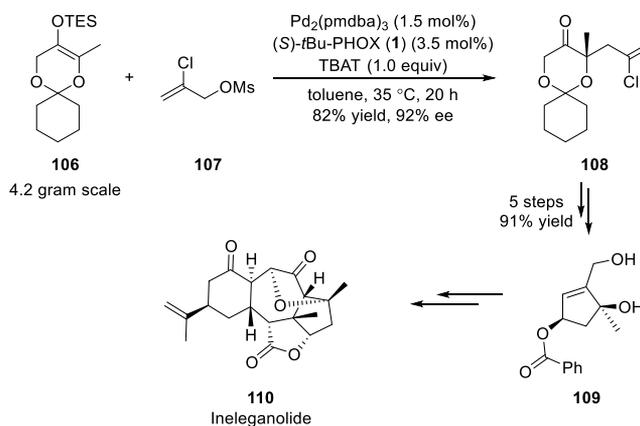
Scheme 24. Intermolecular Tsuji Allylation of Enol Acetates



the Tunge type 1,3-diketones as they can be easily prepared. This intramolecular allylation version facilitates rapid diversification of the α -quaternary stereocenter-containing products. The method tolerates a wide range of functional groups on the allylic part and the enol acetate of both aromatic and aliphatic ketones. The reaction proceeds with enantioselectivity up to 96% *ee* and the selectivity has a strong dependence on concentration in intermolecular acyl-transfer reactions as the lower concentrations gives products with higher enantioselectivity. The present protocol is better for 2-substituted allyl alcohols compared to simple allyl alcohol substrates.

Stoltz disclosed an elegant approach toward the synthesis of the polycyclic norditerpenoid ineganolide (Scheme 25).³⁸ A key Pd/(*S*)-*t*Bu-PHOX (**1**)-catalyzed enantioselective allylic alkylation was employed to synthesize ketone **108**, bearing a chloro-substituted allyl moiety and a methyl group at the α -position, in 82% yield and 92% *ee*. Ketone **108** underwent a series of diastereoselective transformations to provide a 1,3-*cis*-cyclopentenediol **109** in 91% yield over five steps. This diol

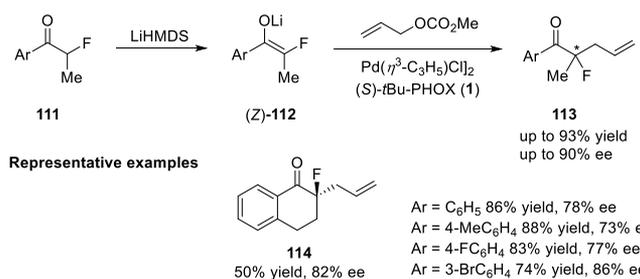
Scheme 25. Synthesis of Polycyclic Norditerpenoid Ineganolide



served as a building block for the synthesis of ineganolide (**110**).

In 2014, Guo and Chen reported a method for the asymmetric synthesis of acyclic α -carbonyl tertiary alkyl fluorides (**113**) using an enantioselective Tsuji-Trost reaction of racemic acyclic α -fluorinated ketones (**111**) (Scheme 26).³⁹

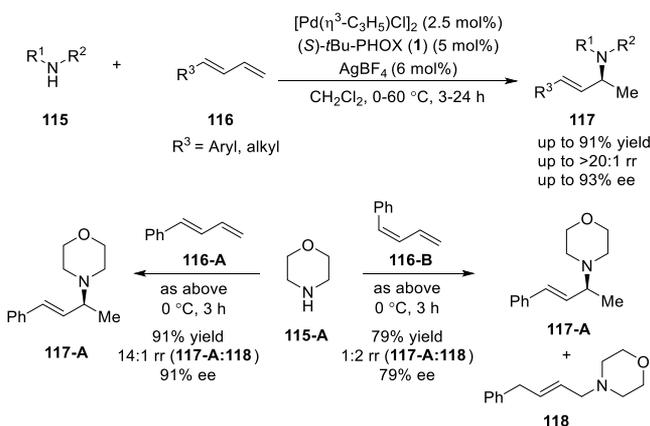
Scheme 26. Asymmetric Synthesis of Acyclic α -Carbonyl Tertiary Alkyl Fluorides



The enantioselectivity for the acyclic α -fluoro ketones (**113**) products formed ranged from 60 to 90% *ee*. The good (*Z*)-configuration of *in situ* generated enolate intermediate and the presence of a fluorine atom in the starting material had a positive effect on the enantioselectivity observed. It is well documented that cyclic ketones give a better level of enantioselectivity compared to acyclic ketones due to the low selectivity of acyclic ketones toward the formation of an *E/Z* mixture of the Pd enolate *in situ*.

Malcolmson developed a Pd/*t*Bu-PHOX (**1**)-catalyzed enantioselective intermolecular addition of aliphatic amines (**115**) with acyclic 1,3-dienes (**116**) (Scheme 27).⁴⁰ The chiral allylic amines (**117**) were synthesized in up to 93% *ee*. The electron-deficient phosphine ligand not only leads to a more active catalyst but also was important to achieve high levels of enantioselectivity. Mechanistic details revealed that the diene stereochemistry has a strong effect on site selectivity as (*Z*)-phenylbutadiene (**116-B**) under optimal conditions furnished a dramatically higher proportion of the 1,4-hydroamination product (**118**) instead of an expected 1,2-hydroamination product (**117-A**) (1:2 ratio) compared to the reaction of the (*E*)-isomer (**116-A**) which also proceeded with reduced enantioselectivity. It was also noted that both hydroamination products are formed exclusively as the (*E*)-isomer, indicating that olefin isomerization is faster than amine attack. Addition-

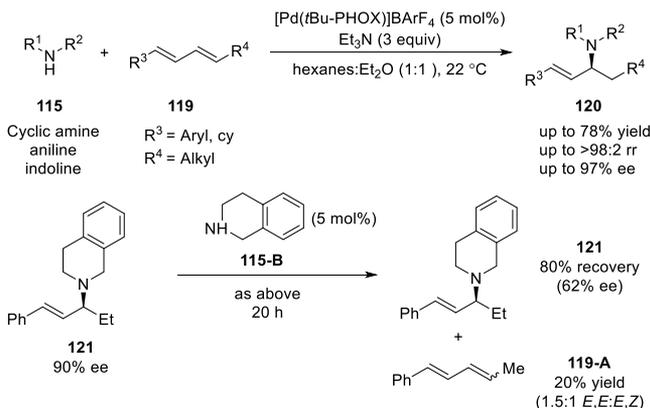
Scheme 27. Enantioselective Hydroamination of Acyclic 1,3-Dienes



ally, 1,2-hydroamination (**117-A**) formed the same enantiomer from either the (*E*)- or (*Z*)-isomer of the starting 1,3-butadiene. This catalytic system is highly efficient for promoting regio- and enantioselective additions of amines to terminal 1,3-dienes, although internal dienes fail to react.

After a year, Malcolmson extended their enantioselective hydroamination strategy to the challenging 1,4-disubstituted acyclic 1,3-dienes (**119**) (Scheme 28).⁴¹ The success of this

Scheme 28. Enantioselective Hydroamination of 1,4-Disubstituted Acyclic 1,3-Dienes

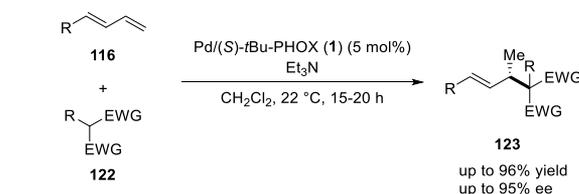


method was largely due to a Pd-PHOX catalyst with a noncoordinating BARF_4 counteranion, triethylamine as an additive and a nonpolar reaction medium. The variety of aryl/alkyl-disubstituted dienes (**119**) reacted with several aliphatic amines, primary anilines and indoline to generate allylic amines (**120**) possessing different α -alkyl groups in good yields and selectivities (up to 78% yield, >98:2 rr, 97% ee). Interestingly, secondary amines, such as piperidine and pyrrolidine, were unreactive under the optimal reaction conditions despite having greater nucleophilicity, perhaps due to the higher *pK*_a values of their conjugate acids compared to the more electron-deficient morpholine, piperazines, and tetrahydroisoquinoline (THIQ) which reacts remarkably well in this reaction. Mechanistic details indicated that the hydroamination is reversible as the ee of the product was found to diminish over time.

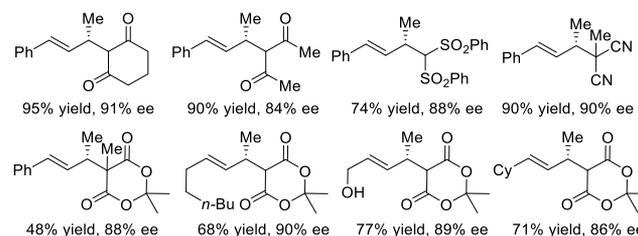
Malcolmson employed a catalytic system of Pd-PHOX for the enantioselective intermolecular hydroalkylation of acyclic

1,3-dienes with Meldrum's acid derivatives and other activated carbon pro-nucleophiles (Scheme 29).⁴² A variety of aryl- and

Scheme 29. Enantioselective Hydroalkylation of Acyclic 1,3-Diene



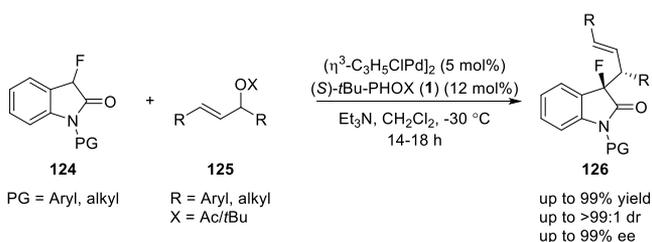
Representative examples



alkyl-substituted dienes (**116**) react with different β -dicarbonyl-like nucleophiles (**122**) to generate allylic stereogenic centers at the carbonyl's β -position in up to 96% yield and 95% ee. Similar to hydroamination (Scheme 28), here the use of triethylamine is essential as it acts as a base which upon deprotonation of carbonyl nucleophile would generate the corresponding ammonium enolate and also its protonated source, might potentially act as an acid source for Pd-H formation within the catalytic cycle. Additionally, it is important to note that the reaction is highly site-selective as addition occurs across the diene's terminal olefin.

Wolf presented a regio-, diastereo-, and enantioselective allylation of 3-fluorinated oxindoles (**124**) using catalytic amounts of Pd and (*S*)-*t*Bu-PHOX (**1**) (Scheme 30).⁴³ This

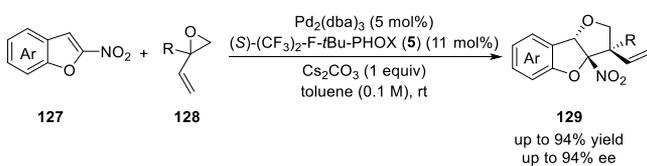
Scheme 30. Enantioselective Allylation of 3-Fluorinated Oxindoles



method offers a synthesis of 3,3-disubstituted fluoro-oxindole alkaloids (**126**) possessing vicinal chiral centers. This protocol was effective with allylic acetates which carried only one aryl terminus and C-C bond formation occurs at less hindered sites irrespective of the origin of the acetyl group.

You reported a stereoselective synthesis of tetrahydrofurobenzofurans (**129**) and tetrahydrofurobenzothiophenes by the dearomatization of nitrobenzofurans (**127**) and nitrobenzothiophenes, respectively using a Pd/*t*Bu-PHOX (**1**)-catalyzed formal [3 + 2] cycloaddition (Scheme 31).⁴⁴ The electronic and steric factors on the phosphine of the PHOX ligand were crucial for the success of this reaction. The products with vicinal stereogenic carbon centers were obtained in good to

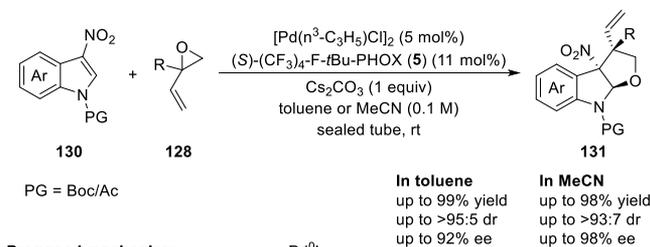
Scheme 31. Enantioselective [3 + 2] Cycloaddition with 2-Nitrobenzofurans



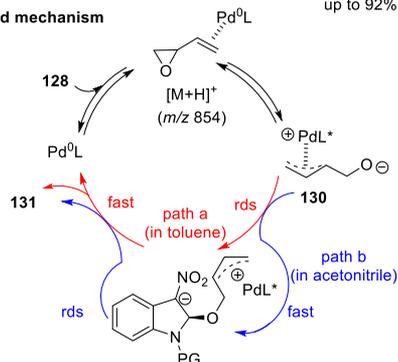
excellent diastereoselectivity (13/1 to >20/1 dr), and enantioselectivity (75–94% *ee*).

You also extended this methodology to the 3-nitroindole substrates (**130**) (Scheme 32). A stereodivergent synthesis of

Scheme 32. Enantioselective [3 + 2] Cycloaddition with 3-Nitroindoles



Proposed mechanism

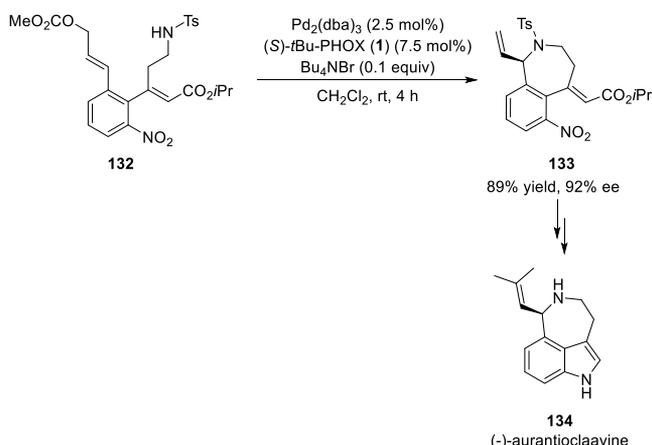


tetrahydrofuroindoles (**131**) is reported through a diastereoselective and enantioselective dearomative formal [3 + 2] cycloaddition by using catalytic Pd and PHOX ligand.⁴⁵ The polarity of the solvent was key to obtain high levels of diastereoselectivity. The use of toluene furnished tetrahydrofuroindole products in good to excellent yields (70–99%), diastereoselectivity (87:13 → 95:5 dr), and enantioselectivity (70–88% *ee*) whereas acetonitrile yielded another diastereomer in good to excellent yields (75–98%) and stereoselectivity (78:22–93:7 dr and 86–98% *ee*). Mechanistic studies suggested that the origin of the diastereodivergency was due to the different rate-limiting steps in different solvents, thereby leading to a reversal of stereocontrol.

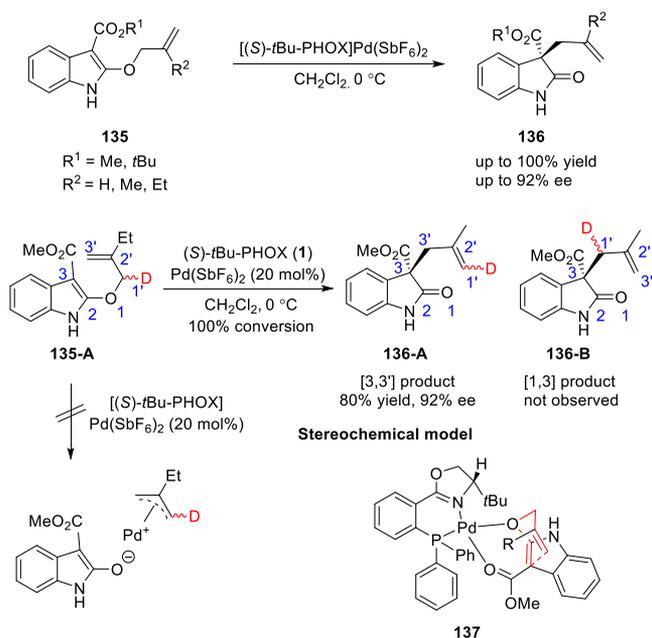
In 2014, Takemoto achieved a catalytic enantioselective total synthesis of (–)-aurantioclavine (**134**) in 16 steps starting from 3-nitro-2-iodophenol (Scheme 33).⁴⁶ The key step involves intramolecular asymmetric amination of allylic carbonate (**132**), which has a TsNHR group, using Pd and (S)-*t*Bu-PHOX (**1**) which proceeded smoothly to furnish a seven-membered heterocycle (**133**) in 89% yield and 92% *ee*. This asymmetric allylic amination reaction is a powerful tool to construct a chiral azepinoindole skeleton.

Kozłowski established a first catalytic, enantioselective Meerwein–Eschenmoser Claisen rearrangement using Pd/*t*-Bu-PHOX (**1**) complex (Scheme 34).⁴⁷ This method allowed

Scheme 33. Catalytic Enantioselective Total Synthesis of (–)-Aurantioclavine



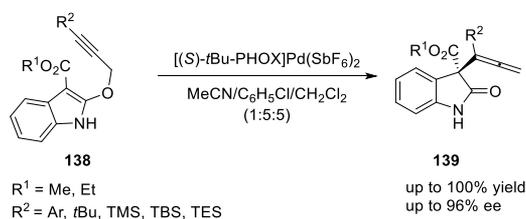
Scheme 34. Enantioselective Meerwein–Eschenmoser Claisen Rearrangement



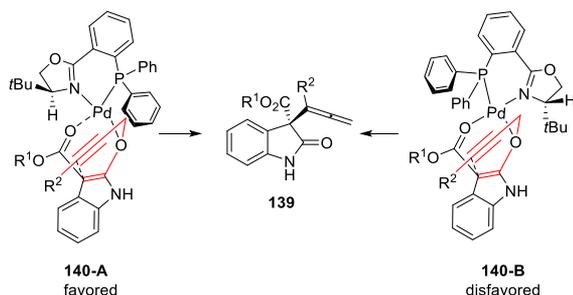
the synthesis of a range of oxindoles (**136**) bearing a quaternary stereocenter. The counterion on Pd(II) was crucial in line with catalyst coordination to the β -amidoester substrate (**135**), the SbF_6^- and BF_4^- complexes provided faster rates and greater turnover than the corresponding perchlorates, triflates, and halides. The Pd/*t*Bu-PHOX (**1**) combination provided the best enantioselectivity with the smaller C3 methyl ester (R^1) and the larger C2' groups (R^2). Deuterium labeling experiments suggested a Lewis acid-catalyzed mechanism and excluded the possibility of π -allyl cation chemistry. In the proposed stereochemical model (**137**), substrate β -amidoester (**135**) shows two-point coordination from both oxygens to the chiral Pd complex.

Kozłowski presented the first Pd/*t*Bu-PHOX (**1**)-catalyzed, enantioselective Saucy–Marbet Claisen rearrangement to generate enantiopure allenyl oxindoles (**139**) bearing a quaternary stereocenter at C3 from propargyl-substituted indole derivatives (**138**) (Scheme 35).⁴⁸ Alkyne substrates possessing *ortho*-substituted aryl groups at R^2 gave high levels

Scheme 35. Enantioselective Saucy–Marbet Claisen Rearrangement



Stereochemical model



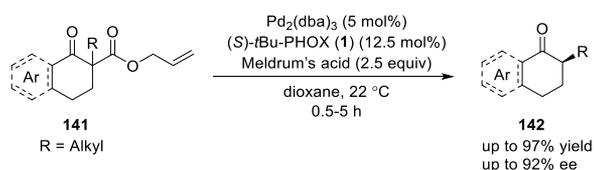
of enantioselectivity and rapid conversion (up to 96% ee). However, alkynes with larger groups like trimethylsilyl (TMS), *tert*-butyl, or *N*-methyliminodiacetic acid (MIDA) boronate were less successful. The alkyne geometry significantly alters the topology of the rearrangement transition state. Additionally, the ester functionality interacts with larger alkyne terminal substituents and destabilizes the less-favorable reaction pathway. Furthermore, improved results were achieved with nonaryl alkynes using Binap and its congeners.

2.1.1.2. Application of PHOX in Decarboxylative Asymmetric Protonation (DAP). PHOX ligands have also been extensively employed in the Pd-catalyzed decarboxylative asymmetric protonation (DAP) to generate products with a tertiary stereocenter adjacent to a carbonyl group.⁴⁹

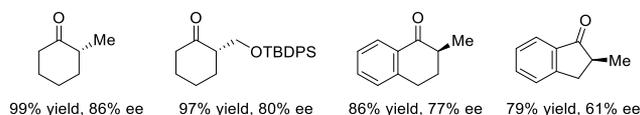
Stoltz reported a Pd/*t*Bu-PHOX (1)-catalyzed DAP of racemic α -aryl- β -ketoallyl esters (**141**) (Scheme 36).⁵⁰ The reaction generated α -alkylated cyclic ketones (**142**) in excellent yields and enantioselectivities (up to 97% yield and 92% ee) with Meldrum's acid as the proton source.

In 2014, Shao reported an enantioselective synthesis of C3-substituted chiral carbazolones (**142-A**) by using Pd/PHOX-catalyzed decarboxylative protonation of α -alkyl- β -keto allyl esters (**141-A**) (Scheme 37).⁵¹ The use of methyl 2-cyclopentanonecarboxylate (**143**) as the proton donor was found to be more effective compared to the normally used

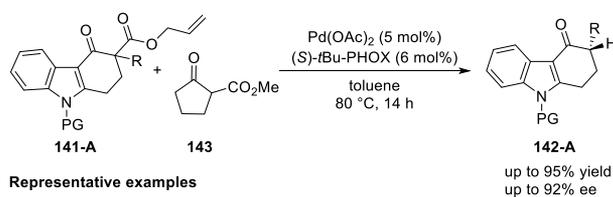
Scheme 36. Enantioselective Decarboxylative Protonation of α -Aryl- β -ketoallyl Esters



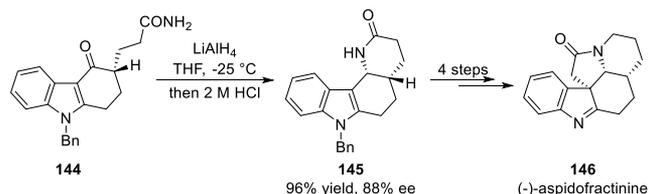
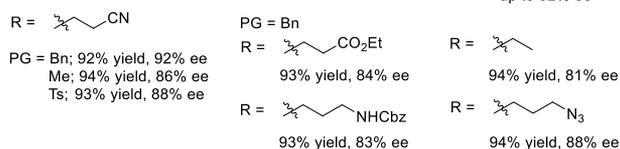
Representative examples



Scheme 37. Enantioselective Synthesis of C3-Substituted Chiral Carbazolones



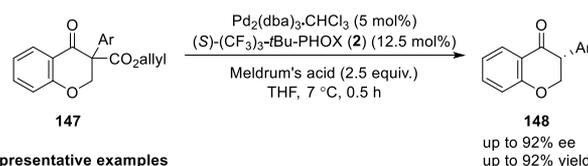
Representative examples



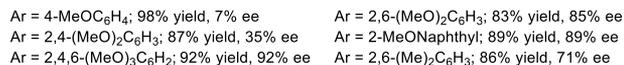
Meldrum's acid. A range of C3-monosubstituted chiral carbazolones (**142-A**) carrying various valuable functionalities such as, nitrile, ester, amine and azide were accessed in excellent yields (up to 95%) with good enantioselectivities (up to 92% ee). The application of this methodology was demonstrated in the synthesis of a key pentacyclic intermediate of the naturally occurring (-)-aspidofractinine (**146**).

Guiry reported the first catalytic asymmetric synthesis of isoflavanones (**148**) containing an α -aryl substituent by using enantioselective decarboxylative protonation of α -aryl- β -ketoallyl ester (**147**) using Meldrum's acid as the proton source (Scheme 38).⁵² It was observed that this method is

Scheme 38. Asymmetric Synthesis of Isoflavanones

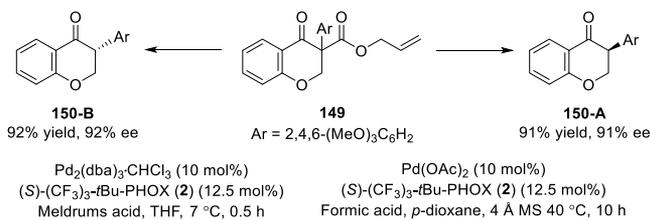


Representative examples



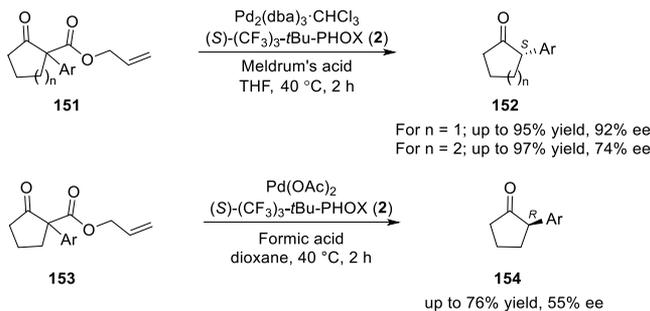
influenced by both the sterics and the electronics on the α -aryl ring of the isoflavanone. The substrate containing coordinating methoxy substituents at both *ortho*-positions seems to be essential to achieve optimal enantioselectivity. This method allowed them to synthesize highly sterically hindered α -aryl ketones with enantioselectivities of up to 92%.

In their following report, Guiry developed a Pd-catalyzed decarboxylative asymmetric protonation of α -aryl- β -ketoallyl esters (**149**) to generate a tertiary α -aryl isoflavanones (**150-A**) using formic acid as a proton source (Scheme 39).⁵³ It is interesting to note that, a switch in the preferred enantiomer formed was observed with formic acid as the proton source compared to their earlier work using Meldrum's acid as the proton source. It is one of the rare examples of an asymmetric protonation wherein dual stereocontrol was observed with the same chiral ligand but with a different achiral proton donor. The Pd-enolate formed after decarboxylation of α -aryl- β -

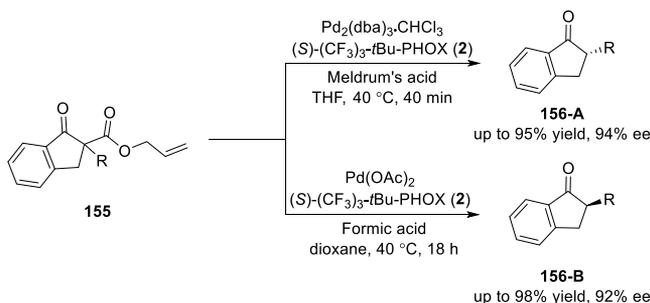
Scheme 39. Synthesis of Tertiary α -Aryl Isoflavanones

ketoallyl esters (**149**) was protonated by Meldrum's acid. Remarkably, the rates of the reactions are significantly different as the Meldrum acid-mediated reaction completes in 30 min, whereas the formic acid reaction takes up to 10 h which suggests the necessity for a carbopalladation to occur and subsequent quenching by formic acid. Alternatively, some precoordination of formic acid to the chiral Pd–enolate complex may result in an inner-sphere-type protonation to a different face of the enolate than with Meldrum's acid.

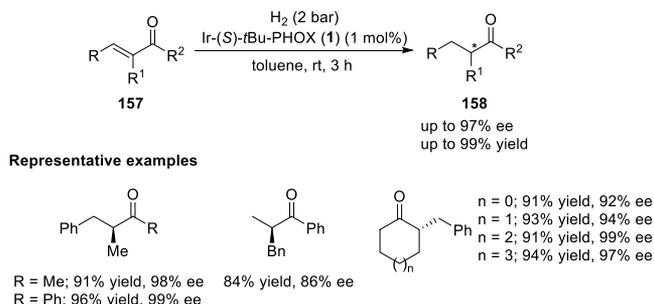
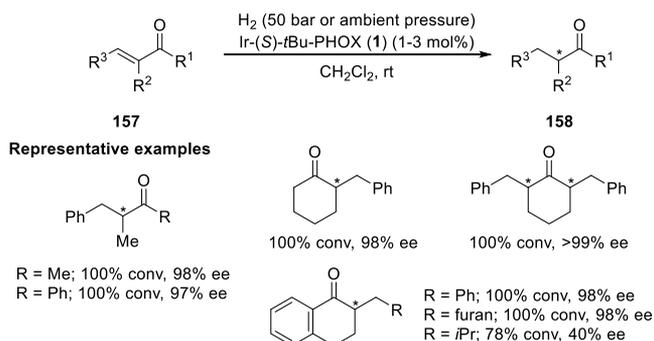
In the same year, Guiry extended the methodology for the synthesis of a series of tertiary α -aryl cyclopentanones (**152**) and cyclohexanones (**154**) from α -aryl- β -keto allyl esters (**151** and **153**) in moderate to good levels of enantioselectivity (Scheme 40).⁵⁴ Similar to earlier methods, good levels of enantioselectivity were achieved for substrates containing aryl groups with mono- and di-*ortho*-substitution.

Scheme 40. Asymmetric Synthesis of Tertiary α -Aryl Cyclopentanones and Cyclohexanones

Guiry further studied a scope of the decarboxylative asymmetric protonation with indanone based α -aryl- β -keto allyl ester substrates (**155**) (Scheme 41).⁵⁵ As seen with other cyclic ketones, both enantiomers of a series of tertiary α -aryl-indanones (**156**) were accessible by simply switching the achiral proton source. In this example of dual stereocontrol, enantioselectivities up to 92% *ee* (*R*) and 94% *ee* (*S*) were achieved using formic acid and Meldrum's acid, respectively.

Scheme 41. Synthesis of Tertiary α -Aryl-1-indanones

2.1.1.3. Application of PHOX in Asymmetric Hydrogenation. Bolm and Hou independently reported the asymmetric hydrogenation of α -substituted enones (Schemes 42 and 43).

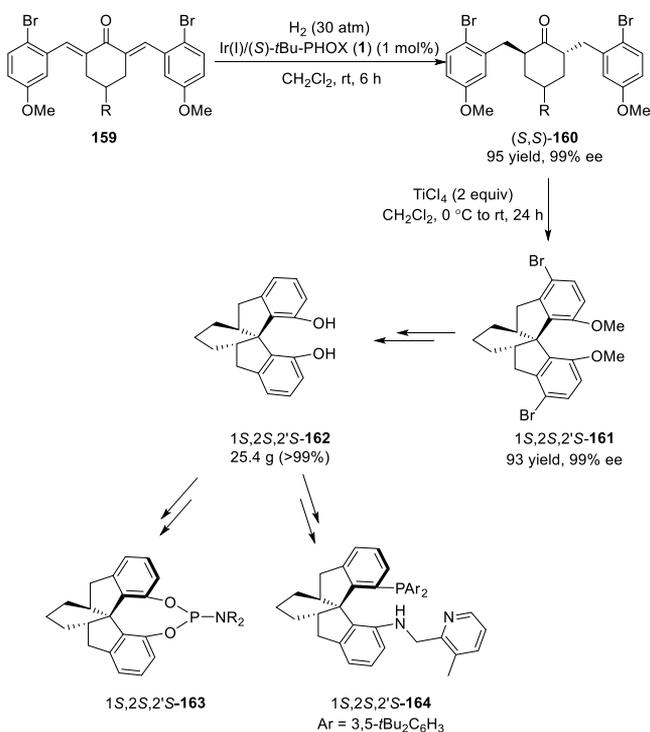
Scheme 42. Asymmetric Hydrogenation of α -Substituted EnonesScheme 43. Asymmetric Hydrogenation of α -Substituted Enones

Bolm discovered a simple and highly efficient asymmetric synthesis of α -substituted ketones (**158**) from α -substituted enones (**157**) (Scheme 42).⁵⁶ Both acyclic and cyclic enones underwent smooth catalytic enantioselective hydrogenations using the Ir complex of *t*Bu-PHOX (**1**) furnishing α -substituted ketones in high yields and enantioselectivities while tolerating a wide variety of substituents.

Hou reported an Ir-catalyzed asymmetric hydrogenation of α -substituted- α,β -unsaturated ketones (**157**) to generate a chiral center at the α -position of ketones (**158**) (Scheme 43).⁵⁷ Different ketone substrates possessing exocyclic alkenes furnished products in high enantioselectivity, even under ambient pressure of hydrogen.

Ding reported an enantioselective synthesis of cyclohexyl-fused chiral spirobiindane derivative (**161**) via a sequence of an Ir-catalyzed asymmetric hydrogenation of α,α' -bis(arylidene)-ketones (**159**), followed by an asymmetric spiroannulation of hydrogenated chiral ketones (**160**) promoted by TiCl_4 (Scheme 44).⁵⁸ A variety of cyclohexyl-fused chiral spirobiindanes (**161**) were synthesized in high yields and excellent stereoselectivities (up to >99% *ee*). The asymmetric synthesis of cyclohexyl-fused spiroindanediol (1*S*,2*S*,2'*S*)-**162**, was carried out in >99% *ee* and 67% overall yield over four steps without chromatographic purification. The (1*S*,2*S*,2'*S*)-**162** was then used to access chiral monodentate phosphoramidites **164** and tridentate phosphorus-aminopyridine **164** and the applications of these ligands were shown in various metal-catalyzed enantioselective reactions including hydrogenation,

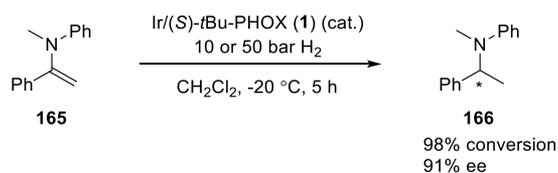
Scheme 44. Asymmetric Hydrogenation of α,α' -Bis(arylidene)ketones



hydroacylation, and [2 + 2] reactions. The catalytic performances of these ligands were very similar to the corresponding well-established spirobiindane backbone based privileged ligands.

Pfaltz discovered an asymmetric hydrogenation of enamines (**165**) catalyzed by cationic Ir complexes derived from *t*Bu-PHOX (**1**) (Scheme 45).⁵⁹ The level of enantioselectivities

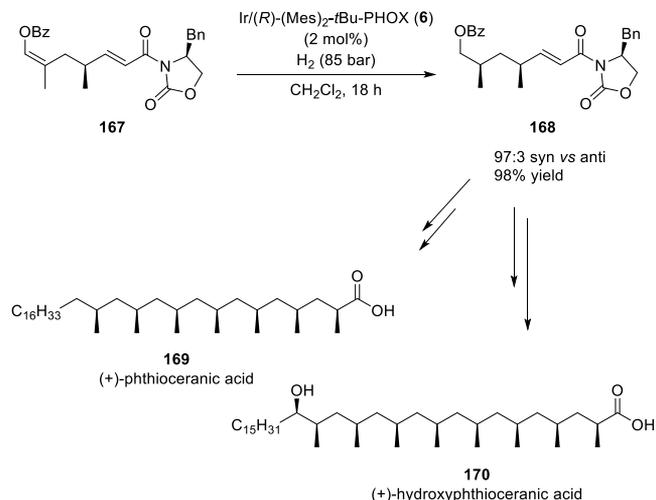
Scheme 45. Asymmetric Hydrogenation of Enamines



observed in these hydrogenations greatly depend on the substitution pattern at the double bond and the nitrogen atom. An *N*-aryl or *N*-benzyl group seems to have a beneficial effect on the enantioselectivity (>90% *ee*), whereas enantioselectivities for the hydrogenation of cyclic and acyclic 1,2-disubstituted enamines were lower.

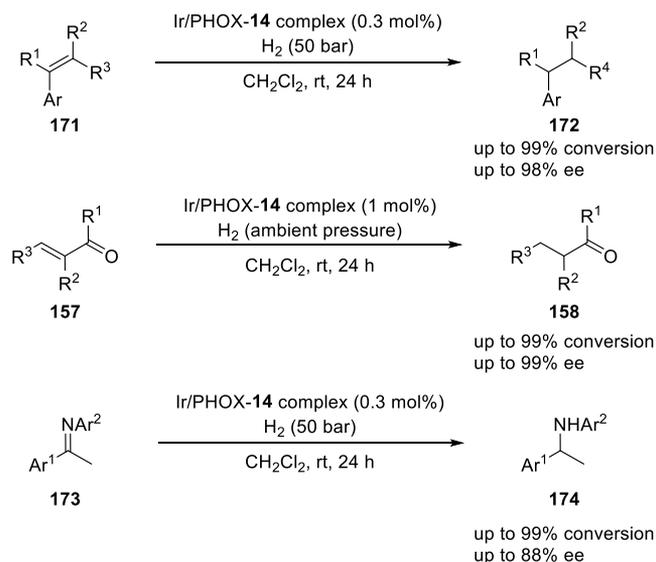
Pfaltz applied an Ir-catalyzed hydrogenation for the stereoselective and flexible synthesis of long-chain polydeoxypropionates (Scheme 46).^{60,61} The Ir complex of chiral PHOX-ligand **6** catalyzed the hydrogenation of **167** with excellent levels of diastereoselectivity. The benzoate anti-**167** were obtained with 96:4 diastereoselectivity and >95% isolated yield. Interestingly the opposite diastereofacial selectivity was obtained when the mesityl group on the phosphine ligand was changed to an *o*-tolyl or a cyclohexyl. Hydrogenated benzoate **168** was further utilized to complete the synthesis of the glycolipid components (+)-phthioceranic acid (**169**) and (+)-hydroxyphthioceranic acid (**170**).

Scheme 46. Stereoselective Hydrogenation of **167**



Hou reported an Ir-catalyzed asymmetric hydrogenation of unfunctionalized alkenes (**171**), α,β -unsaturated esters (**157**), allyl alcohols, α,β -unsaturated ketones (**157**), and ketimines (**173**) using benzylic substituted PHOX ligand **14** (Scheme 47).⁶² A wide range of substrates were successfully reduced to

Scheme 47. Asymmetric Hydrogenation of Unfunctionalized Alkenes

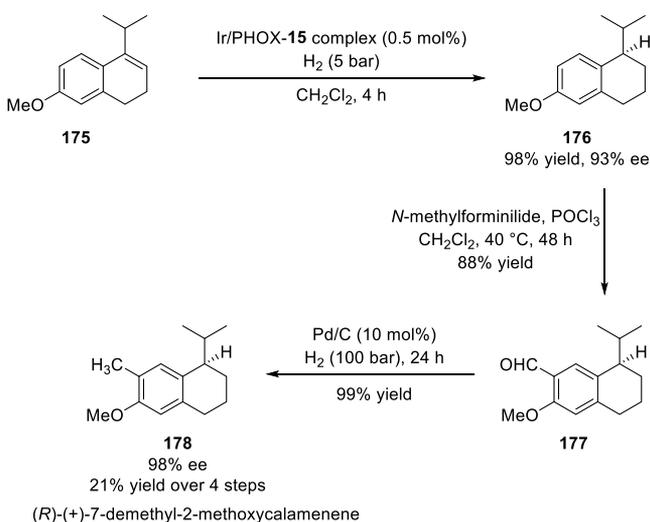


the corresponding chiral products (**172**, **158**, and **174**) with high conversions and high *ee* values (>99% conversion and up to 99% *ee*). The reaction of (*Z*)- and (*E*)-alkenes gave rise to enantiomeric products in almost the similar enantiomeric excess catalyzed by the same Ir-PHOX **14** complex. The reported *P,N*-ligands have a six-membered ring with Ir, whereas ligand **14** which is derived from a benzylic substituted *P,N*-ligand has a seven-membered ring. The increased tether length is more flexible and is believed to have a better chance to fit the steric demands of various substrates. The slightly larger bite angle of ligand was confirmed by X-ray analysis of the corresponding Ir complex.

Pfaltz reported a further Ir-catalyzed asymmetric hydrogenation of unfunctionalized and functionalized alkenes (**175**) using a new *P,N*-ligand **15** introduced from their group

(Scheme 48).⁶³ The application of their methodology was demonstrated in the synthesis of the antitumor natural

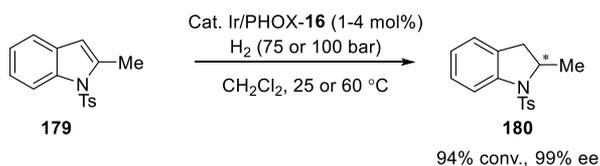
Scheme 48. Asymmetric Hydrogenation of Unfunctionalized Alkenes



product, (R)-(+)-7-demethyl-2-methoxycalamenene (178), a superior approach to an earlier published route with respect to the number of steps and the overall yield (4 steps, 21% overall yield and 98% ee). The catalytic system was also extended to the asymmetric hydrogenation of allylic alcohols, α,β -unsaturated esters and imines which resulted in the corresponding products in good to excellent ees (up to 96%).

Pfaltz described a cationic Ir/chiral *P,N*-ligand 16 system for the efficient asymmetric hydrogenation of 2-substituted *N*-protected indoles (179) (Scheme 49).⁶⁴ The Ir catalyst

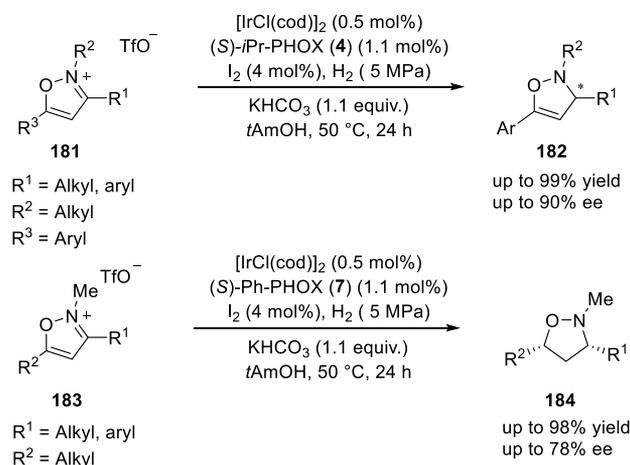
Scheme 49. Asymmetric Hydrogenation of 2-Substituted *N*-Protected Indoles



employed is highly air and moisture sensitive. Various indoles with *N*-Boc-, *N*-acetyl-, and *N*-tosyl protecting groups were hydrogenated in excellent yields and enantioselectivities. The influence of *N*-protection on the reactivity and enantiomeric excess was lessened by employing the right combination of the catalytic system.

Kuano developed an Ir-catalyzed enantioselective hydrogenation of isoxazolium triflates (181 and 183) to furnish enantioenriched 4-isoxazolines (182) or isoxazolidines (184) (Scheme 50).⁶⁵ The hydrogenation of 5-arylisoxazolium triflates (181) exclusively provided the corresponding 4-isoxazolines (182) with good enantioselectivities (up to 90% ee) whereas 5-alkylated isoxazolium triflates (183) selectively furnished *cis*-3,5-disubstituted isoxazolidines (184) with ees up to 78%. The enantioselectivity was strongly affected by the hindrance from the 5-substituent on the isoxazole ring. Interestingly, the commonly occurred and undesired N–O

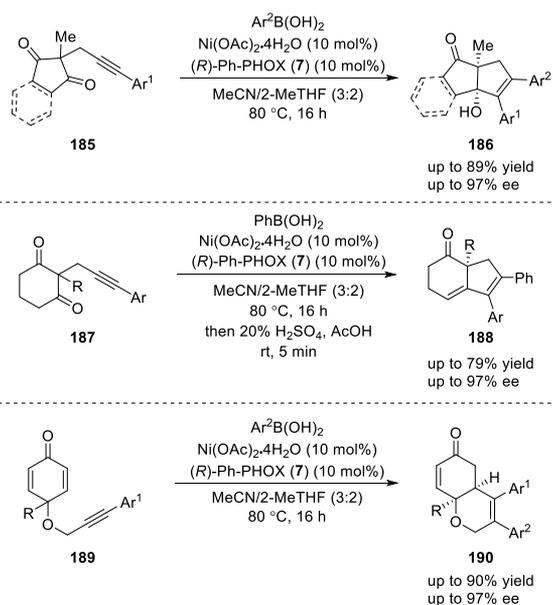
Scheme 50. Enantioselective Hydrogenation of Isoxazolium Triflates



bond cleavage was not observed under the reaction conditions employed.

2.1.1.4. Application of PHOX in Addition of Arylboronic Acids to Alkyne, Allene, or Imine. Lam reported a Ni/(R)-Ph-PHOX (7)-catalyzed reaction of arylboronic acids with alkynes (185, 187, and 189) followed by the enantioselective cyclization of an alkenyl Ni species onto a tethered electrophilic trap such as ketones or enones (Scheme 51).⁶⁶

Scheme 51. Enantioselective Domino Cyclization of Tethered Alkynes

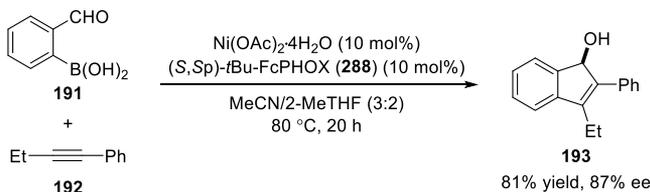


The success of this domino cyclization is reliant upon the formal *anti*-carbonickelation of the alkyne, which is suggested to occur by the reversible *E/Z*-isomerization of an alkenylnickel species.

Furthermore, an intramolecular reaction between 1-phenyl-1-butyne (192) and 2-formylphenylboronic acid (191) using (*S,S*_p)-*t*Bu-FcPHOX (288) (discussed in detail in section 2.3) furnished the expected indene 193 in 81% yield and 87% ee via a *syn*-arylnickelation of the alkyne followed by cyclization of the resulting alkenylnickel species onto the aldehyde (Scheme

52). Interestingly, the same chiral ligand, (*S,S*)-*t*Bu-FcPHOX (288), earlier furnished a product *via anti*-arylnickelation. The

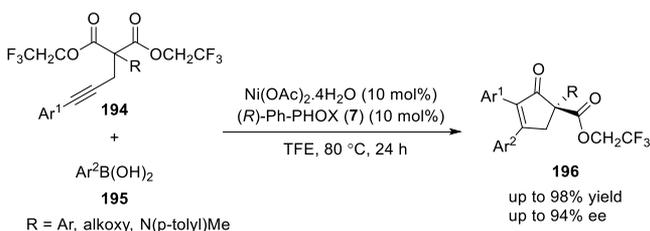
Scheme 52. Intramolecular Reaction between 1-Phenyl-1-butyne and 2-Formylphenylboronic Acid



ability to synthesize enantioenriched products from either a *syn*- or *anti*-carbometallative cyclization further suggests that reversible *E/Z*-isomerization of the alkenylnickel species is operative and also demonstrates the adaptive power of this Ni-based catalytic system.

Lam reported a Ni/(*R*)-Ph-PHOX (7)-catalyzed desymmetrizing arylyative cyclization for the enantioselective synthesis of chiral cyclopent-2-enones (196) by using alkynyl bis(2,2,2-trifluoroethyl) malonates (194) and arylboronic acids (195) (Scheme 53).⁶⁷ A wide variety of cyclopent-2-enones (196)

Scheme 53. Desymmetrizing Arylyative Cyclization of Alkynyl Bis(2,2,2-trifluoroethyl) Malonates

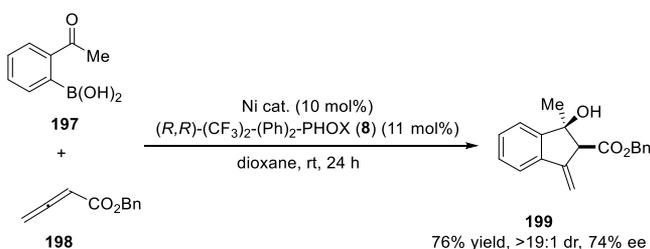


containing a quaternary stereocenter were synthesized in good yields and excellent enantioselectivities (up to 98% and 94% *ee*). This cyclization was promoted by the reversible *E/Z*-isomerization of the alkenylnickel species formed during the reaction.

Lam developed a Ni-catalyzed highly diastereoselective annulation between 2-acetylphenylboronic acid (197) or 2-formylarylboronic acid and activated allenes (198) to furnish 3-methyleneindanols (199) (Scheme 54).⁶⁸ Preliminary results using the chiral phosphinoxazoline ligand, (*R,R*)-(CF₃)₂-(Ph)₂-PHOX (8) furnished the product in 76% yield and good stereoselectivities (19:1 *dr* and 74% *ee*).

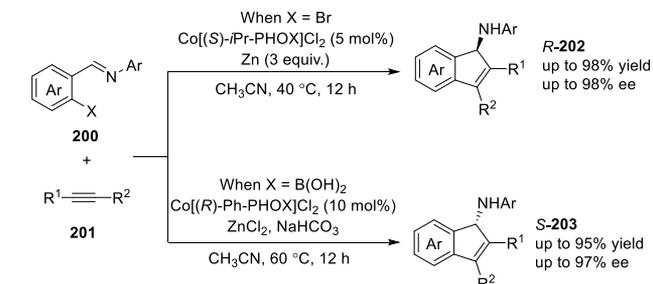
Cheng reported the synthesis of chiral 1-aminoindenes (202/203) through an intramolecular reaction between *o*-imodoylarylboronic acids or aryl halides or pseudohalides

Scheme 54. Diastereoselective Annulations between 2-Acetylphenylboronic Acid and Allene

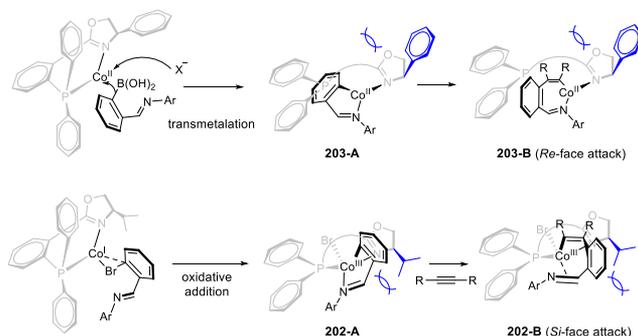


(200) with alkynes (201) using a Co/chiral PHOX-catalyzed enantioselective [3 + 2] annulation reaction (Scheme 55).⁶⁹

Scheme 55. Enantioselective [3 + 2] Annulation Reaction



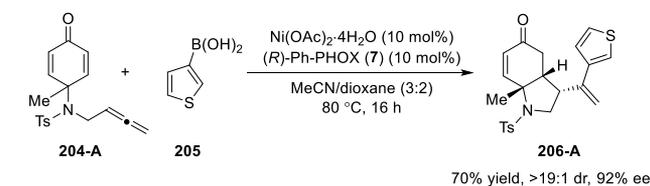
Proposed model



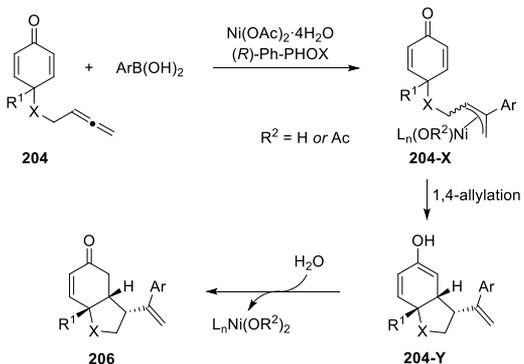
This reaction achieved a controlled synthesis of both enantiomers of variety of 1-aminoindenes (202/203) in high yields and good to excellent enantioselectivities (up to 98% yield and 98% *ee*). The unsymmetrical alkynes reacted regioselectively affording single stereoisomers in high yield and excellent *ee* values. The role of ZnCl₂ was found to be crucial as it dramatically enhanced the yield without any negative effect on enantioselectivity. The configuration of the desired product is dominated and controlled by the steric bulk of the substituent attached to the nitrogen-adjacent carbon on the oxazoline ring. As demonstrated in the proposed model, the phenyl group of complex 203-A forces the R group to be far away from the oxazoline moiety and leads the subsequent intramolecular addition of imine from the *Re*-face, while the isopropyl group of complex 202-A leads to *Si*-face insertion.

Lam and co-workers earlier discovered that the Ni/(*R*)-Ph-PHOX (7) complex is highly effective in promoting enantioselective anticarbometallative cyclizations of alkynyl electrophiles with arylboronic acids.^{66–68} They hypothesized that Ni/(*R*)-Ph-PHOX (7) complex could also promote a catalytic enantioselective intramolecular 1,4-allylation of substrates containing an allene tethered to an electron-deficient alkene. Considering these facts Lam 2018 described the enantioselective Ni-catalyzed arylyative desymmetrization of allenyl cyclohexa-2,5-dienones (204-A) by using arylboronic acids (205) (Scheme 56).⁷⁰ A variety of hexahydroindol-5-ones and hexahydrobenzofuran-5-ones with three contiguous stereocenters were synthesized in moderate to good yield with high diastereo- and enantioselectivities. The proposed mechanism begins with the Ni/(*R*)-Ph-PHOX (7)-catalyzed addition of an arylboronic acid to an allenyl cyclohexa-2,5-dienone (204). The resulting allylnickel species 204-X would undergo intramolecular 1,4-allylation to give nickel enolate 204-Y, which upon protonation would liberate the Ni(II)

Scheme 56. Enantioselective Ni-Catalyzed Desymmetrization of Allenyl Cyclohexa-2,5-dienones



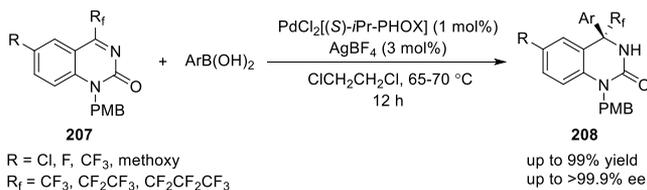
Proposed mechanism



catalyst and a *cis*-fused hexahydroindol-5-one or hexahydrobenzofuran-5-one (**206**).

In 2016, Hayashi reported a Pd-catalyzed asymmetric arylation of fluoroalkyl-substituted 2-quinazolinone derivatives (**207**) with arylboronic acids using (*S*)-*i*Pr-PHOX (**4**) ligand (Scheme 57).⁷¹ A variety of trifluoromethylated and

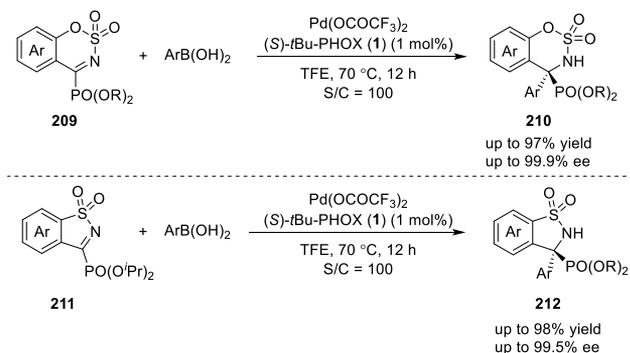
Scheme 57. Pd-Catalyzed Asymmetric Arylation



perfluoromethylated 2-quinazolinone (**208**) products possessing quaternary carbon stereocenters were synthesized in excellent enantioselectivities (>99% *ee*).

Later, Zhou employed a Pd-catalyzed enantioselective addition of arylboronic acids to five- and six-membered cyclic α -ketiminophosphonates (**209/211**) using (*S*)-*t*Bu-PHOX (**1**) ligand (Scheme 58).⁷² The method provided an elegant and

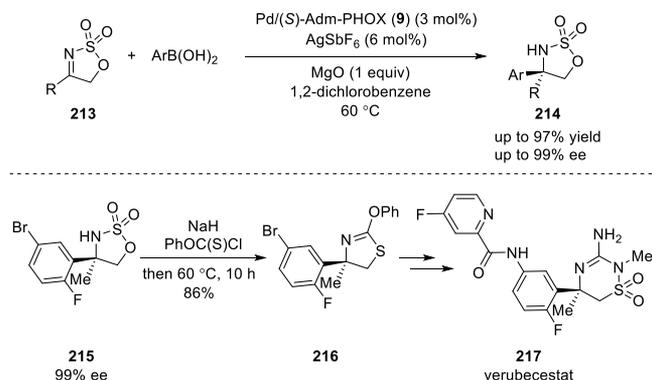
Scheme 58. Enantioselective Addition of Arylboronic Acids to Cyclic α -Ketiminophosphonates



efficient route to access chiral α -aminophosphonates (**210/212**) possessing a quaternary carbon stereocenter in high yields and excellent enantioselectivities (up to 99.9% *ee*). The use of low catalytic loading and a wide substrate scope are the highlights of this arylation methodology.

Chen reported a Pd-catalyzed enantioselective addition of arylboronic acids to cyclic iminosulfates (**213**) using an adamantyl-substituted phosphinooxazoline ligand **9** (Scheme 59).⁷³ This enantioselective arylation tolerates a wide variety of

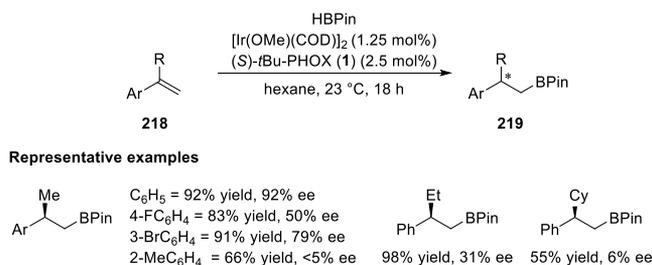
Scheme 59. Enantioselective Addition of Arylboronic Acids to Cyclic Iminosulfates



arylboronic acids as well as cyclic iminosulfates to provide cyclic sulfamidates (**214**) in high yields with excellent *ees* (up to 97% yield and up to 99% *ee*). The methodology was applied to synthesize verubecestat (**217**), a compound under clinical evaluation for the treatment of Alzheimer's disease.

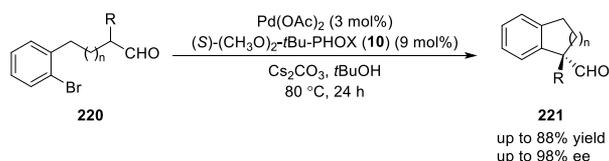
2.1.1.5. Application of PHOX in Asymmetric Borylation of Alkenes. In 2011, Mazet developed an Ir-catalyzed regio- and enantioselective hydroboration of terminal olefins (**218**) using the *t*Bu-PHOX (**1**) ligand (Scheme 60).⁷⁴ The reaction is

Scheme 60. Enantioselective Hydroboration of Terminal Olefins

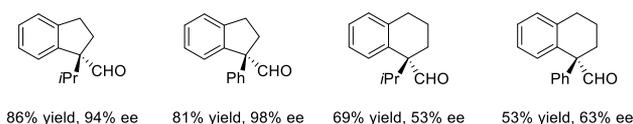


highly dependent on sterics as changing the R group from methyl to ethyl or cyclohexyl or by replacing the phenyl ring with an *o*-tolyl group radically decreased the enantioselectivity of the expected hydroboration products.

2.1.1.6. Application of PHOX in Asymmetric α -Arylation. Buchwald reported a Pd-catalyzed α -arylation of aldehydes (**220**) forming all-carbon-substituted asymmetric centers in high yields and enantioselectivities (Scheme 61).⁷⁵ Generally, substrates with α -aryl substituents gave rise to products with higher optical purity than these with α -alkyl analogues. The efficiency of the method is excellent for substrates forming five-membered rings, but it dropped significantly for substrates forming a six-membered ring; tetrahydronaphthalene deriva-

Scheme 61. Enantioselective α -Arylation of Aldehydes

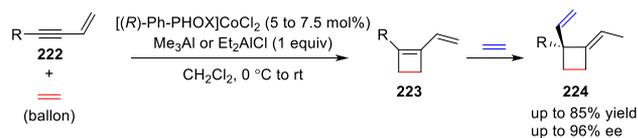
Representative examples



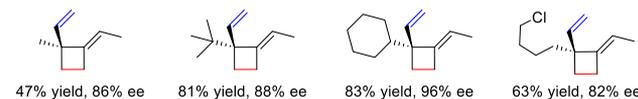
tives were prepared in moderate to good yields with moderate levels of enantioselectivity.

2.1.1.7. Application of PHOX in Asymmetric [2 + 2] Cycloaddition. In 2018, Rajanbabu reported a Co/(*R*)-Ph-PHOX (7)-catalyzed [2 + 2] cycloaddition between 1,3-enynes (222) and ethylene followed by an enantioselective hydrovinylation of the resulting vinylcyclobutene (223) to give highly functionalized cyclobutanes (224) with an all-carbon quaternary stereocenter, as the (*E*)-isomer (Scheme 62).⁷⁶ The

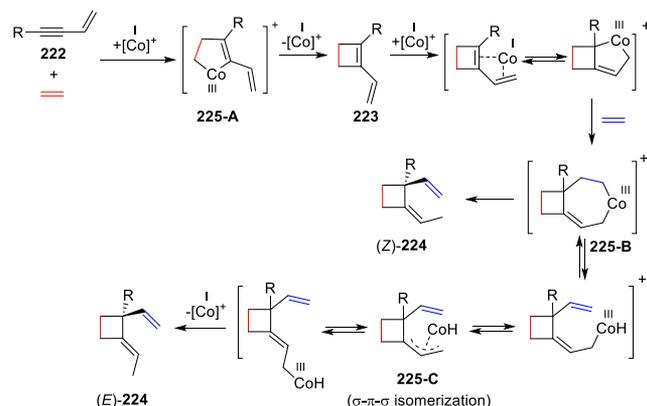
Scheme 62. Asymmetric [2 + 2] Cycloaddition between 1,3-Enynes and Ethylene



Representative examples



Mechanism:

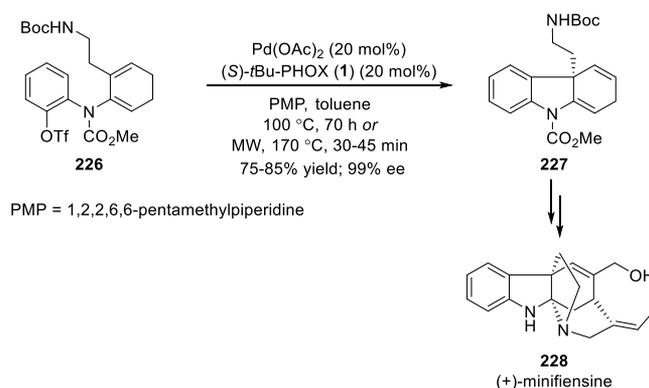


reaction proceeds in a tandem fashion to form three highly selective C–C bonds in one pot using a single chiral Co catalyst. The use of an activator, Et₂AlCl, was important to promote this cycloaddition reaction. The cycloaddition initiates with an oxidative dimerization of ethylene and the enyne (222) in the coordination sphere of an activated Co(I) species to afford a metallacyclopentene 225-A, which after reductive elimination provides cyclobutene 223. This diene 223 further undergoes oxidative dimerization with ethylene to deliver the metallacycloheptene 225-B. Sterically congested 225-B, (*Z*)-allylcobalt(III)-hydride undergoes (*Z*)/(*E*)-isomerization through an η^3 -(allyl) intermediate 225-C, which

upon β -hydrogen elimination and reductive elimination finally leads to the (*E*)-224 isomer as the major product. The ratio of (*Z*)- and (*E*)-isomers depended on the nature of the R substituent and the nature of the ligand used.

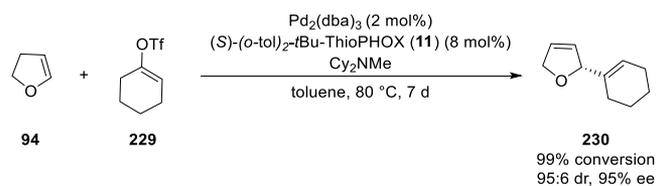
2.1.1.8. Application of PHOX in Asymmetric Heck Reaction. Overman and Wroblewski reported a synthesis of (+)-minifiensine (228), which involves an asymmetric Heck-cyclization of dienyl aryl triflate 226 using a catalytic amount of Pd and (*S*)-*t*Bu-PHOX (1) as the key step to provide dihydrocarbazole 227 in 99% ee (Scheme 63).⁷⁷ It is noteworthy that microwave heating (170 °C) was employed to accelerate this catalytic transformation.

Scheme 63. Asymmetric Heck-Cyclization of Dienyl Aryl Triflate 226



In 2009, Guiry reported a Pd-catalyzed intermolecular asymmetric Heck reaction between 2,3-dihydrofuran (94) and a range of triflates using HetPHOX ligands (Scheme 64).⁷⁸

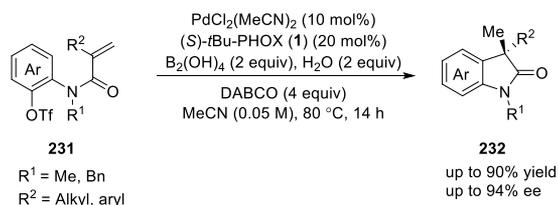
Scheme 64. Intermolecular Asymmetric Heck Reaction



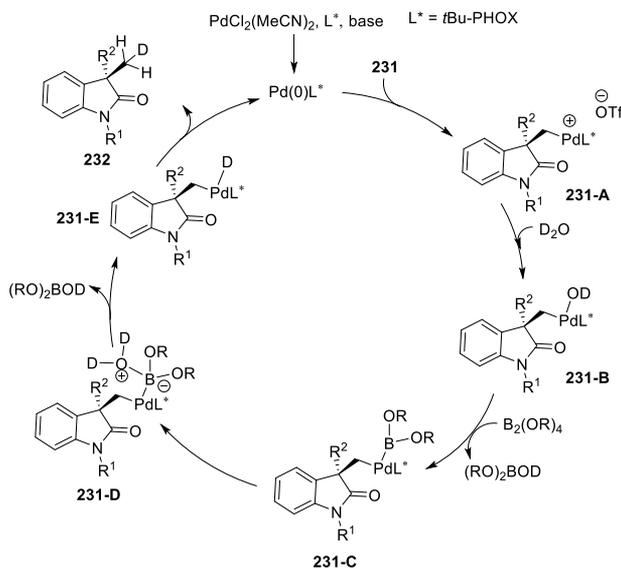
The HetPHOX ligand derived from *tert*-leucinol and di-*o*-tolylphosphine, (*S*)-(*o*-tol)₂-*t*Bu-ThioPHOX (11) proved the most effective affording *ee* values of up to 96, 95, and 94% in the phenylation, cyclohexenylation (using triflate (229)), and naphthylation, respectively, of 2,3-dihydrofuran.

Zhu reported an asymmetric reductive Heck reaction using a catalytic amount of Pd, (*S*)-*t*Bu-PHOX (1) and diboron-H₂O as a hydride source (Scheme 65).⁷⁹ This method was applied to synthesize a library of enantioenriched oxindoles (232) possessing a C3-quaternary stereocenter in excellent yields and enantioselectivities. Alkenes possessing aryl and alkyl groups at R² were compatible. The use of D₂O instead of H₂O as a D-donor enabled the synthesis of CH₂D substituted oxindoles. The catalytic cycle initiates with oxidative addition of the *t*Bu-PHOX (1) ligated Pd(0) to aryl triflate 231, followed by intramolecular carbopalladation, generating a cationic alkyl-Pd(II) intermediate 231-A which reacts with B₂(OH)₄ and H₂O in a series of steps to afford alkyl-Pd(II)-H species 231-E. Finally, reductive elimination from 231-E provides the desired

Scheme 65. Asymmetric Reductive Heck Reaction



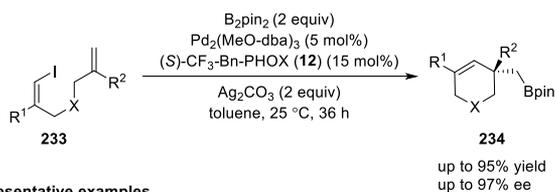
Proposed mechanism



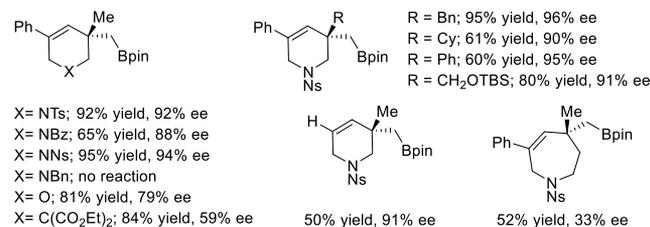
product **232** with simultaneous regeneration of the $\text{Pd}(0)/t\text{Bu-PHOX}$ (**1**) catalyst.

Tong developed a Pd-catalyzed asymmetric vinylborylation of (*Z*)-1-iodo-diene (**233**) with B_2Pin_2 using (*S*)- $\text{CF}_3\text{-Bn-PHOX}$ (**12**) (Scheme 66).⁸⁰ This method allowed them to

Scheme 66. Asymmetric Vinylborylation



Representative examples

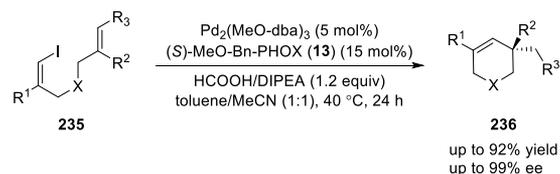


synthesize a variety of 3,3-disubstituted tetrahydropyridines (**234**) derivatives in good yields and high enantioselectivities. The choice of the tether between vinyl iodide and the alkene had a strong effect on the reaction outcome, as a tether with a strong coordinating atom with Pd had a positive effect and this protocol was limited to the synthesis of a 6-membered cyclic product. This reaction begins by the oxidative addition of $\text{Pd}(0)$ to vinyl iodide followed by a Ag-mediated transmetalation with B_2Pin_2 to form a vinyl-Pd(II)-Bpin species

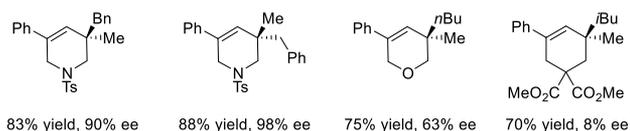
which, upon intramolecular enantioselective carbopalladation followed by reductive elimination, furnished the expected product. Mechanistic studies revealed that the transmetalation step occurs before the alkene insertion, which was complementary to the previous understanding of a similar reaction.

In 2017, Tong developed an asymmetric reductive Heck cyclization of (*Z*)-1-iodo-1,6-dienes (**235**) using $\text{Pd}_2(\text{dba-OMe})_3$ and (*S*)-MeO-Bn-PHOX (**13**) as the ligand (Scheme 67).⁸¹ This method provided a facile access to chiral

Scheme 67. Asymmetric Reductive Heck Cyclization



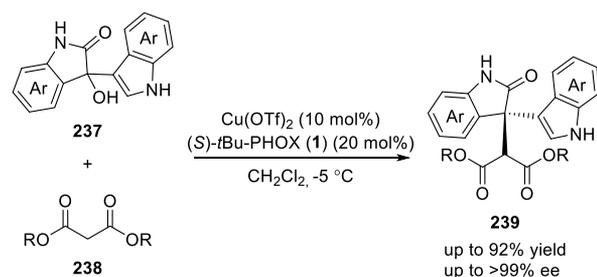
Representative examples



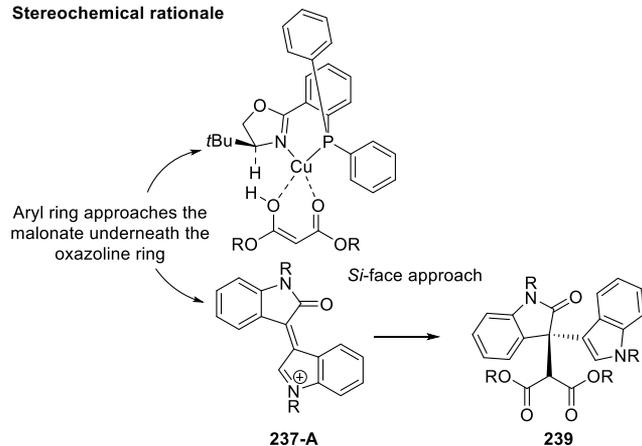
quaternary tetrahydropyridines (**236**) with good to excellent yields and enantioselectivities. Additionally, this method tolerates susceptible β -hydrogen elimination and a substrate bearing a trisubstituted alkene. The linker between the vinyl iodides and alkenes as well as substituent R^1 , R^2 , and R^3 had a strong influence on the yield and enantioselectivity of product.

2.1.1.9. Application of PHOX in Asymmetric Alkylation. In 2018, Bisai reported a Cu-catalyzed asymmetric alkylation of 3-hydroxy-2-oxindole (**237**) with a variety of malonates (**238**) using the *t*Bu-PHOX (**1**) ligand (Scheme 68).⁸² The presence of an indole moiety at C3 is critical for success and no reaction

Scheme 68. Asymmetric Alkylation of 3-Hydroxy-2-oxindole



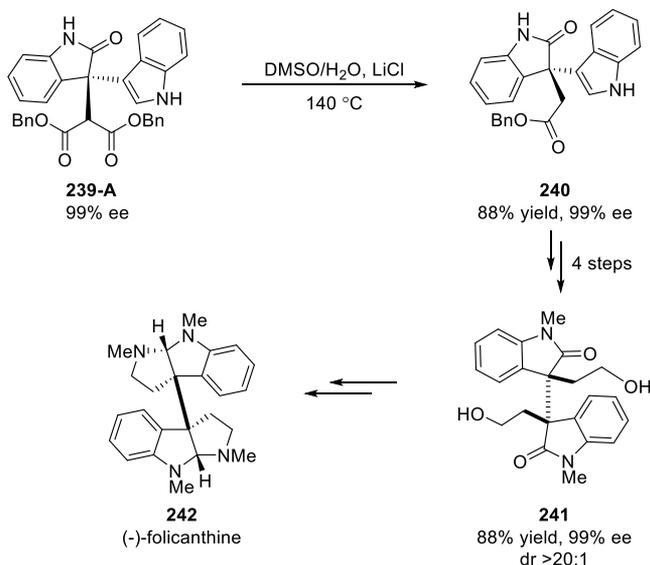
Stereochemical rationale



occurred when indole was replaced with an alkyl group. This observation suggested *in situ* formation of a highly reactive intermediate **237-A** followed by an enantioselective malonate addition. The mechanistic studies confirmed that the reaction is reversible in nature and the involvement of a Cu(II)-complex with a distorted trigonal bipyramid (TBP) geometry.

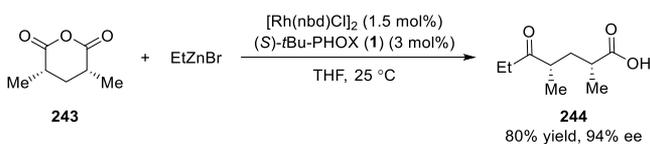
The application of the method was illustrated in the formal total synthesis of (–)-folicanthine (**242**) by synthesizing a C₂-symmetric dimeric 2-oxindole **241** possessing an all-carbon quaternary stereocenter in 5 steps (Scheme 69).

Scheme 69. Synthesis of (–)-Folicanthine



2.1.1.10. Application of PHOX in Desymmetrizing Cross-Coupling. Rovis reported a Rh/*t*Bu-PHOX (**1**)-catalyzed cross-coupling between sp³ organozinc reagents and 3,5-dimethylglutaric anhydride (**243**) (Scheme 70).⁸³ A variety

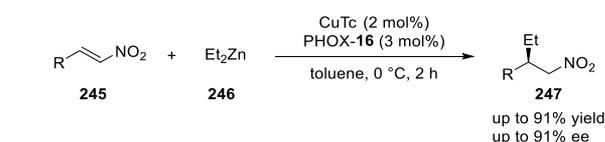
Scheme 70. Desymmetrizing Cross-Coupling



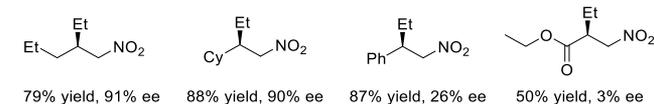
of *syn*-deoxypolypropionates (**244**) were synthesized in excellent yields and good to excellent enantioselectivities. This catalytic system worked well with alkyl and benzyl zinc reagents possessing various functionalities, however it was less efficient with phenyl and isopropyl zinc reagents.

2.1.1.11. Application of PHOX in Asymmetric Conjugate Addition. Jung reported a Cu-catalyzed asymmetric conjugate addition of alkylzinc reagents to nitroalkenes (**245**) and cyclic enones by using the newly synthesized *P,N*-ligand **16** (Scheme 71).⁸⁴ A variety of chiral nitroalkanes (**247**) and β-alkyl cyclic ketones were synthesized in good yields and good enantioselectivity (up to 92% yield and 95% ee). Computational studies suggested that the chiral substituents in the oxazoline moiety of *P,N*-ligand **16** are not crucial for the selectivity whereas the other alkyl substituent in the bridging moiety is involved in the steric repulsion during the transition state.

Scheme 71. Asymmetric Conjugate Addition



Representative examples



Metal complexes of PHOX ligands with one stereocenter (**1–17**) have been extensively studied in the past decade. These complexes have been successfully applied in various asymmetric transformations. Palladium complexes were excellent for (I) decarboxylative allylic alkylation and protonation, (II) Heck reaction, (III) hydroamination and alkylation of diene, (IV) [3 + 2] cycloaddition, (V) Meerwein-Eschenmoser and Saucy-Marbet Claisen rearrangement, (VI) aryl boronic acid addition to various imines. Iridium complexes were mostly utilized in hydrogenation of diverse types of alkenes and imines whereas nickel complexes showed excellent results when employed in annulation reactions between aryl boronic acids and alkynes, allenes and imines. Cobalt complexes were specifically successful in (I) intramolecular reactions between *o*-imidoarylboronic acids or aryl halides or pseudohalides with alkynes, and (II) [2 + 2] cycloadditions between 1,3-enynes and ethylene. Copper complexes were successfully employed in (I) asymmetric alkylations of 3-hydroxy-2-oxindole, and (II) asymmetric conjugate additions of alkylzinc reagents to nitroalkenes while rhodium complexes found their application in desymmetrizations of 3,5-dimethylglutaric anhydride with alkyl zinc bomides. It is evident from the literature covered in this section of the review that PHOX ligands with only one stereocenter are adaptable with various metals and hence researchers should seek to continue to expand their utilization in asymmetric catalysis.

2.1.2. Phosphinoxazoline Ligands with Stereoaxis or Stereocenter. This section deals with the application of phosphinoxazoline ligands (**248a–m**) possessing a stereoaxis or stereocenter in metal-catalyzed enantioselective reactions (Figure 3).

2.1.2.1. BiphPHOX Ligands. BiphPHOX ligands (**248a–b**) possess a chiral oxazoline ring and exist as an equilibrium mixture of diastereomers in solution due to rotation around the internal bond of the biphenyl groups. Interestingly, when these ligands coordinate to Pd or Ir, only one of two possible diastereomeric complexes are formed. The Zhang group extensively utilized the metal-complexes of BiphPHOX ligands (**248a–b**) in the Ir-catalyzed asymmetric hydrogenation of variably substituted olefins and in the Ni-catalyzed arylation of cyclic aldimines and ketimines.

In 2013, Zhang reported the first asymmetric hydrogenation of α-alkylidene succinimides (**249a**) using an Ir/(*S*)-*i*Pr-BiphPHOX (**248a**) complex (1 mol %) to afford hydrogenated products (**249b**) in excellent yields (>99%) and enantioselectivities (up to 99% ee) under 20 bar H₂ (Scheme 72).⁸⁵ The reactions performed under reduced catalytic loading (0.05 mol %) and reduced pressure (1 bar) were successful although at the expense of a prolonged reaction time. The *i*Pr substituent on the oxazoline ring had a strong impact on the enantioselectivity (99% ee). The α-alkylidene succinimide

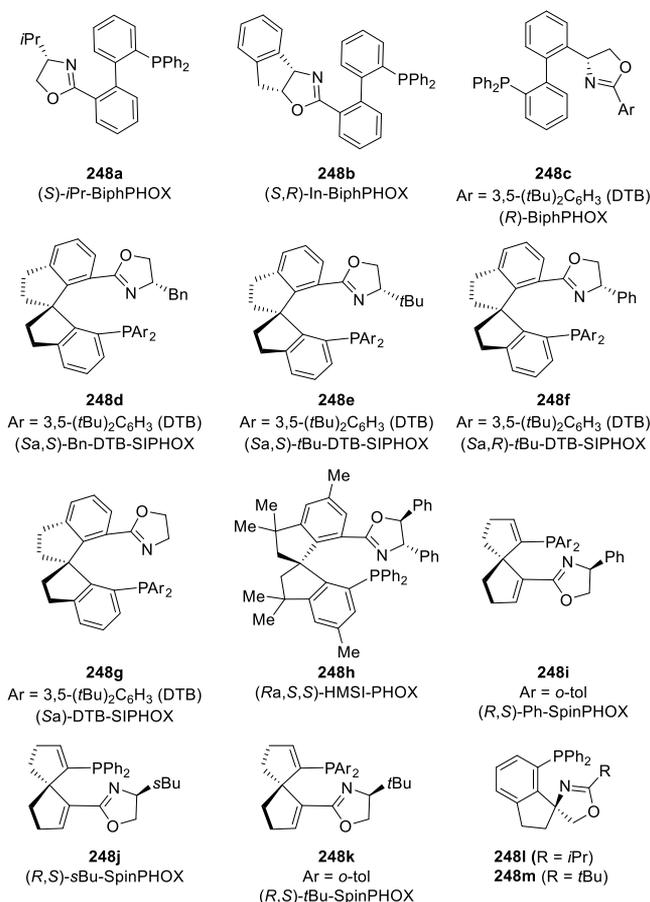
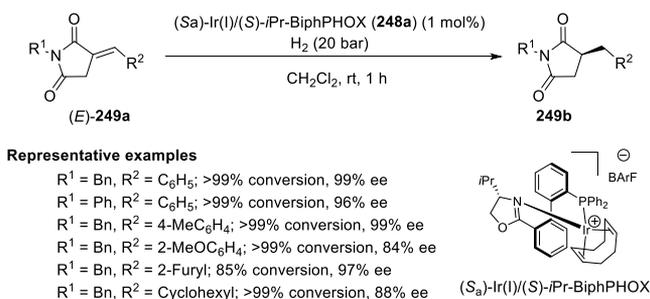


Figure 3. Phosphinoxazoline ligands with a stereocenter or stereoaxis.

Scheme 72. Asymmetric Hydrogenation of α -Alkylidene Succinimides

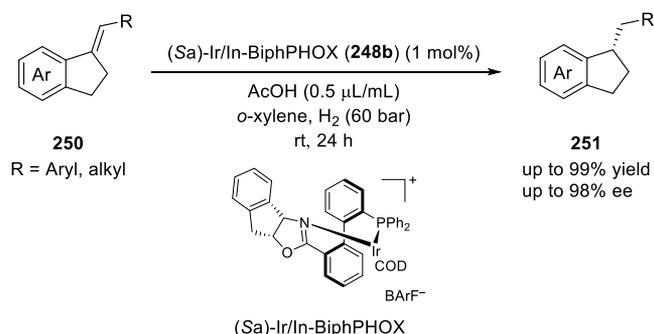


(249a) with (*E*)-configuration was essential for the success of hydrogenation whereas the *N*-protecting group did not affect the yield and enantioselectivity of the reaction.

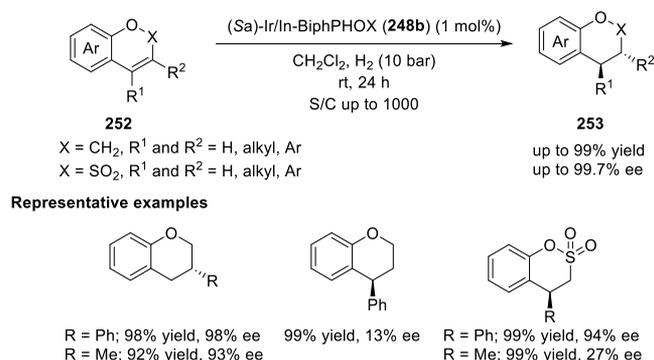
In a subsequent study, Zhang described the first asymmetric hydrogenation of unfunctionalized exocyclic C=C bonds (**250**) with Ir and In-BiphPHOX (**248b**) delivering the expected chiral 1-benzyl-2,3-dihydro-1H-indene products (**251**) in up to 98% *ee* (Scheme 73).⁸⁶ The use of coordinating solvents like THF and dioxane dramatically decreased the conversion by deactivating the Ir catalyst while the additive acetate ion plays a crucial role in improving the enantioselectivity.

Afterward, Zhang reported the asymmetric hydrogenation of substituted 2*H*-chromenes and substituted benzo[*e*][1,2]-oxathiine 2,2-dioxides (**252**) (Scheme 74).⁸⁷ A variety of 2*H*-chromenes possessing 3-aryl/alkyl substituents were hydro-

Scheme 73. Asymmetric Hydrogenation of Unfunctionalized Exocyclic Alkenes



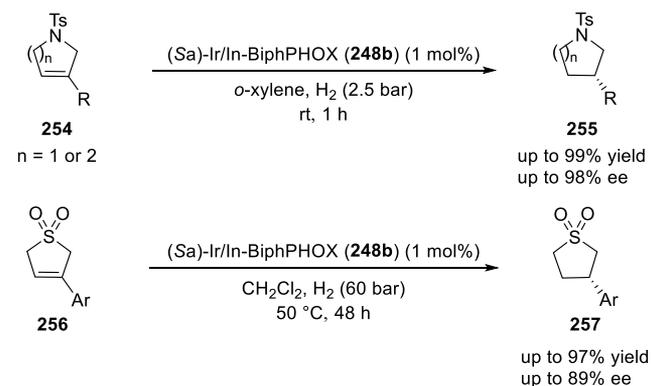
Scheme 74. Asymmetric Hydrogenation of Substituted 2*H*-Chromenes and Benzo[*e*][1,2]oxathiine 2,2-Dioxides



genated to the corresponding chiral 3-substituted chromenes (**253**) in high yields (92–99%) with excellent enantioselectivities (>99% *ee*). The 4-phenyl substituent on 2*H*-chromenes also gave the corresponding product in excellent yield but with poor enantioselectivity. Interestingly, benzo[*e*][1,2]oxathiine 2,2-dioxides with phenyl and methyl substituents produced the desired products in excellent yields but with contrasting enantioselectivity for phenyl (94% *ee*) and methyl substituents (27% *ee*).

Similarly, Zhang extended their catalytic system for the asymmetric hydrogenation of 3-substituted 2,5-dihydropyrroles (**254**) and 3-substituted 2,5-dihydrothiophene 1,1-dioxides (**256**) (Scheme 75).⁸⁸ The hydrogenation of 3-substituted 2,5-dihydrothiophene 1,1-dioxides was more

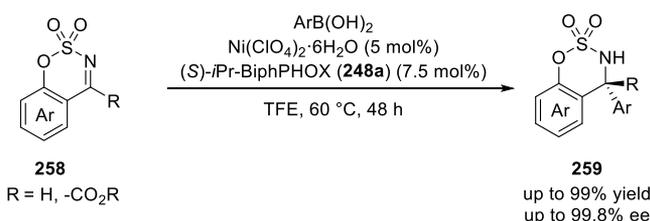
Scheme 75. Asymmetric Hydrogenation of 3-Substituted 2,5-Dihydropyrroles and 2,5-Dihydrothiophene 1,1-Dioxides



challenging compared to the 3-substituted 2,5-dihydropyrroles and hence, a higher temperature and hydrogen pressure were required to achieve full conversions.

Later on, Zhang employed *i*Pr-BiphPHOX (**248a**) in a Ni(II)-catalyzed asymmetric addition of arylboronic acids to cyclic aldimines and ketimines (**258**) furnishing products with excellent yields (up to 99%) and enantioselectivities (>99% *ee*) (Scheme 76).⁸⁹ Ligand *i*Pr-BiphPHOX (**248a**) coordinates

Scheme 76. Asymmetric Arylation of Cyclic Aldimines and Ketimines

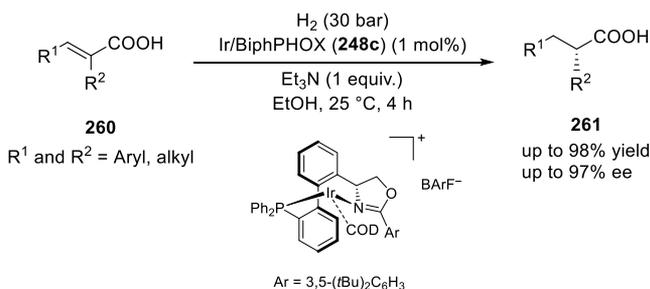


with Ni(II) to form a complex with (*S*)-axial chirality, while the complex with (*R*)-axial chirality was disfavored because of the steric hindrance of the *i*Pr group and the anion coordinated to Ni(II). Crystallographic studies confirmed the (*S*)-configuration and tetrahedral geometry of the Ni(II) complex. Interestingly, DFT calculations suggested that in solution the configuration of the Ni(II) complex changes from tetrahedral to planar.

Ligand **248c** is architecturally very similar to BiphPHOX (**248a–b**) and it has been applied in the asymmetric hydrogenation of unsaturated acids.

In 2017, Zhang developed a series of highly modular phosphinoxazoline ligands from readily available (*S*)-(+)-2-phenylglycinol. These ligands were utilized in the Ir-catalyzed asymmetric hydrogenation of α,β -unsaturated carboxylic acids (**260**) to provide chiral α -substituted carboxylic acids (**261**) (up to 97% *ee*, 98% yield, 2000 TON) (Scheme 77).⁹⁰ Ligand

Scheme 77. Asymmetric Hydrogenation of α,β -Unsaturated Acids



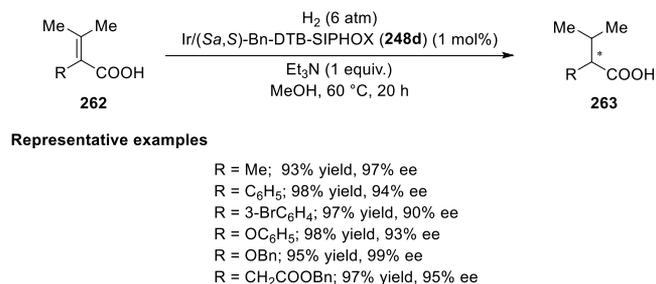
248c possessing a 3,5-(*t*Bu)₂C₆H₃ substituent on the oxazoline was found to be optimal. Changing the 3,5-(*t*Bu)₂C₆H₃ substituent to a phenyl or a *t*Bu drastically reduced the reactivity and enantioselectivity in hydrogenation. The role of Et₃N as an additive was crucial as the reactivity dropped dramatically without it.

2.1.2.2. SIPHOX Ligands. SIPHOX ligands (**248d–g**) have been employed in the Ir-catalyzed asymmetric hydrogenation of olefins, Pd-catalyzed Narasaka–Heck cyclization, Pd-catalyzed enantioselective formal [6 + 4] cycloaddition of

vinyl oxetanes with azadienes and Ni-catalyzed enantioselective arylation of cyclic *N*-sulfonyl imines.

Zhou reported the asymmetric hydrogenation of α,β -unsaturated carboxylic acids (**262**) possessing tetra-substituted olefins using Ir and chiral *P,N*-ligands (**248d**) based on the spiro-backbone (Scheme 78).⁹¹ This method offers a direct

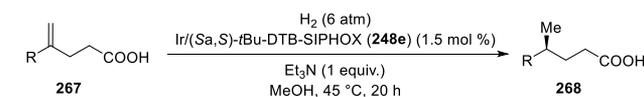
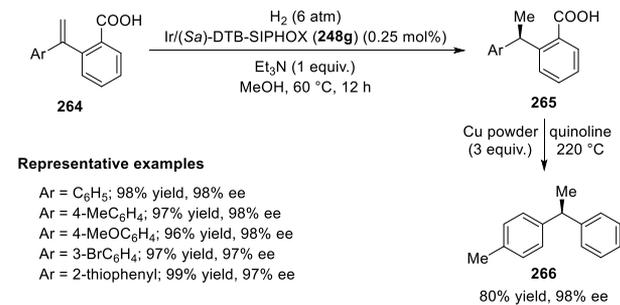
Scheme 78. Asymmetric Hydrogenation Reaction of α,β -Unsaturated Carboxylic Acids



approach to chiral carboxylic acids possessing an α -stereocenter having aryl, alkyl, aryloxy, and alkyloxy substituents. The substituents on both phosphorus (3,5-di-*t*-butylphenyl) and the oxazoline ring of **248d** had a strong effect on the outcome of the reaction. A chiral induction model was proposed which showed that the (*R*)-aryloxy or (*R*)-alkyloxy- β,β -dimethyl acrylic acids **262** prefer to coordinate to catalyst (*Sa,S*)-**248d** with *Re*-facial selectivity and consequently generates products **263** preferably with (*S*)-configuration.

In 2013, Zhou extended the Ir-catalyzed enantioselective hydrogenation strategy to 1,1-diarylethenes (**264**) and 1,1-dialkylethenes (**267**) by using a carboxylic acid as a directing group (Scheme 79).⁹² The carboxylic acid group is essential

Scheme 79. Enantioselective Hydrogenation



Representative examples

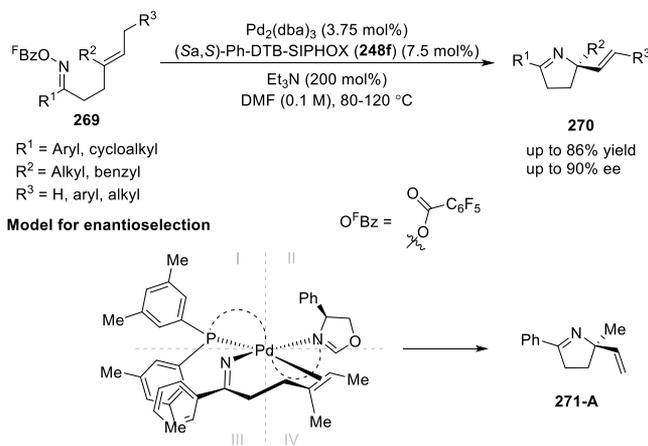
- R = Et; 97% yield, 97% *ee*
- R = *i*Pr; 95% yield, 99% *ee*
- R = *i*Bu; 94% yield, 89% *ee*
- R = PhCH₂CH₂; 97% yield, 94% *ee*

for the success of this method as no reaction was observed without it or with the corresponding ester. The diphenylethene substrates having a carboxylic acid group either at the *meta*- or *para*-position could not be hydrogenated under these reaction conditions. Importantly, no reaction occurred in the absence of the base triethylamine. These experiments revealed that the carboxylic acid reacts with a base and acts as an anchor by

coordinating with the Ir catalyst. This enables the catalyst to discriminate between the prochiral faces of the substrates and catalyze their hydrogenation with high levels of enantioselectivity.

In 2017, Bower developed a Pd-catalyzed highly enantioselective Narasaka-Heck cyclization starting from oxime esters with tethered trisubstituted alkenes (**269**) using Spinol-derived chiral ligands **248f** (Scheme 80).⁹³ This method provides

Scheme 80. Enantioselective Narasaka–Heck Cyclization

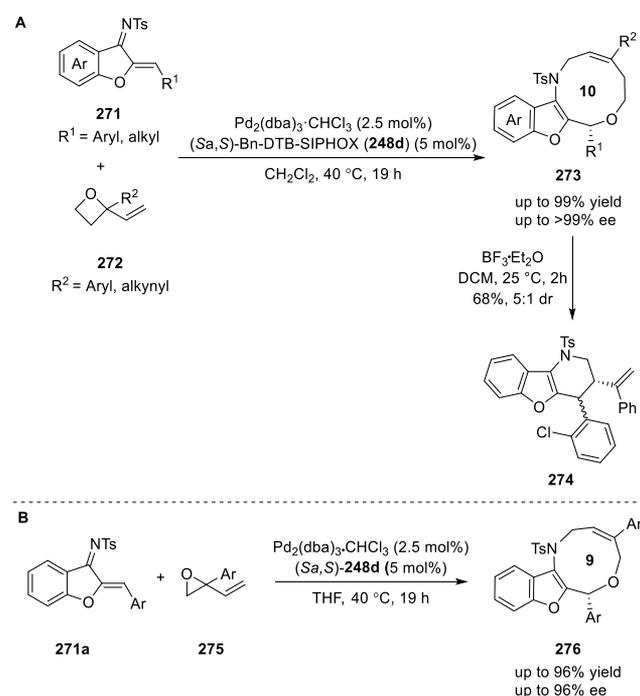


access to dihydropyrrole derivatives (**270**) with a nitrogen-containing stereocenter in up to 86% yield and 90% *ee*. It is important to note that the alkene geometry is critical for reaction success, as cyclization with the (*Z*)-isomer proceeds with considerably lower *ees* and yields compared to the corresponding (*E*)-isomer. Additionally, alkenes with 1,2-disubstitution resulted in a mixture of dihydropyrrole and pyrrole products due to competing β -hydride elimination. The proposed reaction mechanism suggested the enantioselective migratory insertion of alkenes into Pd–N bond was the key step.

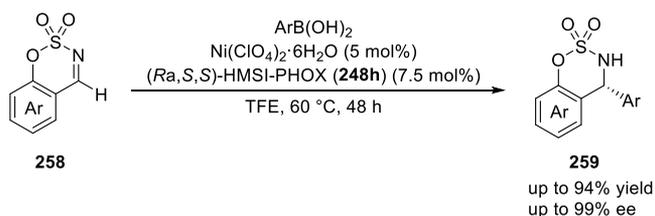
Zhao reported a highly enantioselective synthesis of benzofuran/indole-fused ten-membered heterocycles (**273**) via a formal [6 + 4] cycloaddition of vinyl oxetanes (**272**) with azadienes (**271**) (Scheme 81A).⁹⁴ A wide range of benzofuran- and indole-fused heterocycles were accessed in excellent yields and enantioselectivities. The use of aryl- and alkynyl-substituted vinyl oxetanes as substrates was successful whereas an alkyl-substituted vinyl oxetane failed to furnish the desired product, possibly due to the difficulty in the formation of the Pd– π -allyl intermediate. Furthermore, a unique fragmentation of these ten-membered heterocycles (**273**) was achieved under Lewis acid catalysis to furnish a thermodynamically more favorable six-membered ring (**274**). Additionally, this method was also employed to generate nine-membered heterocycles (**276**) by reacting azadiene (**271a**) with vinyl epoxide (**275**) via a formal [5 + 4] cycloaddition reaction (Scheme 81B).

Lin reported a Ni-catalyzed enantioselective arylation of cyclic *N*-sulfonyl imines (**258**) with arylboronic acids (Scheme 82).⁹⁵ A newly developed chiral phosphinooxazoline ligand, (*Ra,S,S*)-**248h**, based on the hexamethyl-1,1'-spirobiindane backbone (HMSI-PHOX), which is a derivative of SIPHOX, provided optically active amines in high yields (up to 94%) and enantioselectivities (up to 99% *ee*).

Scheme 81. Enantioselective Formal [6 + 4] Cycloaddition of Vinyl Oxetanes with Azadienes



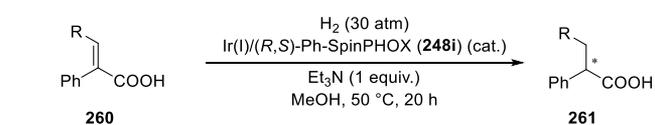
Scheme 82. Enantioselective Arylation of Cyclic *N*-Sulfonyl Imines



2.1.2.3. SpinPHOX Ligands. SpinPHOX ligands (**248i–k**) have been employed in the Ir-catalyzed asymmetric hydrogenation of α -aryl- β -substituted acrylic acids, exocyclic α,β -unsaturated carbonyl compounds, and 3-ylidenephthalides.

Ding reported the enantioselective hydrogenation of a series of α -aryl- β -substituted acrylic acids (**260**) by using an Ir-(*R,S*)-SpinPHOX (**248i**) based catalytic system (Scheme 83).⁹⁶ A series of biologically interesting α -aryl acetic acids (**261**) were synthesized in excellent yields and enantioselectivity (up to 96% *ee*). The addition of triethylamine as a basic additive was essential for both conversion and enantioselectivity due to the poor solubility and potential impact of the carboxylate group

Scheme 83. Enantioselective Hydrogenation α -Aryl- β -Substituted Acrylic Acids



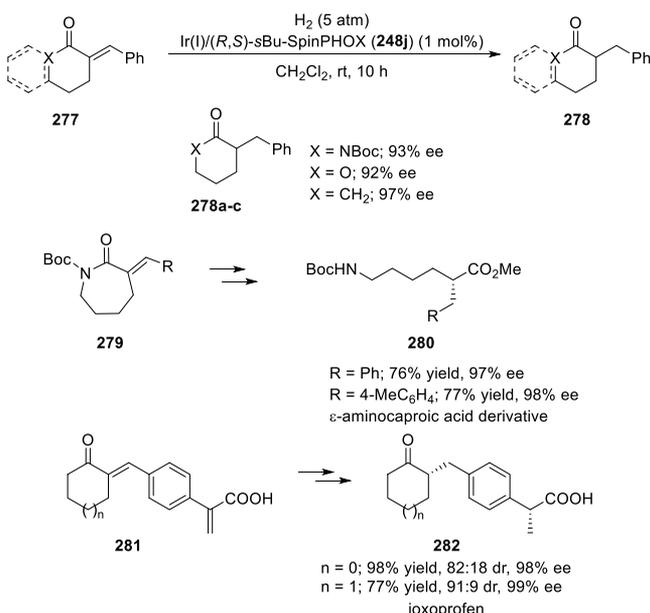
Representative examples

- R = H, >99% conversion, 88% *ee*
- R = Me, >99% conversion, 94% *ee*
- R = C₆H₅, >99% conversion, 94% *ee*
- R = Cyclopentyl, >99% conversion, 95% *ee*

on the catalysis. Additionally, hydrogenation of the (*Z*)-isomer with (*R,S*)-SpinPHOX (**248i**) was not as successful as the conversion to products was too low. It was found that the chirality at the spiro backbone of (*R,S*)-SpinPHOX (**248i**) had a significant impact on the asymmetric induction of the reaction. The (*R*)-configuration in the spiro backbone and an (*S*)-configuration on the oxazoline component was found to be the matched ligand whereas the corresponding diastereomeric ligand (*S,S*)-SpinPHOX gave lower conversion and enantioselectivity for the opposite enantiomer.

The Ir/SpinPHOX (**248j**) catalytic system was extended to the enantioselective hydrogenation of six- and seven-membered exocyclic α,β -unsaturated carbonyl compounds (**277**) with a focus on the challenging lactam derivatives (Scheme 84).⁹⁷ A series of optically active carbonyl compounds (**278**)

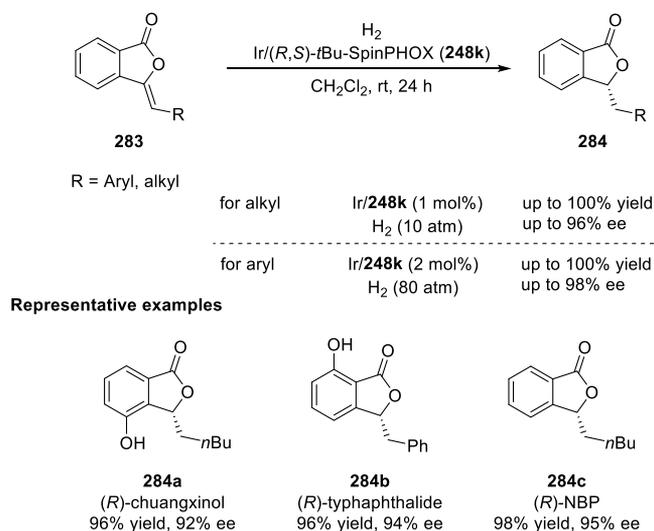
Scheme 84. Enantioselective Hydrogenation of Exocyclic α,β -Unsaturated Carbonyl Compounds



such as lactams, lactones and cyclic ketones with an α -chiral carbon stereocenter was prepared in excellent enantiomeric excess (up to 97%). An excellent stereoselectivity was observed when either (*R,S*)-**248j** or (*S,S*)-**248j** were employed in the reaction and opposite enantiomers were formed preferentially, which indicated that the spiro chirality of the ligand primarily controls the sense of asymmetric induction while the chirality of the oxazoline moiety might have some influence on the level of enantioselectivity. Additionally, the application of this methodology was shown by synthesizing an ϵ -aminocaproic acid derivative (**280**) and the nonsteroidal anti-inflammatory drug loxoprofen (**282**).

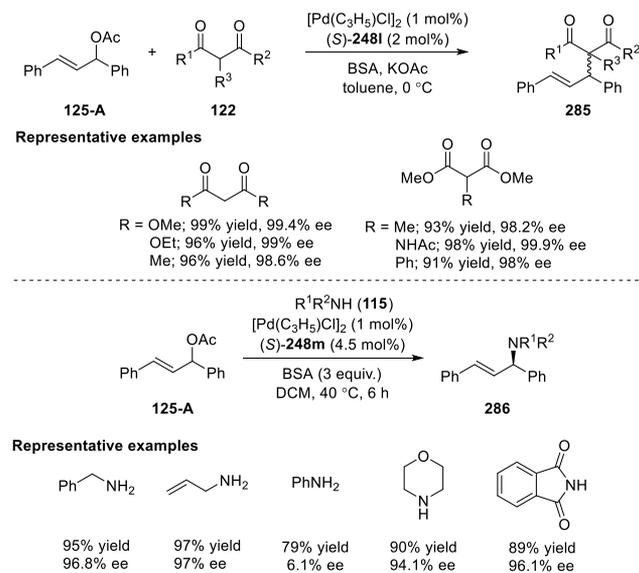
In 2018, Ding reported the enantioselective hydrogenation of 3-ylidenephthalides (**283**) by using an Ir/SpinPHOX (**248k**) catalyst (Scheme 85).⁹⁸ This method provides a straightforward approach to a wide variety of 2-substituted chiral phthalides (**284**) in high yields with excellent enantioselectivities (up to >99% yield and 98% ee). The application of this methodology was demonstrated in the synthesis of chiral drugs and natural products such as (*R*)-chuangxinol (**284a**), (*R*)-typhaphthalide (**284b**), and (*S*)-3-*n*-butylphthalide (NBP) (**284c**), a constituent of celery seed oil.

Scheme 85. Enantioselective Hydrogenation of 3-Ylidenephthalides



In 2018, Teng reported a new rigid phosphinooxazoline ligand (**248l,m**) possessing a chiral spiro core and it was applied in Pd-catalyzed asymmetric allylic alkylation and amination with *ees* up to 99% (Scheme 86).^{99,100}

Scheme 86. Pd-Catalyzed Asymmetric Allylic Alkylation and Amination



To conclude this section, metal-complexes of PHOX ligands with Stereoaxis or Stereocenter (**248a–m**) have been employed in various asymmetric transformations. Iridium complexes were successful in the hydrogenation of a variety of alkenes whereas nickel complexes were excellent when used in the addition of aryl boronic acids to imines. Palladium complexes found their application in (I) Narasaka-Heck cyclization, (II) [6 + 4] cycloadditions of vinyl oxetanes with azadienes, and (III) allylic alkylation and amination.

2.1.3. Phosphinooxazoline Ligands with a Stereoplane. Ferrocene phosphinooxazoline (FcPHOX) ligand (other acronyms include FOXAP, Phosferrox, FOX) is the major contributor in this category of *P,N*-ligands (Figure 4).

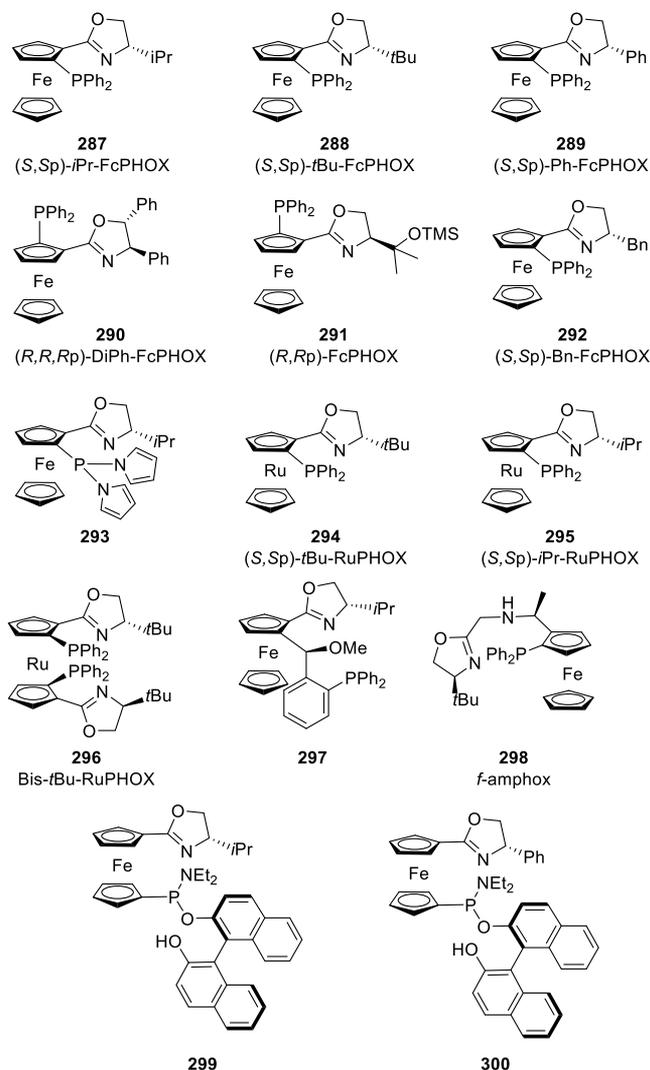


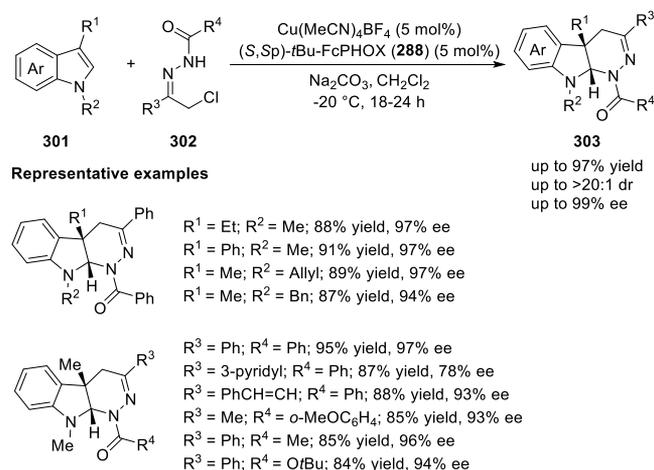
Figure 4. FcPHOX ligands.

This ligand was first reported by Richards and Uemura in 1993 for Pd-catalyzed asymmetric allylic alkylation and since then has been employed in a myriad of metal-catalyzed asymmetric transformations.¹⁰¹

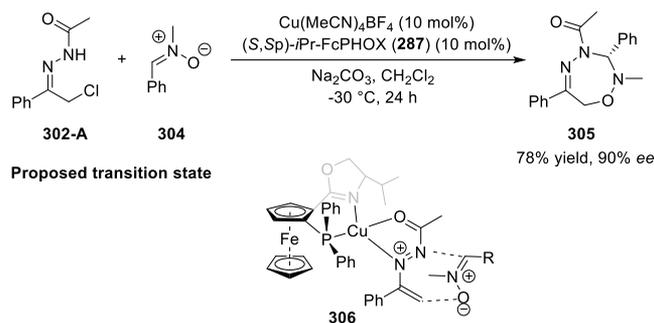
2.1.3.1. FcPHOX Ligands for Asymmetric Cycloaddition Reactions. In 2014, Wang developed a Cu/(*S,S*)-*t*-Bu-FcPHOX (**288**)-catalyzed asymmetric inverse-electron-demand *aza*-Diels–Alder reaction of indoles (**301**) with *in situ* formed azoalkenes (**302**).¹⁰² This method provided access to a variety of biologically important [2,3]-fused indoline tetrahydropyridazine heterocycles (**303**) in good yields (up to 97%) with high regioselectivity and diastereoselectivity (>20:1 dr), and excellent enantioselectivity (up to 99% *ee*). The success of this reaction lies with the coordination of the chiral Cu/FcPHOX (**288**) complex to the *in situ* formed azoalkene.

Later, Wang successfully employed azoalkenes in an unprecedented Cu/(*S,S*)-*i*-Pr-FcPHOX (**287**)-catalyzed asymmetric 1,3-dipolar [3 + 4] cycloaddition with nitrones (**304**) to generate rapid access to biologically important 1,2,4,5-oxatriazepanes (**305**) in excellent regioselectivity and enantioselectivity (**Scheme 88**).¹⁰³ Interestingly, the [3 + 2] cycloadducts which could have potentially been formed were not observed. Alkyl-substituted nitrones resulted in only the

Scheme 87. Asymmetric Inverse-Electron-Demand *aza*-Diels–Alder Reaction of Indoles



Scheme 88. Asymmetric 1,3 Dipolar [3 + 4] Cycloaddition with Nitrones

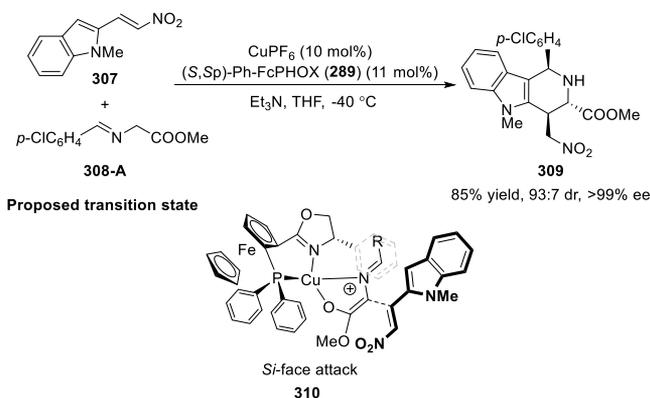


racemic products and *ortho*-substituted aryl hydrazones and alkyl α -chloro-*N*-acyl hydrazone were not suitable substrates for this reaction. A proposed transition state **306** depicts that the *in situ* generated azoalkene coordinates with Cu through nitrogen and oxygen. The bulky isopropyl group of the oxazoline ring blocks the backside of the coordinated azoalkene, and hence the nitron approaches the R group to avoid unfavorable steric congestion between the diphenylphosphine group in the chiral ligand and the R group of the nitron.

Deng reported the first Cu/(*S,S*)-Ph-FcPHOX (**289**)-catalyzed asymmetric [3 + 3] cycloaddition of azomethine ylides (**308-A**) with 2-indolyl nitroethylenes (**307**) which afforded the highly substituted tetrahydro- γ -carboline derivatives (**309**) in moderate to high yields, and excellent levels of stereoselectivity (up to >98:2 dr, > 99% *ee*) (**Scheme 89**).¹⁰⁴ This reaction is highly chemoselective toward the formation of the [3 + 3] cycloadduct over the [3 + 2] cycloadduct (up to 94:6 ratio). An alkyl-substituted azomethine ylide afforded the [3 + 2] cycloadduct in 87% yield instead of the expected [3 + 3] cycloadduct, presumably due to the less-reactive nature of the aliphatic imine. Because of the steric effects of the bulkier phenyl group in the oxazoline ring and the diphenylphosphine group of the ligand, the reaction is proposed to involve *Si*-face attack of nucleophilic complex **310**, generated *in situ* from the chiral Cu/FcPHOX (**289**) and azomethine ylide (**308-A**).

During the Michael addition, the carbanion generated adjacent to the nitro group is stable enough at lower temperature and therefore suppresses the Mannich cyclization

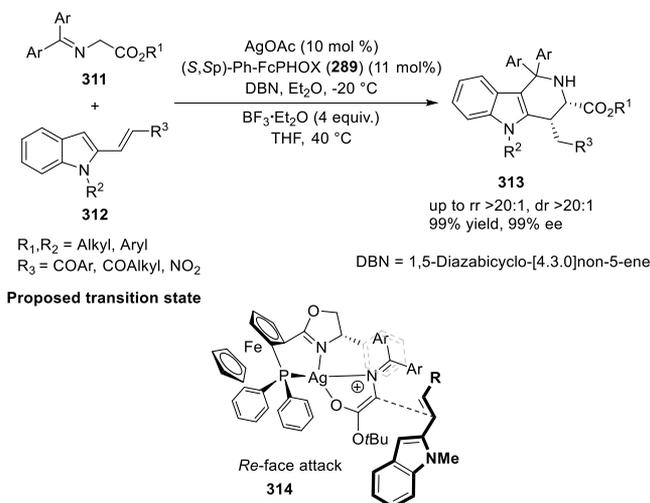
Scheme 89. Asymmetric [3 + 3] Cycloaddition of Azomethine Ylides with 2-Indolylnitroethylenes



which gives the [3 + 2] cycloaddition product. Also, similar levels of stereoselectivity were observed for both the [3 + 3] and [3 + 2] cycloadducts suggesting that the Michael addition should be the crucial step for asymmetric induction.

Following their earlier work, Deng described the first example of the Ag(I)/(*S,S*)-Ph-FcPHOX (**289**)-catalyzed regioselective and stereoselective [3 + 3] annulation of ketone-derived azomethine ylides (**311**) with 2-indolylethylenes (**312**) (Scheme 90).¹⁰⁵ This tandem method

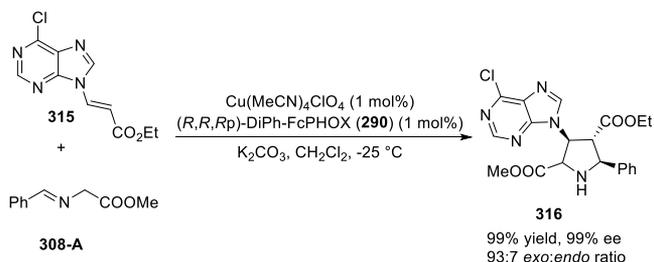
Scheme 90. Regioselective and Stereoselective [3 + 3] Annulation of Ketone-Derived Azomethine Ylides with 2-Indolylethylenes



involved a Michael addition followed by a $\text{BF}_3\text{-Et}_2\text{O}$ -promoted Friedel–Crafts reaction. Like their earlier report, the traditional [3 + 2] cycloaddition was prevented by using sterically hindered ketone-derived azomethine ylides (>20:1 rr). A wide variety of highly substituted tetrahydro- γ -carboline derivatives (**313**) were obtained in high yields (up to 99%) with excellent stereoselectivities (up to >20:1 dr, up to 99% ee). Remarkably, the stereochemistry for the [3 + 3] annulation of the ketone-derived azomethine ylides was different from that of aldehyde-derived azomethine ylides although the same ligand Ph-FcPHOX (**289**) was used. This was due to the favored *Re*-face attack of the nucleophilic ketone-derived azomethine ylide to 2-indolylethylenes because of the steric effect generated by the two bulky phenyl groups in the nucleophile.

In 2014, Guo reported a synthetic method to access chiral azacyclic nucleoside analogues (**316**) via a Cu/(*S,S*,*R_p*)-diPh-FcPHOX (**290**)-catalyzed highly *exo*- and enantioselective 1,3-dipolar cycloaddition of azomethine ylides (**308-A**) with β -nucleobase substituted acrylates (**315**) (Scheme 91).¹⁰⁶ A

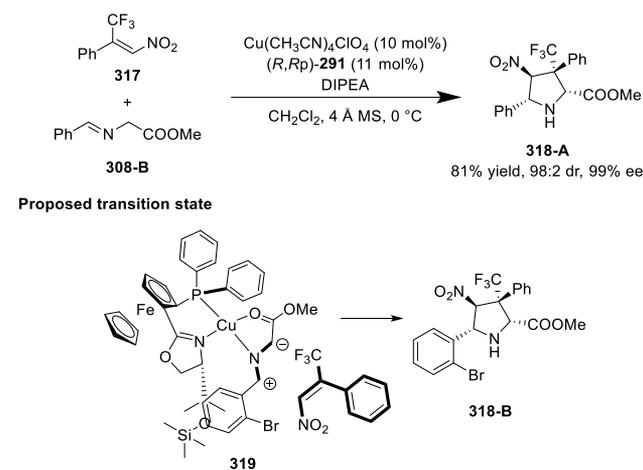
Scheme 91. Highly *exo*- and Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides with β -Nucleobase Substituted Acrylates



variety of azacyclic nucleoside analogues (**316**) were synthesized in high yields (up to 99%), excellent *exo*- (up to 93:7) and enantioselectivities (>99% ee). The use of dipolarophiles including pyrimidine-, benzimidazole-, imidazole-, benzotriazole-, and indole-substituted acrylates, afforded the desired pyrrolidine derivatives with excellent results. It is important to note that the (*E*)-geometry of β -nucleobase acrylate is essential since the reaction of the (*Z*)-isomer of β -nucleobase acrylate **315** furnished the expected products in low conversion along with poor enantioselectivity.

In 2016, Zhou developed the first catalytic asymmetric synthesis of pyrrolidines (**318-A**) possessing a trifluoromethylated quaternary stereogenic center at the C-3 position of the pyrrolidine ring using the Cu/FcPHOX (**291**)-catalyzed 1,3-dipolar [3 + 2] cycloaddition between azomethine ylides (**308-B**) and β -trifluoromethyl β,β -disubstituted nitroalkenes (**317**) (Scheme 92).¹⁰⁷ This *exo*-selective method provided different pyrrolidine derivatives (**318-A**) with high diastereoselectivities (up to >98:2 dr) and excellent enantioselectivities (up to >99.9 ee). Azomethine ylides bearing an alkyl-substituent and an *ortho*-hydroxy substituent on the aromatic ring failed to give

Scheme 92. [3 + 2] Cycloaddition between Azomethine Ylides and β -Trifluoromethyl β,β -Disubstituted Nitroalkenes

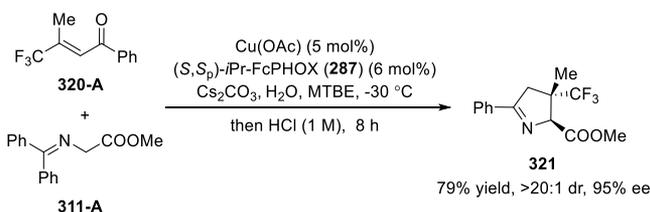


any product. Additionally, azomethine ylides derived from alanine did not react under this catalytic protocol.

The proposed transition state **319** shows that the position of the substituents on the aromatic ring of azomethine ylides affects the result through their steric impact. This rationalizes the higher enantioselectivities observed for *ortho*-substituted azomethine ylides than the corresponding *para*- and *meta*-analogues whereas the substituents on the aromatic rings of β -trifluoromethyl nitroalkenes had a limited effect on the enantioselectivity of the reaction.

In 2017, Liu and Zhang reported a Cu/(*S,S*)_p-iPr-FcPHOX (**287**)-catalyzed asymmetric Michael addition of ketone-derived azomethine ylides (**311-A**) to β -trifluoromethyl β,β -disubstituted enones (**320-A**) and subsequent hydrolytic cyclization to generate 1-pyrrolines (**321**) (Scheme 93).¹⁰⁸ This method

Scheme 93. Asymmetric Michael Addition of Ketone-Derived Azomethine Ylide to β -Trifluoromethyl β,β -Disubstituted Enones

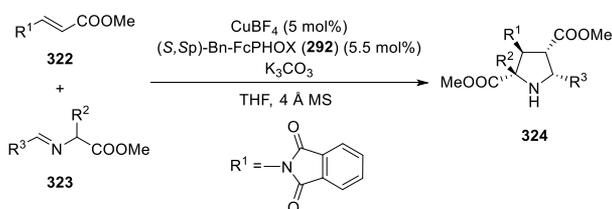


offers a facile entry to highly functionalized 1-pyrrolines (**321**) bearing two contiguous stereocenters in excellent stereoselectivities (up to >20:1 dr, 98% ee). Remarkably, the addition of trace amounts of water is essential for the chemoselective formation of 1-pyrrolines, rather than pyrrolidines (formed via direct 1,3-dipolar cycloaddition). The addition of 6 equiv of water changed the ratio between 1-pyrroline to pyrrolidine from 9:1 to >100:1. Similar levels of chemoselectivity were achieved when ethanol was used instead of water.

In 2017, Deng reported the first example of a Cu/(*S,S*)-Bn-FcPHOX (**292**)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides (**323**) with β -phthaliminoacrylate esters (**322**) to generate pyrrolidine β -amino esters (**324**) in high yields with excellent diastereo- and enantioselectivities (up to 98%, > 20:1 dr, > 99% ee) (Scheme 94).¹⁰⁹ It was noted that less reactive aliphatic-substituted azomethine ylides and azomethine ylides (**323**) derived from alanine were well tolerated in the reaction furnishing the corresponding pyrrolidines (**324**) in excellent stereoselectivities.

In 2018, Yang and Deng reported the first example of a highly efficient and stereoselective synthesis of chiral bicyclic 3-

Scheme 94. 1,3-Dipolar Cycloaddition of Azomethine Ylides with β -Phthaliminoacrylate Esters

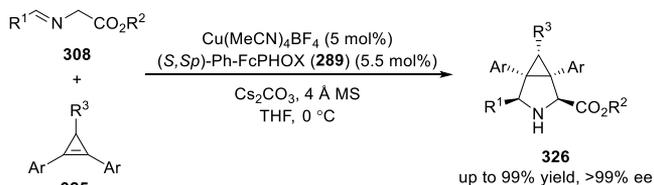


Representative examples

When R³ = Ph; R² = H; 96% yield, 20:1 dr, >99% ee with K₃CO₃ at 0 °C for 5 h
 R³ = Cy; R² = H; 87% yield, 20:1 dr, 98% ee with Cs₂CO₃ at 0 °C for 3 h
 R³ = 4-ClC₆H₄; R² = Me; 83% yield, 20:1 dr, >99% ee with Cs₂CO₃ at rt for 12 h

azabicyclo[3.1.0]hexanes (**326**) using a Cu/(*S,S*)-Ph-FcPHOX (**289**)-catalyzed asymmetric [3 + 2] cycloaddition of azomethine ylides (**308**) with trisubstituted cyclopropenes (**325**) (Scheme 95).¹¹⁰ With this new desymmetrization

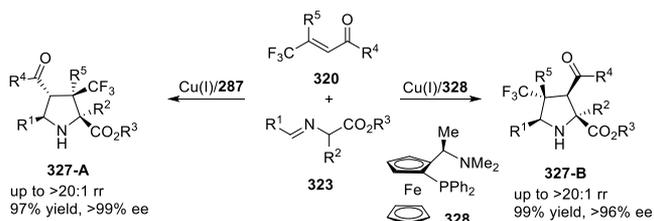
Scheme 95. Stereoselective Synthesis of Chiral Bicyclic 3-Azabicyclo[3.1.0]hexanes



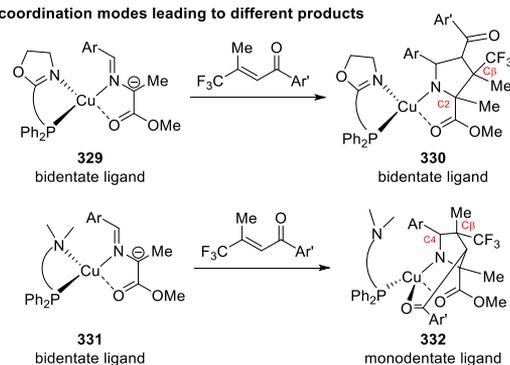
process, the asymmetric construction of 3-azabicyclo[3.1.0]-hexane derivatives (**326**) possessing five contiguous stereogenic centers and two bridgehead quaternary stereogenic centers was achieved in high yields (up to 99%) and enantioselectivities (up to 99% ee). A variety of functionalities (CO₂R, CN, CONMe₂) on the cyclopropane ring and aliphatic-substituted azomethine ylides were well tolerated.

In 2018, Liu and Zhang reported an unprecedented ligand-controlled regiodivergent Cu(I)/chiral *P,N*-ligand (**287/328**)-catalyzed asymmetric intermolecular [3 + 2] cycloaddition of α -substituted iminoesters (**323**) with β -fluoromethyl β,β -disubstituted enones (**320**) (Scheme 96).¹¹¹ This novel

Scheme 96. Asymmetric Intermolecular [3 + 2] Cycloaddition of α -Substituted Iminoesters



Different coordination modes leading to different products

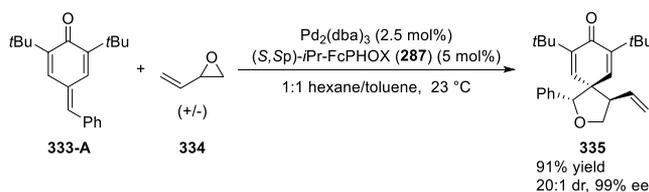


method allowed for the enantioselective regiodivergent synthesis of pyrrolidines (**327 A-B**) bearing two adjacent quaternary stereocenters or two discrete quaternary stereocenters, in high yields (up to >99%), and high regio- (up to >20:1 rr), diastereo- (up to >20:1 dr), and enantioselectivity (up to >99% ee). Mechanistic studies provided insights into the ligand controlled origins of the regioselective control of the cycloaddition. The phosphorus and nitrogen atoms of (*S,S*)-iPr-FcPHOX (**287**), remain coordinated to the Cu(I) throughout the whole catalytic process, and **327-A** was

obtained as the main product due to a combination of the electron distribution across the complex, steric hindrance effects, and a π - π interaction between the two aryl rings of the iminoester **323** and enone **320**. In contrast ligand **328** acts as a pseudobidentate ligand. The formation of an O-Cu bond with the carbonyl oxygen atom of the enone **320** and dissociation of the amine from the Cu(I) center occurs which makes ligand **328** monodentate and results in switching the regioselectivity of the reaction to form product **327-B**.

In 2016, Zhao developed an unprecedented formal [3 + 2] cycloaddition of *p*-quinone methides (**333-A**) with vinyl epoxides (**334**) under Pd/(*S,S*)-*i*-Pr-FcPHOX (**287**) catalysis (Scheme 97).¹¹² A wide range of spiro[4.5]decanes (**335**)

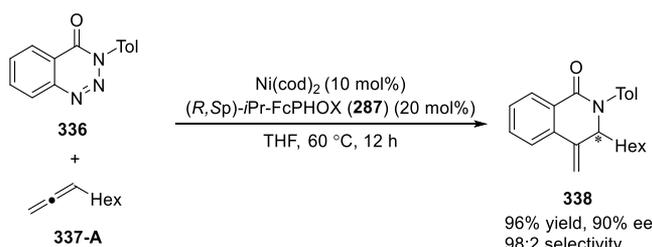
Scheme 97. Formal [3 + 2] Cycloaddition of *p*-Quinone Methides



were obtained in high efficiency and stereoselectivity. It is noteworthy that the bulky *t*-butyl substituents on the *para*-quinone methide structure were important for the high diastereoselectivity and enantioselectivity of this catalytic transformation. Changing the *t*-butyl to the smaller isopropyl or methyl groups led to a drastically reduced dr and *ee* of the reaction (up to 5:1 dr, up to 30% *ee*). Importantly, a variety of aryl and alkyl-substituted *p*-quinone methides were tolerated as substrates.

In 2010, Murakami reported a Ni/(*S,S*)-*i*-Pr-FcPHOX (**287**)-catalyzed denitrogenative annulation of 1,2,3-benzotriazin-4(3*H*)-ones (**336**) with allenes (**337-A**) (Scheme 98). A

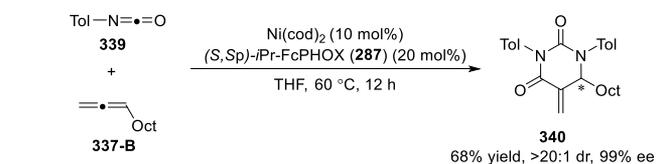
Scheme 98. Denitrogenative Annulation of 1,2,3-Benzotriazin-4(3*H*)-ones with Allenes



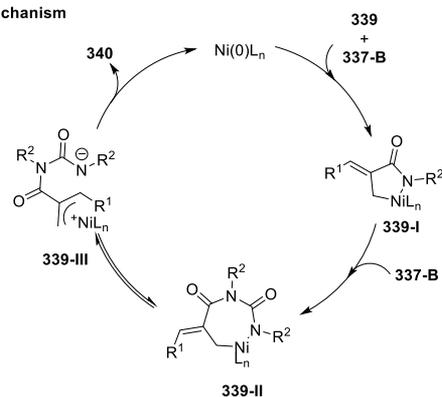
variety of substituted 3,4-dihydroisoquinolin-1(2*H*)-ones (**338**), found in a wide variety of plant alkaloids and bioactive compounds, were synthesized in high regio- and enantioselectivity (up to 99% yield and 97% *ee*).¹¹³ This process tolerates a variety of functionalities and worked well with sterically and electronically different *N*-aryl substituents. The regioselectivity was significantly affected by the sterics of the allene substituent as changing the hexyl group to a cyclohexyl group led to a drop in regioselectivity from 98:2 to 73:27, whereas the enantioselectivity remained unaltered.

In 2010, Murakami developed a Ni/(*S,S*)-*i*-Pr-FcPHOX (**287**)-catalyzed enantioselective cycloaddition between isocyanate (**339**) and allene (**337-B**) (Scheme 99).¹¹⁴ This process involves the [2 + 2 + 2] cycloaddition of two

Scheme 99. Enantioselective Cycloaddition between Isocyanate and Allene



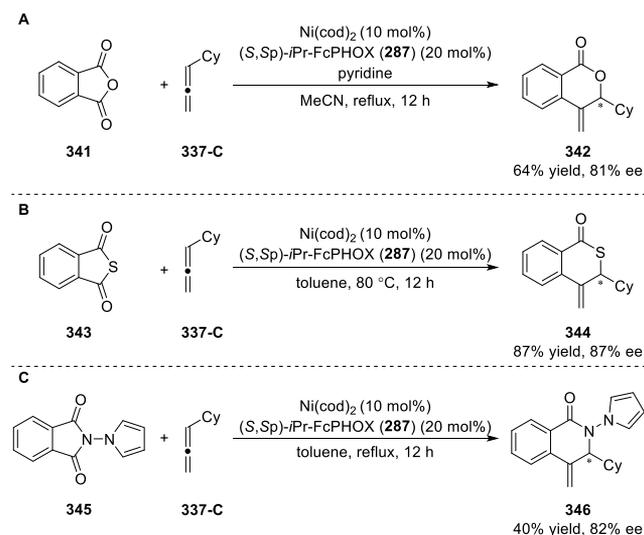
Proposed mechanism



molecules of isocyanate and one molecule of allene, providing an efficient access to enantiomerically enriched dihydropyrimidine-2,4-diones (**340**). This method is limited to aryl isocyanates since various alkyl isocyanates failed to undergo this cycloaddition. Surprisingly, electron-rich aryl isocyanates furnished products with higher regioselectivity compared to electron-deficient aryl isocyanates. A mechanistic cycle involves intermolecular Ni(0) oxidative cyclization between the allene (**337-B**) and isocyanate (**339**), followed by the addition of one more molecule of isocyanate to generate a zwitterionic π -allylnickel species (**339-III**) which, upon cyclization at the more substituted carbon of the allyl moiety, affords product **340** along with Ni(0).

In 2011, Matsubara developed a decarbonylative cycloaddition of phthalic anhydride (**341**) with allenes (**337-C**) to give δ -lactone derivatives (**342**) (Scheme 100A).¹¹⁵ The reaction proceeds via asymmetric insertion of a carbon-carbon

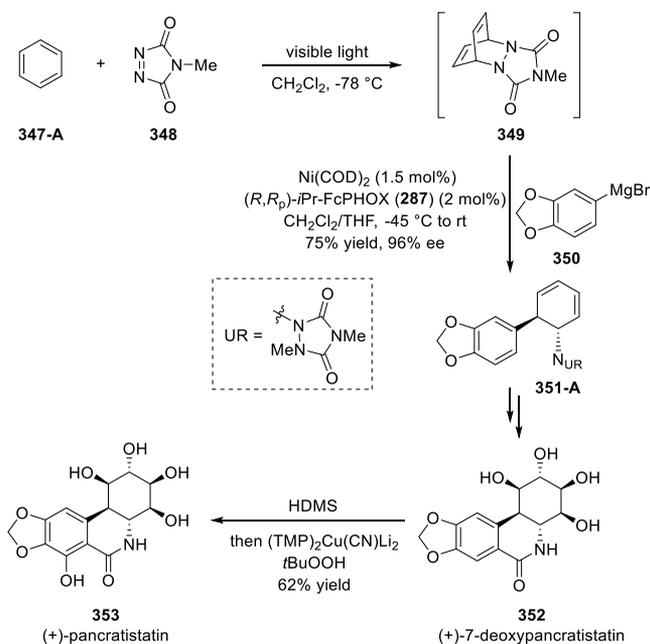
Scheme 100. Decarbonylative Cycloaddition of Phthalic Anhydride with Allenes



double bond into a carbon–oxygen bond. The use of (*S,S*)-*i*Pr-FcPHOX (**287**) afforded chiral δ -lactone derivatives (**342**) in moderate yields and enantioselectivities of up to 81%. This decarbonylation was also extended to thiophthalic anhydride (**343**) and *N*-pyrrole-substituted phthalimide (**345**), which furnished the corresponding chiral cycloadducts (**344/346**) in high yield and enantioselectivities of up to 87% and 82% *ee*, respectively (Scheme 100B,C).

In 2017, Sarlah reported a concise synthesis of (+)-pancratistatin (**353**) and (+)-7-deoxypancratistatin (**352**) from benzene (**347-A**) using a dearomative 1,2-transcarboamination approach in six and seven steps in 19% and 12% overall yields, respectively (Scheme 101).¹¹⁶ The key step was to install the

Scheme 101. Synthesis of (+)-Pancratistatin and (+)-7-Deoxypancratistatin



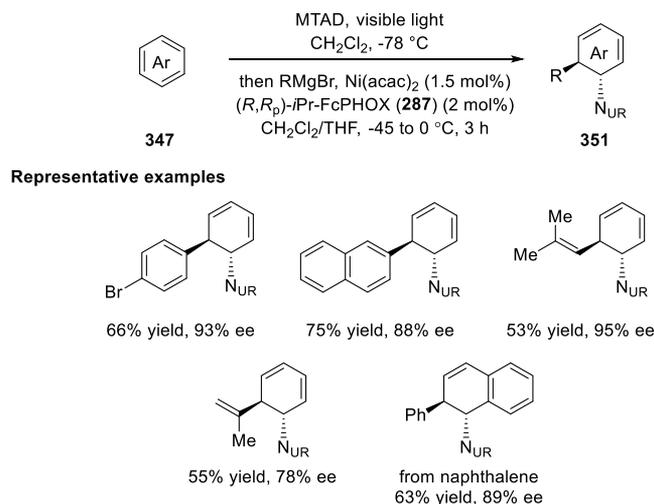
first two vicinal stereocenters which involved visible light-promoted *para*-cycloaddition of the benzene with the *N*-*N* arenophile, *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD, **348**), to generate the MTAD-benzene cycloadduct **349**. The cycloadduct **349** was further reacted with aryl Grignard reagent **350** using a catalytic amount of Ni/(*R,R*)-*i*Pr-FcPHOX (**287**) to generate the desired dearomatized product **351-A** in 75% yield as a single diastereoisomer (*trans*) with high enantioselectivity (96% *ee*) on a decagram scale. The diene intermediate **351-A** was further used to complete the synthesis of the (+)-pancratistatin core.

The cycloadduct **349** comprises bis-allylic bridgehead positions bearing an electron-deficient urazole and hence it is prone for oxidative addition. Mechanistically, the catalytic process involves anti- π -coordination of the diene to the metal complex, oxidative addition, transmetalation to generate a symmetric η^5 -complex which, upon enantiodiscrimination of the enantiotopic termini of the cyclohexadienyl system, yields the product enantioselectively.

In 2018, Sarlah applied their novel dearomative *trans*-1,2-carboamination strategy to a range of aromatic precursors (**347**) including naphthalene and a series of Grignard reagents using an air-stable Ni(acac)₂ and (*R,R*)-*i*Pr-FcPHOX (**287**) to

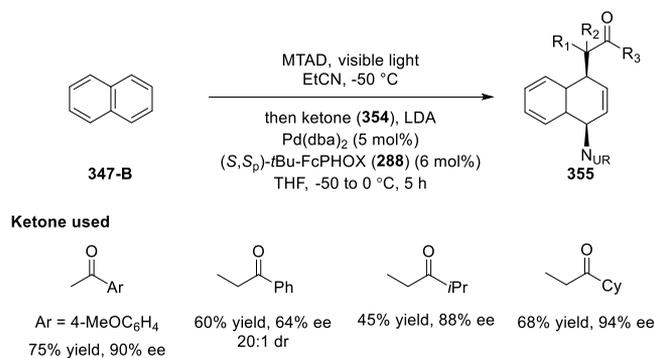
obtain diene products (**351**) with exclusive 1,2-*trans* selectivity, and high enantioselectivity (Scheme 102).¹¹⁷ Interestingly, the methodology was also feasible with different vinyl Grignard reagents which allowed for the enantioselective installation of an alkene moiety.

Scheme 102. Dearomative *trans*-1,2-Carboamination



In subsequent studies, Sarlah developed a Pd/(*S,S*)-*t*Bu-FcPHOX (**288**)-catalyzed enantioselective ring-opening reaction of the cycloadduct derived from naphthalene (**347-B**) and MTAD using lithium enolates derived from ketone (**354**) (Scheme 103).¹¹⁸ The method is highly step- and atom-

Scheme 103. Enantioselective Ring-Opening Reaction

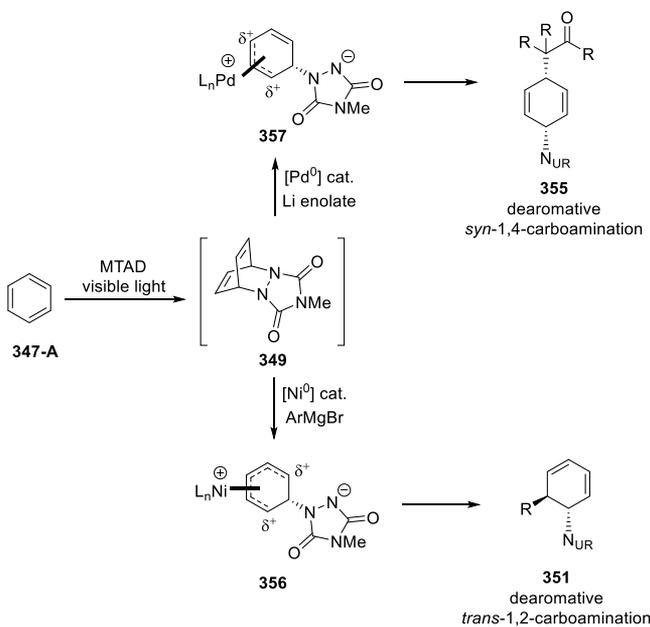


economical and delivers products with exclusive *syn*-1,4-selectivity and high enantioselectivity (up to 94% *ee*). Compared to the Ni-catalyzed process, the present protocol is limited to specific substrates. Additionally, enantioselective ring-opening with ester-derived lithium enolates was also achieved by using a [Pd(allyl)Cl]₂ and (*R*)-DTBM-SEGPHOS combination.

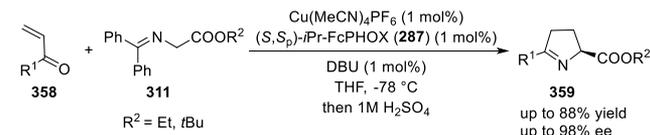
The complementary selectivity observed in Pd and Ni catalysis is likely due to the result of the inner-sphere delivery of the Grignard reagent in the case of cationic Ni η^5 -complex **356** and outer sphere attack of the enolate on Pd η^3 -intermediate **357** (Scheme 104).

2.1.3.2. FcPHOX Ligands for Asymmetric 1,4- and 1,2-Addition. In 2011, Zajac reported an enantioselective reaction between glycine derivatives (**311**) and α,β -unsaturated ketones (**358**) using a Cu complex of (*S,S*)-*i*Pr-FcPHOX (**287**) ligand

Scheme 104. Mechanistic Details



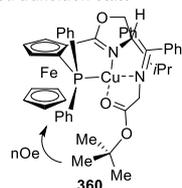
(Scheme 105).¹¹⁹ The chiral Michael adducts (359) formed were directly transformed into the cyclized product upon acid/

Scheme 105. Enantioselective Reaction between Glycine Derivatives and α,β -Unsaturated Ketones

Representative examples

when $R^2 = \text{Et}$
 $R^1 = \text{C}_6\text{H}_4$; 85% yield, 96% ee
 $R^1 = p\text{-BnOC}_6\text{H}_4$; 81% yield, 98% ee
 $R^1 = p\text{-CF}_3\text{C}_6\text{H}_4$; 78% yield, 84% ee
 when $R^2 = t\text{Bu}$
 $R^1 = \text{C}_6\text{H}_4$; 88% yield, 88% ee
 $R^1 = p\text{-BnOC}_6\text{H}_4$; 79% yield, 92% ee
 $R^1 = p\text{-CF}_3\text{C}_6\text{H}_4$; 77% yield, 90% ee
 when $R^2 = \text{Et}$
 $R^1 = \text{Me}$; 70% yield, 92% ee
 $R^1 = t\text{Bu}$; 78% yield, 92% ee

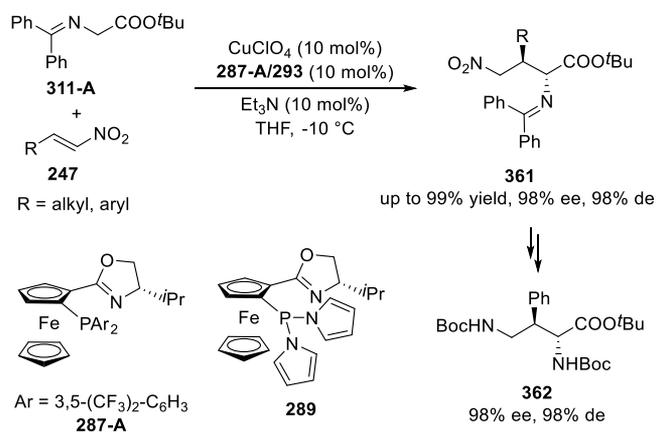
Proposed transition state



base workup. The use of acrylonitrile, methyl acrylate or phenylvinyl sulfone as Michael acceptors afforded cycloaddition products exclusively instead of the expected chiral Michael addition adducts. The mechanistic studies performed showed that structure 360 retains a distorted tetrahedral geometry around Cu. It is believed that the phenyl groups of the diphenylphosphine and the imine in 311 occupy a coplanar conformation due to possible π -stacking, with the ester *t*-butyl group underneath the complex. This orientation requires the electrophilic, α,β -unsaturated ketone (358) to approach the nucleophile from the *Si*-face and eclipse the phenyl groups.

In 2010, Hou reported a Cu-catalyzed asymmetric Michael addition of glycine derivatives (311-A) to nitroalkenes (247) using a derivative of the (*S,S*_p)-*i*Pr-FcPHOX (287-A) ligand (Scheme 106).¹²⁰ This method provided a route to prepare a variety of β -substituted- α,γ -diaminobutyric acid derivatives (361) in high diastereo- and enantioselectivities (up to 98% de, 98% ee). The *ortho*-substituted nitrostyrene derivatives

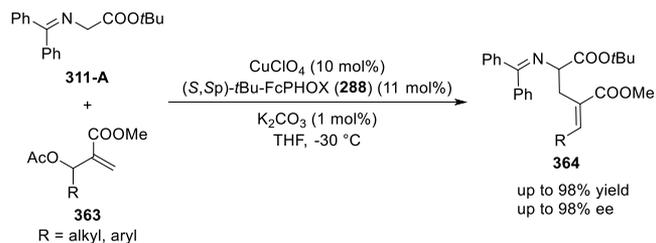
Scheme 106. Asymmetric Michael Addition of Glycine Derivatives to Nitroalkenes



provided much lower enantioselectivities (76 to 89% ee) with the (*S,S*_p)-*i*Pr-FcPHOX ligand. FcPHOX 289 with a P-bound pyrrole group possessing strong π -acceptor and weak σ -donor properties dramatically improved the enantioselectivity (up to 93% ee) for this class of substrates.

In 2009, Pu reported a Cu/(*S,S*_p)-*t*Bu-FcPHOX (288)-catalyzed enantioselective synthesis of 4-alkylidene glutamic acid derivatives (364) from the reaction of a glycinate Schiff base (311-A) with activated alkyl- and aryl-substituted allylic acetates (363) (Scheme 107).¹²¹ The presence of electron-

Scheme 107. Enantioselective Synthesis of 4-Alkylidene glutamic Acid Derivatives

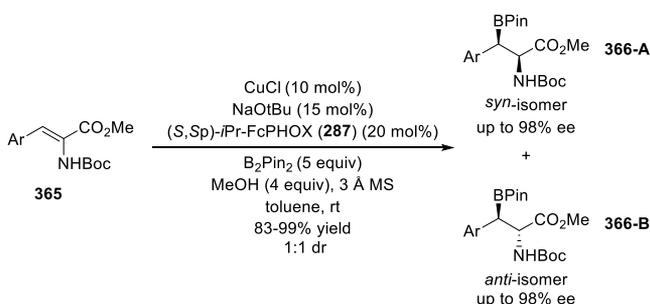


withdrawing groups was essential, as no product was formed when glycine *t*-butyl ester (311-A) reacted with simple allylic acetate. This suggested that the reaction proceeds *via* a tandem conjugate addition–elimination pathway.

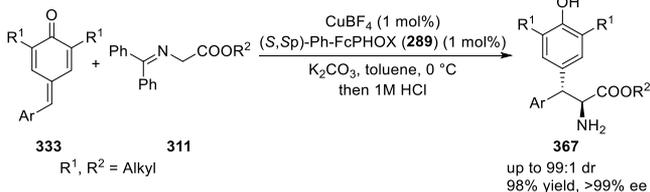
In 2014, Lin reported the Cu/(*S,S*_p)-*i*Pr-FcPHOX (287)-catalyzed asymmetric borylation of β -substituted α -dehydroamino acid derivatives (365) using B₂Pin₂ to furnish enantioenriched *syn*- and *anti*- β -boronate- α -amino acid derivatives (366) in a 1:1 ratio (Scheme 108).¹²² The double bond geometry in the β -phenyl-substituted substrate was very important since the use of the (*E*)-isomer did not afford any product under these reaction conditions. Changing an aryl group to an alkyl group in the starting alkene afforded the product in high yield but with poor enantioselectivity (<30%) for both regioisomers.

In 2016, Deng described a Cu/(*S,S*_p)-Ph-FcPHOX (289)-catalyzed highly enantioselective catalytic 1,6-conjugate addition of glycine Schiff bases (311) to *p*-quinone methides (333) (Scheme 109).¹²³ A series of *p*-quinone methides (333) derived from aryl aldehydes reacted with glycine Schiff bases to provide nonracemic β -Ar,Ar'- α -amino acid derivatives (367) with two contiguous stereogenic centers in high yields with

Scheme 108. Asymmetric Borylation of β -Substituted α -Dehydroamino Acid Derivatives



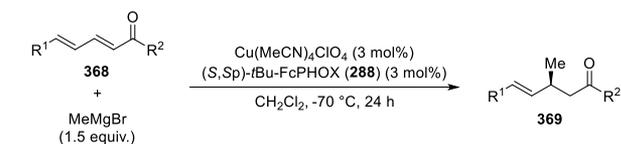
Scheme 109. Enantioselective 1,6-Conjugate Addition of Glycine Schiff Bases



excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to >99% ee).

In 2013, Zhang developed a $\text{Cu}/(S,S_p)\text{-}t\text{Bu-FcPHOX}$ (**288**)-catalyzed regio- and enantioselective 1,4-conjugate addition reaction of alkyl Grignard reagents to $\alpha,\beta,\gamma,\delta$ -unsaturated ketones (**368**) (Scheme 110).¹²⁴ A series of γ,δ -unsaturated

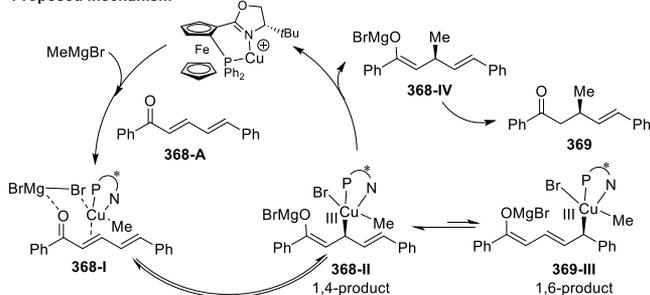
Scheme 110. Regio- and Enantioselective 1,4-Conjugate Addition Reaction of Alkyl Grignard Reagents



Representative examples

when $\text{R}^2 = \text{Ph}$	when $\text{R}^1 = \text{Ph}$
$\text{R}^1 = \text{Ph}$; 86% yield, 94% ee	$\text{R}^2 = p\text{-CF}_3\text{C}_6\text{H}_4$; 92% yield, 95% ee
$\text{R}^1 = p\text{-MeC}_6\text{H}_4$; 90% yield, 76% ee	$\text{R}^2 = p\text{-Naphthyl}$; 70% yield, 83% ee
$\text{R}^1 = o\text{-ClC}_6\text{H}_4$; 83% yield, 96% ee	$\text{R}^2 = 2\text{-Furyl}$; 86% yield, 89% ee

Proposed mechanism

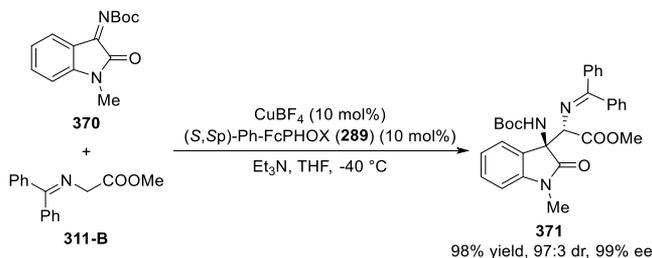


ketones (**369**) were obtained in high yields with high enantioselectivity (up to 92% yield and 96% ee). The increase in the steric hindrance of the Grignard reagent had a negative impact on enantioselectivity as well as on reaction yield. The mechanism is proposed to involve the formation of π -complex **368-I** between Cu -ligand, MeMgBr and substrate **368-A**. Later, Cu(III) σ -complex **368-II** forms via oxidative addition, which is stabilized by the diconjugated system. This stability

accounts for the preference of the 1,4-selectivity over 1,6-selectivity. Finally, the reductive elimination of **368-II** delivers Cu-FcPHOX and the 1,4-addition product **369**.

In 2018, Deng developed the $\text{Cu(I)}/(S,S_p)\text{-Ph-FcPHOX}$ (**289**)-catalyzed diastereo- and enantioselective Mannich reaction of glycine Schiff bases (**311-B**) with isatin N -Boc ketimines (**370**) (Scheme 111).¹²⁵ A wide range of 3-

Scheme 111. Diastereo- and Enantioselective Mannich Reaction of Glycine Schiff Bases

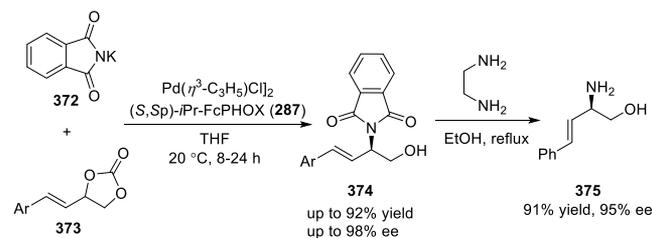


substituted 3-aminoindole compounds (**371**) were obtained in high yields (up to 98%) with excellent enantioselectivities (>99% ee in most cases) and moderate to high diastereoselectivities (up to 97:3 dr). The reactivities and stereoselectivities of the Mannich reaction were greatly reliant on the steric hindrance of the ester groups employed. The methyl and ethyl glycine esters were most suitable, whereas the diastereoselectivities decreased when isopropyl or benzyl esters were tested. The t -butyl glycine ester Schiff base was found to be unreactive. The N -protection of isatin is crucial as no reaction occurred with isatin possessing a free NH. The imine derived from N -methyl isatin was found to be the best substrate whereas changing to either an N -benzyl or an N -acetyl isatin produced disappointing diastereoselectivities.

2.1.3.3. FcPHOX Ligands for Asymmetric Allylic Alkylation. In 2013, Zhang reported a $\text{Pd}/(S,S_p)\text{-}i\text{Pr-FcPHOX}$ (**287**)-catalyzed asymmetric allylic amination of 4-aryl-1,3-dioxolan-2-one (**373**) to synthesize chiral β -aryl- α,β -unsaturated amino alcohols (**375**) (Scheme 112).¹²⁶ A wide variety of chiral amino alcohols (**374**) were obtained in good to excellent yields (up to 92%) and enantioselectivities (up to 98% ee) under mild reaction conditions.

In 2017 and 2018, Zhang and Wang independently published a series of papers based on a Pd/Cu dual catalyst system for the asymmetric α -allylation of Schiff base activated amino acids (Scheme 113).¹²⁷⁻¹³³

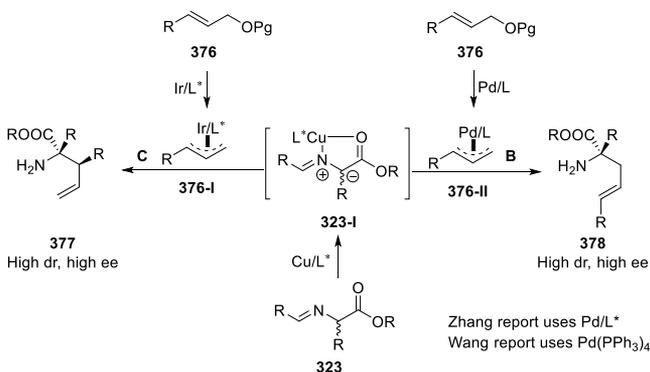
Scheme 112. Asymmetric Allylic Amination of 4-Aryl-1,3-dioxolan-2-ones



Representative examples

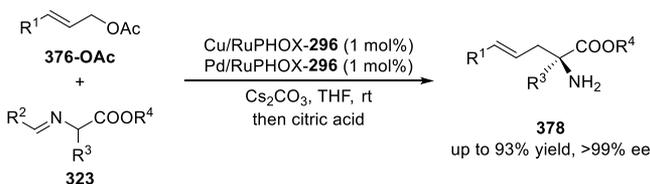
$\text{Ar} = \text{C}_6\text{H}_5$; 92% yield, 95% ee	$\text{Ar} = 4\text{-CF}_3\text{C}_6\text{H}_4$; 91% yield, 91% ee
$\text{Ar} = 4\text{-MeC}_6\text{H}_4$; 82% yield, 92% ee	$\text{Ar} = 1\text{-Naphthyl}$; 72% yield, 88% ee
$\text{Ar} = 2\text{-FC}_6\text{H}_4$; 92% yield, 98% ee	$\text{Ar} = 2\text{-Naphthyl}$; 70% yield, 87% ee

Scheme 113. Asymmetric α -Allylation of Schiff Base Activated Amino Acids



Zhang reported a Pd/Cu cooperative catalytic system for the asymmetric α -allylation of Schiff bases derived from imine esters (**323**) (Scheme 114).¹²⁷ A dimeric *t*Bu-RuPHOX (**296**)

Scheme 114. Cu/Pd-Catalyzed Asymmetric α -Allylation of Schiff Base

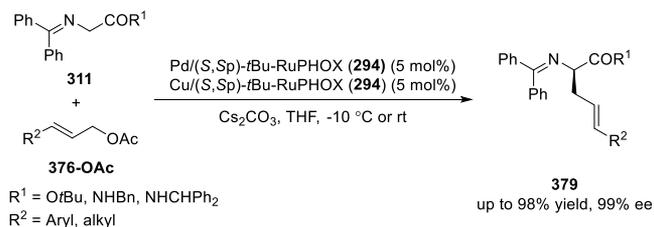


was found to be a common ligand of choice. A wide variety of α,α -dialkyl α -amino acid derivatives (**378**) were synthesized in high yields and with excellent enantioselectivities (up to >99% *ee*). The method was easily extended to the asymmetric allylation of a range of small peptides. The catalytic system utilizes chiral complexes of Cu and Pd with the chiral ligand, *t*Bu-RuPHOX (**296**), and the use of the same ligand on both metals avoids the possible problem of ligand exchange and also makes it practically simple. The catalytic cycle involves the simultaneous generation of a five-membered *N,O*-bidentate metalated nucleophilic species **323-A** between Cu and the Schiff base and the electrophilic α -allyl Pd intermediate **376-II**. This intermediate further reacts to give allylated product in high selectivity. Both studies results suggested that the rigid structure of the five-membered *N,O*-bidentate metalated azomethine ylide **323-A** enables the asymmetric induction from the chiral ligand (Scheme 113).

Zhang found that the aldehyde-derived glycine esters (**323**) always furnished bisallylated products. This limitation was solved in the subsequent studies involving asymmetric allylation of ketone-derived prochiral glycine ester and amide derivatives (**311**) using the catalytic Cu/Pd cooperative system (Scheme 115).¹²⁸ This time ligand (*S,S*)-*t*Bu-RuPHOX (**294**) performed better compared to the earlier investigated dimeric ligand *t*Bu-RuPHOX (**296**). A range of α -substituted α -amino acid derivatives (**379**) were efficiently synthesized in high yields and with excellent enantioselectivities under mild conditions (up to 98% yield and 99% *ee*).

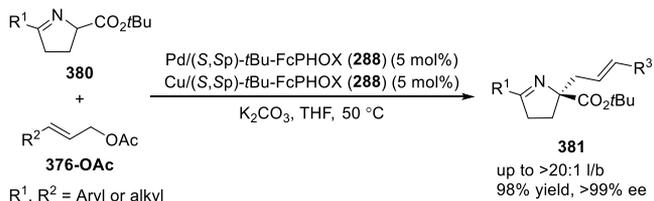
Later, Zhang expanded the scope of this asymmetric allylation to 1-pyrroline-5-carboxylic esters, cyclic imino esters (**380**) to generate a variety of 3,4-2*H*-pyrrole (**381**) derivatives bearing a quaternary stereogenic center in high yields and excellent enantioselectivities (up to 98% yield and

Scheme 115. Cu/Pd-Catalyzed Asymmetric α -Allylation of Schiff Bases



>99% *ee*) (Scheme 116).¹²⁹ Similar to earlier studies, mechanistic investigations uncovered that the synergistic

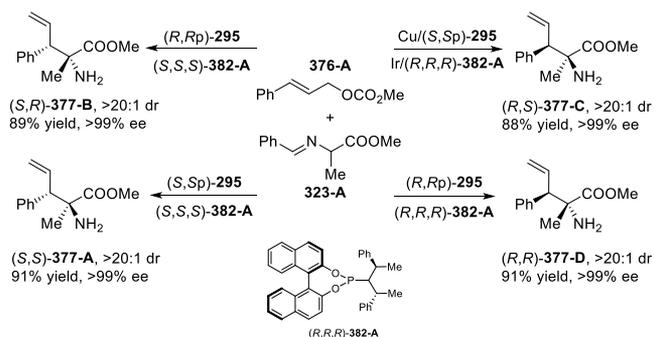
Scheme 116. Asymmetric Allylation to 1-Pyrroline-5-carboxylic Esters



action of the two chiral metal complexes is responsible for its high reactivity and excellent enantioselectivity; the steric hindrance and electronic factors of the electrophiles and the nucleophiles are crucial for the formation of the linear products.

In a recent report, Zhang introduced a synergistic Ir/Cu-catalyzed allylic alkylation of imine esters to construct a range of α,α -disubstituted α -amino acids (**377-A–D**) bearing two vicinal stereocenters with excellent levels of enantio- and diastereoselectivity (up to >99% *ee* and >20:1 *dr*) (Scheme 117).¹³⁰ The (*S,S*)-*i*Pr-RuPHOX (**295**) ligand on Cu and

Scheme 117. Ir/Cu-Catalyzed Allylic Alkylation of Imine Esters

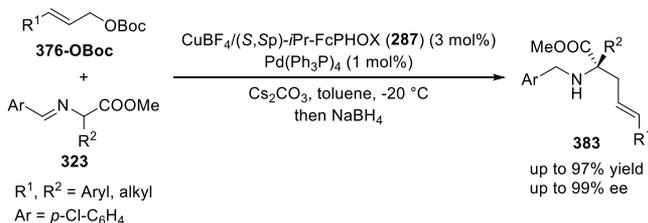


Feringa's chiral phosphoramidite ligands (**382-A**) on Ir were necessary for the success of the reaction. Significantly, the two chiral catalysts allowed complete control over the absolute and relative configuration, affording all stereoisomers of the desired products. This methodology was applied to synthesize dipeptides and analogues of bioactive molecules bearing vicinal stereocenters in a stereodivergent manner. The mechanism is proposed to involve the generation of a five-membered *N,O*-bidentate metalated nucleophilic species (**323-I**) using the Cu/*i*Pr-RuPHOX (**295**) complex followed by interception of the *in situ* formed reactive allyl Ir intermediate (**376-I**) to generate

enantiopure α,α -disubstituted α -amino acid derivatives (**377**) bearing vicinal stereocenters (Scheme 113). It is important to note that the well-defined geometry of intermediates **323-I** and **376-I** allows for the control of the configurations of both stereocenters.

At the same time, Wang independently reported a Pd/Cu dual catalyst system for the asymmetric α -allylation of Schiff bases derived from imine esters (**323**) to synthesize a variety of α,α -dialkyl α -amino acid derivatives (**383**) in high yields and with excellent enantioselectivities (up to 97% yield, > 99% *ee*) (Scheme 118).¹³¹ Similar to Zhang's report, the presence of

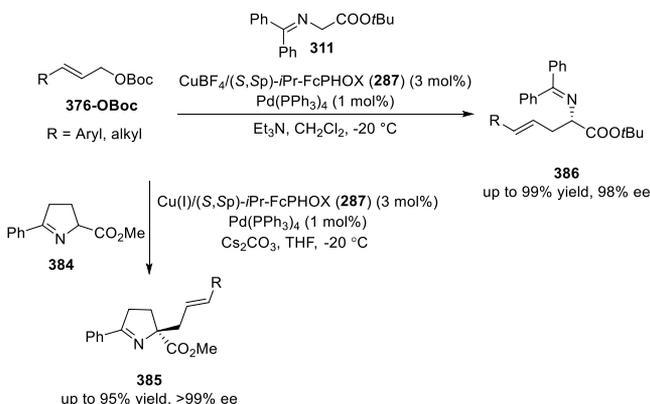
Scheme 118. Pd/Cu-Catalyzed Allylic Alkylation of Imine Esters



Cu and Pd is indispensable to this reaction as no product was observed in the absence of either. Wang's catalytic system involves Cu(I) and chiral ligand **287** which *in situ* generates the chiral complex (**323-A**) from the Schiff base of imine ester (Scheme 116). Unlike Zhang's report, the achiral ligand Ph₃P was used with Pd to generate the achiral π -allylpalladium intermediate **376-II** (Scheme 113). Besides this, the ³¹P NMR spectroscopic analysis confirmed that either negligible or no ligand scrambling was observed from Cu to Pd. This observation confirmed that the rigid structure of the five-membered *N,O*-bidentate chiral Cu complex **323-A** controls the stereoselectivity of the allylation.

Wang further employed this synergistic Cu/Pd catalytic system for the stereoselective α -allylation of both acyclic (**311-A**) and cyclic ketimine esters (**384**) (Scheme 119).¹³² The

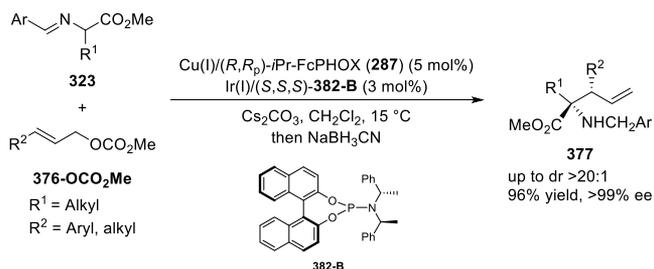
Scheme 119. Stereoselective α -Allylation of Acyclic and Cyclic Ketimine Esters



combination of the Cu/(*S,S*_p)-*iPr*-FcPHOX (**287**) complex and an achiral palladium complex delivered an array of biologically important α -allyl α -amino acid derivatives (**386**) and 2*H*-pyrrole derivatives (**385**) in excellent yields and enantioselectivities (up to 99% yield, >99% *ee*).

Like Zhang, Wang established a stereodivergent synergistic Cu/Ir catalyzed α -allylation of aldimine esters to generate a series of α -amino acid derivatives (**377**) possessing vicinal stereocenters in high yield and excellent stereoselectivity (Scheme 120).¹³³ For the success of reaction, the use of

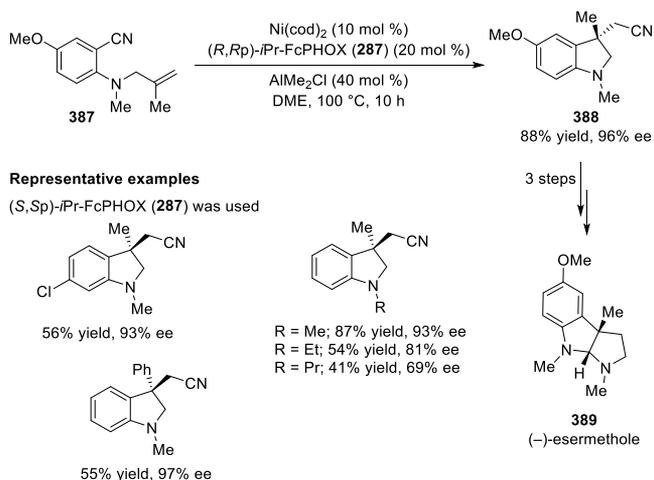
Scheme 120. Stereodivergent Synergistic Cu/Ir Catalyzed α -Allylation of Aldimine Esters



(*S,S*_p)-*iPr*-FcPHOX (**287**) ligand on Cu and Feringa's chiral phosphoramidite ligands **382-B** on Ir was necessary. All four stereoisomers of **377** were accessed in good yield (up to 96%) with excellent enantioselectivity (>99% *ee*) and exclusive diastereoselectivity (>20:1 *dr*) from the same set of starting materials with the current dual Cu/Ir catalysis by simply selecting a pairwise combination of two chiral catalysts. This outcome suggested that the two distinct metal catalysts exert almost absolute control over the corresponding stereogenic centers, respectively. Additionally, the dual catalysts can be prepared *in situ* from a mixture of Cu(MeCN)₄BF₄, [Ir(cod)-Cl]₂, (*S,S*_p)-*iPr*-FcPHOX (**287**), and (*R,R,R*)-**382-B** in a one-pot protocol to furnish the expected allylated products (**377**) in comparable levels of yield and stereoselectivity.

2.1.3.4. FcPHOX Ligands for Asymmetric Intramolecular Arylcyanation/Diarylation of Alkenes. In 2008, Nakao described an intramolecular arylation of alkenes to synthesize a range of synthetically interesting nitriles possessing a benzylic quaternary carbon stereocenter (Scheme 121).¹³⁴ The combination of Ni(cod)₂ along with the chiral ligand, (*R,R*)-*iPr*-FcPHOX (**287**) and the Lewis acid, AlMe₂Cl, efficiently formed product **388** in 96% *ee* and 88% yield, which is a key intermediate in the subsequent synthesis of

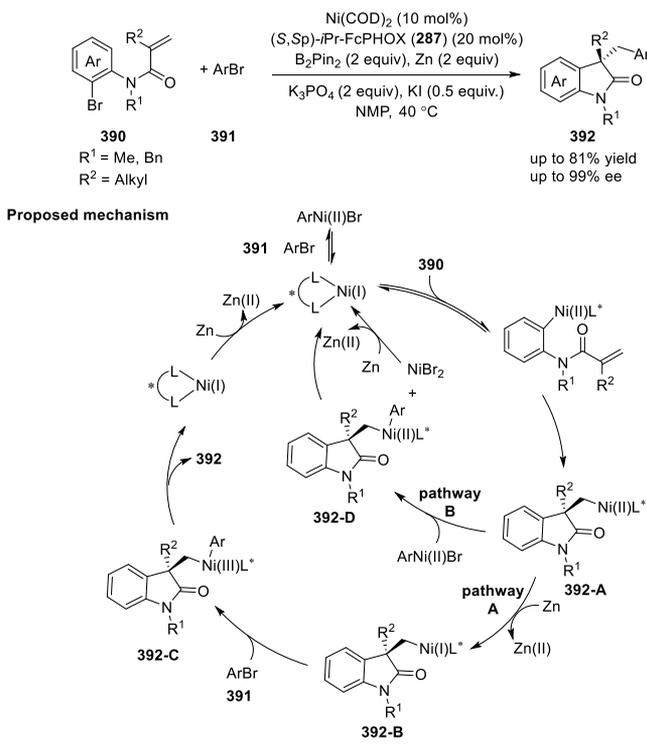
Scheme 121. Asymmetric Intramolecular Arylcyanation of Alkenes



(-)-esermethole (**389**). Later in 2010, the scope of the methodology was expanded by synthesizing a variety of enantiomerically enriched 3,3-disubstituted indoline derivatives.¹³⁵ It was observed that the electron density on the benzene ring slightly affected the enantioselectivity, possibly through altering the ability of the nitrogen or olefin to coordinate to Ni. Surprisingly, aryl–halogen bonds were tolerated whereas activation of C–CN bonds was achieved exclusively. Additionally, the size of the *N*-substituents significantly affected both the chemical yield and enantioselectivity as the bulkier substituents on the nitrogen slow down oxidative addition of the Ar–CN bond as well as coordination of the double bond to Ni. Mechanistic studies revealed that the AlMe₂Cl promoted η²-nitrile complex formation by coordinating with the cyano nitrogen.

An enantioselective diarylation of activated alkenes was reported by Kong wherein structurally distinguishable aryl bromides react together *via* a domino Heck cyclization/reductive cross coupling process using a catalytic amount of Ni/(*S,S*)-*i*Pr-FcPHOX (**287**) (Scheme 122).¹³⁶ This method

Scheme 122. Enantioselective Diarylation of Activated Alkenes

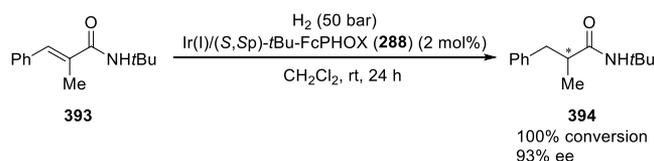


allowed direct access to various bis-heterocycles **392** bearing an all-carbon quaternary center in moderate to good yields (up to 81%) with excellent enantioselectivity (up to 99% *ee*). Experimental evidence suggested that (i) no intermediacy of arylboronic reagent instead B₂Pin₂ acts as a coreducing agent; (ii) the enantioselective-determining step of the reaction is the migratory insertion, and it should be irreversible; (iii) the cyclization process is not the turnover-limiting step. A plausible mechanism of the reaction involved two reaction pathways. Initial oxidative addition of aryl bromide **391** to the Ni(0) species followed by an intramolecular carbonickelation results in the formation of a σ-alkyl-Ni(II)Br species **392-A**. In pathway A, **392-A** was then reduced by stoichiometric Zn/

Pin₂B₂ to generate σ-alkyl-Ni(I)Br species **392-B**, which further undergoes a second oxidative addition with aryl bromide **391** to form the σ-alkyl-Ni(III)ArBr species **392-C**. Finally, reductive elimination of **392-C** affords the desired product **392** and regenerates the Ni(0) catalyst upon reduction with Zn/Pin₂B₂. Pathway B involves transmetalation between both Ni(II) centers **392-A** and ArNi(II)Br to form the σ-alkyl-Ni(II)ArBr species **392-D**, which generates product **392** following reductive elimination.

2.1.3.5. FcPHOX Ligands for Ir-Catalyzed Asymmetric Hydrogenation. In 2009, Hou developed an asymmetric hydrogenation of α,β-unsaturated amides (**393**) using an Ir/(*S,S*)-*t*Bu-FcPHOX (**288**) catalytic system to produce amides (**394**) with an α-chiral center in high yield and excellent enantioselectivity (Scheme 123).¹³⁷ The presence of hydrogen

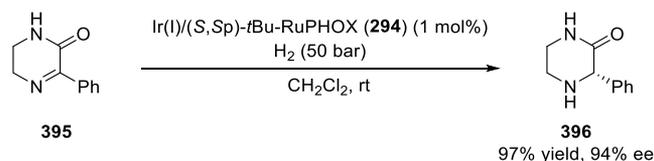
Scheme 123. Asymmetric Hydrogenation of α,β-Unsaturated Amides



on the amide nitrogen is imperative for the enantioselectivity of the reaction. Interestingly, amides having an aliphatic substituent at the β-position were also suitable substrates.

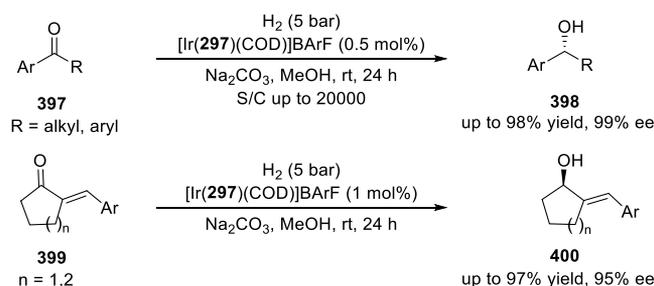
In 2017, Zhang developed a Ir/(*S,S*)-*t*Bu-RuPHOX (**294**)-catalyzed asymmetric hydrogenation of 5,6-dihydropyrazin-2(1H)-ones (**395**) to synthesize chiral piperazin-2-ones (**396**) in excellent yields and with moderate to high *ees* (up to 97% yield, up to 94% *ee*) (Scheme 124).¹³⁸ This asymmetric hydrogenation was easily extended to protected and unprotected amide substrates.

Scheme 124. Asymmetric Hydrogenation of 5,6-Dihydropyrazin-2(1H)-ones



Zhang reported the Ir-catalyzed asymmetric hydrogenation of simple ketones (**397**) and *exo*-α,β-unsaturated cyclic ketones (**399**) using a novel planar chiral ferrocene phosphino-oxazoline ligand **297** (Scheme 125).¹³⁹ A variety of ketones (**397/399**) were converted into their corresponding secondary

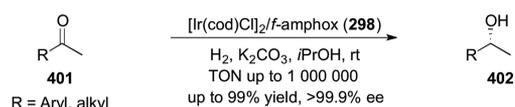
Scheme 125. Asymmetric Hydrogenation of Ketones



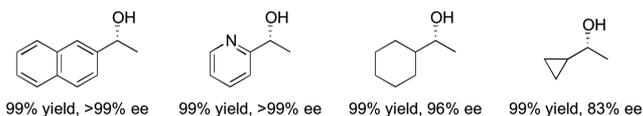
alcohols (398/400) in up to 98% yield and 99% *ee*. The Ir-297 complex was very stable and displayed high catalytic activity (0.005 mol %, S/C = 20 000) during the asymmetric hydrogenation of acetophenone on a 4.80 g scale providing alcohol product in 95% yield and 96% *ee*. Deuterium labeling studies confirmed that the reaction proceeds with hydrogen gas rather than via transfer hydrogenation with the alcoholic solvent.

Zhang, Dong and Lan reported a novel modular electron-donating tridentate ligand having a chiral ferrocenylphosphine motif linked to the oxazoline unit through a secondary amine (Figure 4). The highly active and air-stable ferrocene aminophosphooxazoline (*f*-amphox, 298) ligands were applied in the Ir-catalyzed asymmetric hydrogenation of various ketones to generate alcohol derivatives in excellent yields and enantioselectivities (Scheme 126-131).¹⁴⁰⁻¹⁴⁶

Scheme 126. Asymmetric Hydrogenation of Methylketones



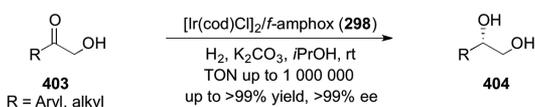
Representative examples



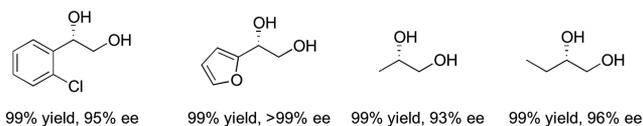
The initial application of this Ir-*f*-amphox catalyst in the asymmetric hydrogenation of simple ketones (401) provided the corresponding secondary alcohols (402) in excellent enantioselectivities (up to 99.9% *ee*) and activities (up to 1 000 000 TON) (Scheme 126).¹⁴⁰ It was observed that the (*S,S,S*,*R*_{FC}) configuration of the *f*-amphox is very critical for enantioselectivity and reactivity.

Later, various α -hydroxy ketones (403) were converted to the corresponding chiral vicinal 1,2-diols (404) with excellent outcomes (TON up to 1 000 000, up to 99% yield, >99% *ee*) (Scheme 127).¹⁴¹

Scheme 127. Asymmetric Hydrogenation of α -Hydroxy Ketones

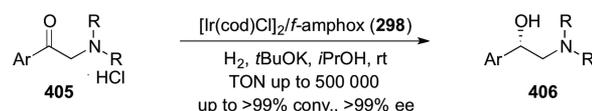


Representative examples

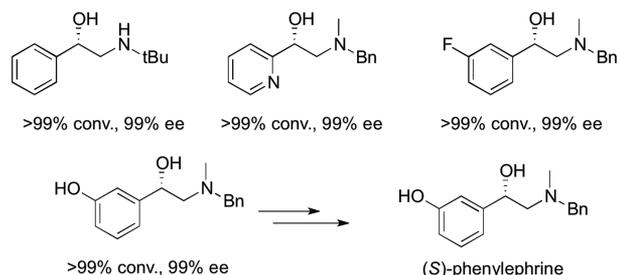


Similarly, the asymmetric hydrogenation of α -amino ketones (405) afforded the corresponding chiral 1,2-amino alcohols (406) in excellent activities and enantioselectivities (TON was up to 500 000, >99% conversion, >99% *ee*). The hydrogenated product possessing 3-hydroxy functionality on benzene ring is the key intermediate of (*S*)-phenylephrine, an enantiomer of an important α -adrenergic receptor agonist (Scheme 128).¹⁴²

Scheme 128. Asymmetric Hydrogenation of α -Amino Ketones

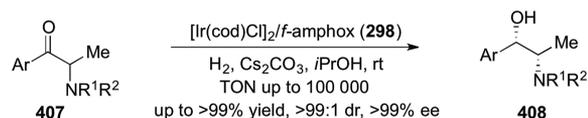


Representative examples

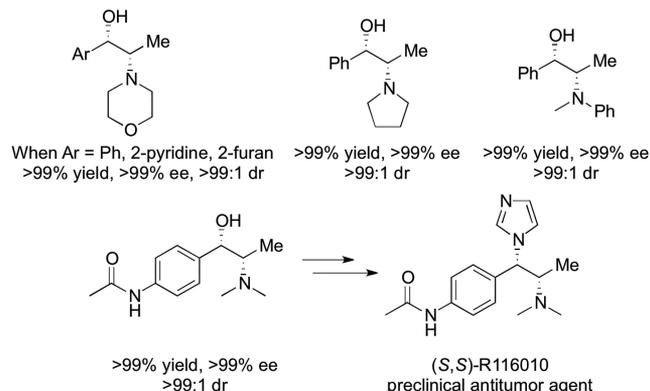


Asymmetric hydrogenation of a series of racemic α -amino β -unfunctionalized ketones (407) via a dynamic kinetic resolution (DKR) process allowed for the construction of a series of chiral 1,2-amino alcohols (408) bearing vicinal stereocenters with excellent results (all products >99% *ee* and >99:1 dr, TON up to 100 000). The success of this DKR was due more to the base-mediated rapid racemization of the substrate than hydrogenation. As expected, no reaction occurred without a base. The catalytic asymmetric hydrogenation with the process of DKR provided a powerful synthetic strategy for the synthesis of a key chiral intermediate of the preclinical antitumor agent (*S,S*)-R116010 (Scheme 129).¹⁴³

Scheme 129. Asymmetric Hydrogenation of α -Amino Ketones via Dynamic Kinetic Resolution



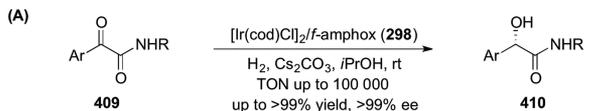
Representative examples



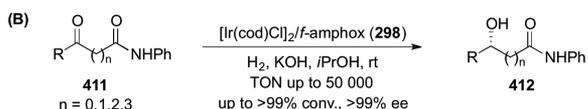
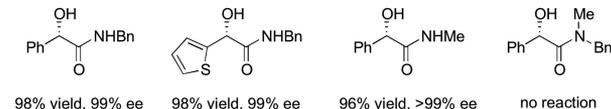
Further, the asymmetric hydrogenation of a wide range of prochiral α -, β -, γ -, and δ -keto amides (409/411) was achieved to deliver a range of chiral hydroxy amides (410/412) with excellent results (TON was up to 100 000, >99% conversion and >99% *ee*). A DFT study suggested that noncovalent interactions between the ligand and substrate play an

important role in achieving high enantioselectivity (Scheme 130A,B).^{144,145}

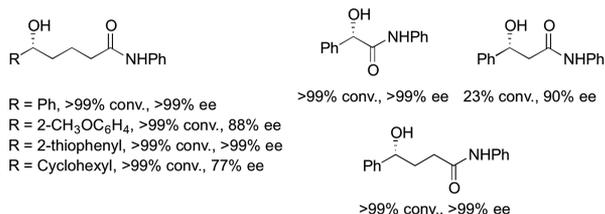
Scheme 130. Asymmetric Hydrogenation of Ketoamides



Representative examples



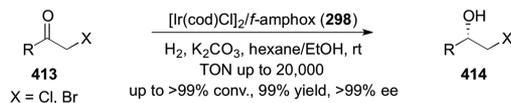
Representative examples



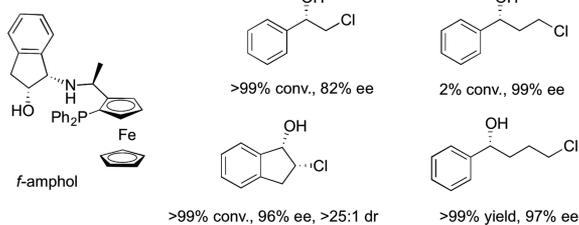
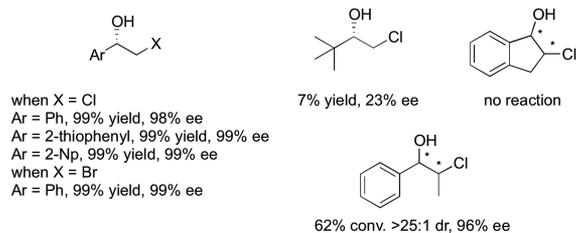
Finally, the asymmetric hydrogenation of prochiral halogenated ketones (413) was also achieved to produce chiral halohydrins (414) with excellent results (TON up to 20 000, up to 99% yield and >99% ee) (Scheme 131).¹⁴⁶

Mechanistic studies for the asymmetric hydrogenation of acetophenone indicated that the formation of intermediate 415 is kinetically and thermodynamically favored (Scheme 132).

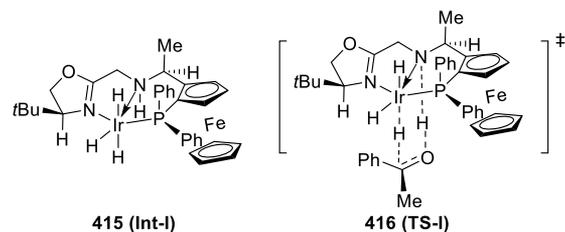
Scheme 131. Asymmetric Hydrogenation of Halogenated Ketones



Representative examples



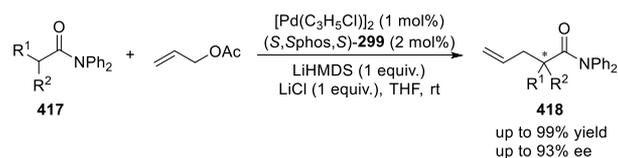
Scheme 132. Mechanistic Studies for Asymmetric Hydrogenation of Acetophenone with *f*-Amphox



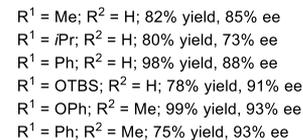
Then, the hydrogenation of acetophenone with intermediate 415 takes place via transition state 416 which forms the major product 402. Studies showed that in 415 the right-hand side is occupied by the ligand's cyclopentadiene moiety and an equatorial phenyl group, which blocks the right-hand side during hydrogenation and hence acetophenone is thought to approach the Ir-center of 415 by placing the larger group at the unencumbered left-hand side.

2.1.3.6. *Asymmetric Allylation with 1,1'-P,N-Ferrocene Ligand.* In 2008, Hou developed a Pd-catalyzed asymmetric allylic alkylation of acyclic amides (417) using the 1,1'-*P,N*-ferrocene ligand (299) (Scheme 133).¹⁴⁷ Among the various

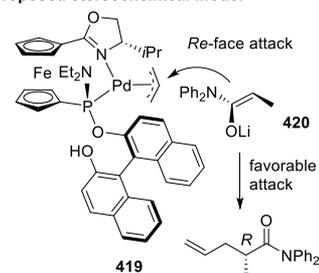
Scheme 133. Asymmetric Allylic Alkylation of Acyclic Amides



Representative examples



Proposed stereochemical model

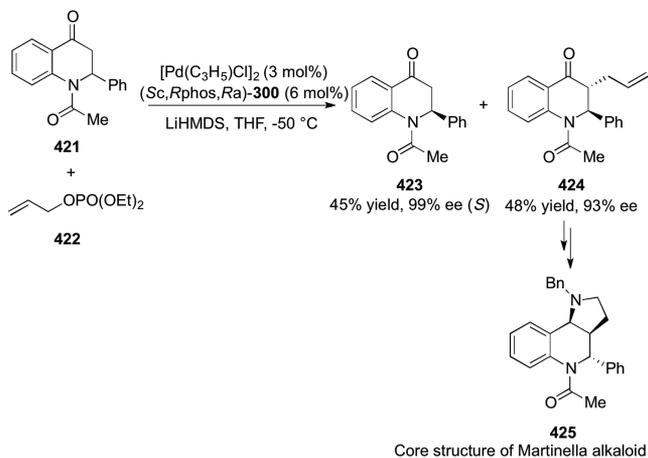


ligands tested, (*S_cS_{phos}S_a*)-299 afforded the allylated products in high yields (up to 99%) with excellent enantioselectivities (up to 93% ee). The nature of the substituents on the amide nitrogen and the use of allyl acetate instead of the corresponding carbonate or phosphonate had a significant influence on the efficiency and enantioselectivity of the reaction. The application of (*S_cS_{phos}S_a*)-299 without a stereogenic center in the oxazoline decreased the yield (65%) and ee of the product (55%) suggesting its importance. Also, the product configuration was determined by the stereochemistry of the Binol component rather than that of the phosphorus atom. The presence of a lithium counterion and the exact amount of base was crucial for the success of the reaction. In the proposed stereochemical model, the Binol subunit and the nucleophile occupies the same side of the π -allyl complex which favors *Re* face attack to provide the product with (*R*)-configuration.

Later in 2009, Hou reported the highly efficient kinetic resolution of 2,3-dihydro-2-substituted 4-quinolones (421)

using a Pd/(*S*,*R*_{phos},*R*)-**300**-catalyzed asymmetric allylic alkylation (AAA) (Scheme 134).¹⁴⁸ This method provided

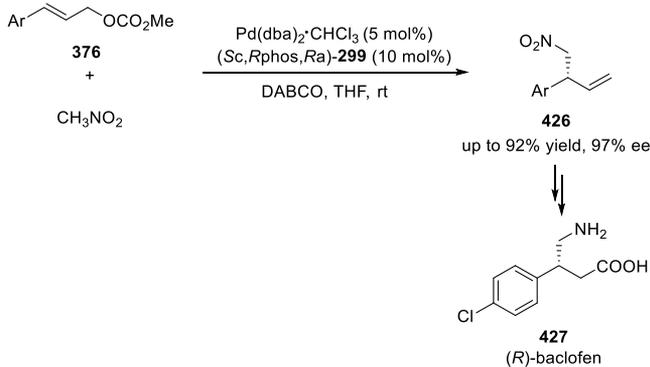
Scheme 134. Kinetic Resolution of 2,3-Dihydro-2-substituted 4-Quinolones



the allylated products, 2,3-disubstituted 2,3-dihydro-4-quinolones (**424**), with *trans*-selectivity in 37–48% yields and 83–93% *ee* along with 37–47% yields of recovered starting materials (**423**) in 87–99% *ee* (*S*-factor of 40–145). It is noteworthy that this method incorporates chiral centers at both α - and β -positions of the ketone. The nitrogen substituent of **421** also played a role in the reaction, as for example, when the acetyl group of 4-quinolone was replaced by H or Boc, both the allylated product and recovered substrates were obtained in lowered *ee*. The application of the methodology was demonstrated in the synthesis of pyrrolo-[3,2-*c*]quinoline (**425**), a core structural motif of biologically active *Martinella* alkaloids.

In 2012, Hou reported a Pd/(*S*,*R*_{phos},*Ra*)-**299**-catalyzed asymmetric allylic alkylation (AAA) between allylic carbonate (**376**) and nitromethane (Scheme 135).¹⁴⁹ Among the various

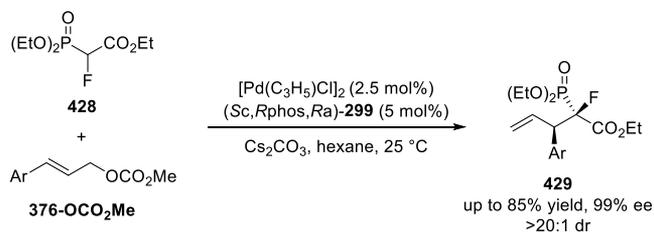
Scheme 135. Asymmetric Allylic Alkylation of Nitromethane



ligands tested, (*S*,*R*_{phos},*Ra*)-**299** afforded branched allylated products (**426**) in high yields with excellent regio- and enantioselectivities. The synthetic application of the method was shown by preparing (*R*)-baclofen **427**, an antispasmodic and (*R*)-rolipram, an anti-inflammatory agent and antidepressant.

In 2014, Hou reported a Pd/(*S*,*R*_{phos},*Ra*)-**299**-catalyzed asymmetric allylic alkylation of α -fluoro-alkylphosphonates (**428**) with monosubstituted allylic substrates (**376**) to afford allylated products (**429**) with two chiral centers in high regio-, diastereo- and enantioselectivities (Scheme 136).¹⁵⁰ The

Scheme 136. Asymmetric Allylic Alkylation of α -Fluoro-alkylphosphonates



reaction was highly diastereoselective for all allyl substrates tested possessing either electron-donating or electron-withdrawing substituents on the phenyl ring whereas the regioselectivity was sensitive to the substituent on the aryl group of the carbonates (**376**). The reaction of cinnamyl carbonate furnished the expected product with >20:1 branch to linear ratio, whereas any other substituent on the phenyl ring of carbonates (**376**) lowered the b/l ratio to 7:1. Additionally, highly functionalized products with two adjacent stereogenic centers and three functional groups were easily elaborated to more complex products.

To conclude this section, metal-complexes of PHOX ligands (**287–300**) with a stereoplane have been employed in various asymmetric cycloaddition reactions. Copper and nickel complexes were extensively employed in (I) [4 + 2], [4 + 3], [3 + 3], [2 + 2 + 2] cycloadditions, (II) 1,2- and 1,4-additions. Copper complexes in combination with palladium were excellent for asymmetric α -allylation of Schiff base activated amino acids. Nickel complexes were also used in intramolecular arylation and diarylation of alkenes whereas iridium complexes were successful in alkene, imine and ketone hydrogenations.

2.1.4. Phosphino-oxazoline with Phosphorus Bonded to N- and O-Atom. This section deals with the application of phosphino-oxazoline ligands with phosphorus bonded to N- and O-atom (**430a–k**) in Ir-catalyzed asymmetric hydrogenations. The phosphino-oxazoline ligands discussed in this section are shown in Figure 5.

The Andersson group reported a series of papers on the applications of *P,N*-ligands of type **430a–d** in the Ir-catalyzed asymmetric hydrogenation of various types of olefins (Scheme 137).

In 2008, Andersson described the Ir-catalyzed asymmetric hydrogenation of a variety of di- and trisubstituted enol phosphinates (**431**) using ligand **430a** (Scheme 138).^{151,152} A range of olefin substrates possessing both aromatic and aliphatic substituents afforded hydrogenated products (**432**) with excellent enantioselectivities (up to >99% *ee*). Trisubstituted enol phosphinates were hydrogenated in better yields and selectivities than the related 1,1-disubstituted compounds. More importantly, enol phosphinates were stable toward degradation under the hydrogenation reaction conditions employed.

In 2009, the first Ir-catalyzed asymmetric hydrogenations of vinyl boronates (**433**) was developed using ligand **430a/b**

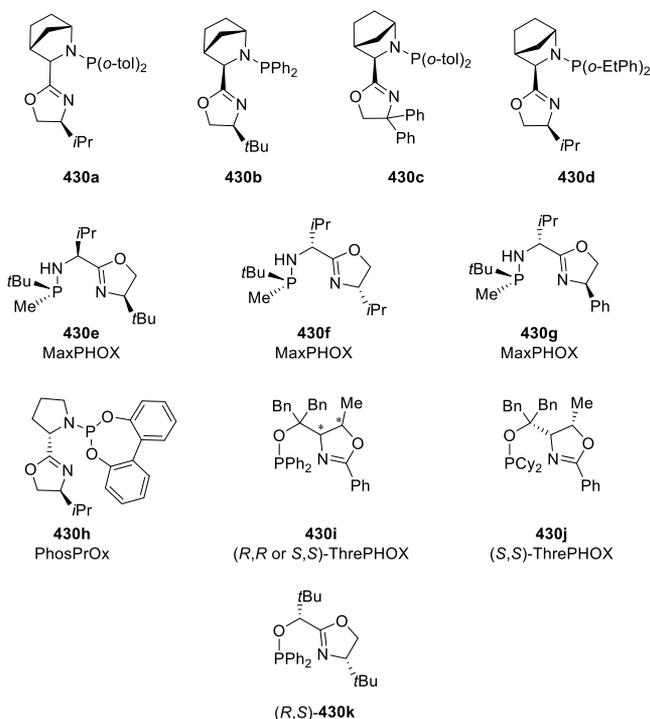
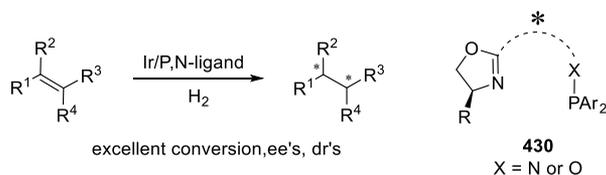
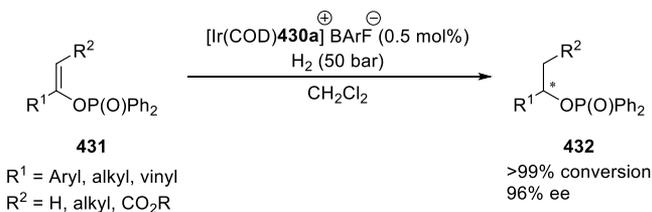


Figure 5. Phosphino-oxazoline ligands with Phosphorus Bonded to N- and O- Atom.

Scheme 137. Ir-Catalyzed Asymmetric Hydrogenation of Olefins



Scheme 138. Ir-Catalyzed Asymmetric Hydrogenation of Di- and Trisubstituted Enol Phosphinates

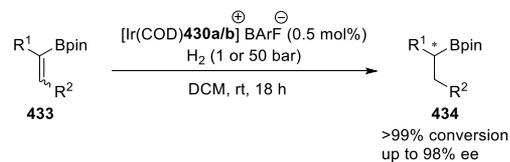


under low catalyst loadings (0.5 mol %) and pressure (as low as 1 bar) (Scheme 139).¹⁵³ For most of the vinyl boronates, the selectivity was either decreased or even reversed with decreased hydrogen pressure suggesting the possibility of different mechanisms at play at different concentrations of hydrogen. Vinyl boronates having aromatic or polarizing groups gave good results (98% ee), whereas aliphatic substituents on vinyl boronates were less successful as they gave hydrogenated products with <50% ee.

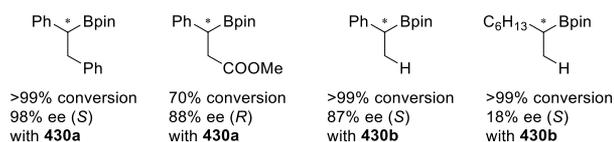
Andersson subsequently employed ligand 430b for the Ir-catalyzed asymmetric hydrogenation of cyclic allylic amines (435) thereby synthesizing chiral piperidines (436) in good to excellent enantioselectivities (Scheme 140).¹⁵⁴

In 2011, Andersson reported the enantioselective synthesis of β,β -disubstituted aldehydes (438) using the Ir-catalyzed

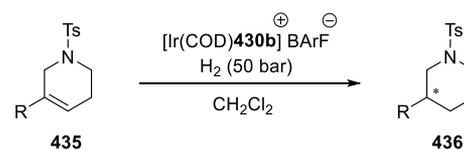
Scheme 139. Ir-Catalyzed Asymmetric Hydrogenations of Vinyl Boronates



Representative examples



Scheme 140. Ir-Catalyzed Asymmetric Hydrogenation of Cyclic Allylic Amines

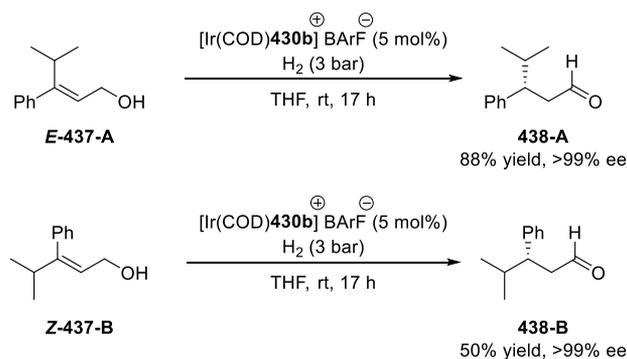


Representative examples

$\text{R} = \text{Me}$; >99% conversion, 97% ee
 Bu ; >99% conversion, 81% ee
 Bn ; 97% conversion, 92% ee
 CH_2OH ; >99% conversion, 97% ee

asymmetric isomerization of (*E*)- and (*Z*)-trisubstituted allylic alcohols (437) (Scheme 141).¹⁵⁵ The Ir complex of the bulkier

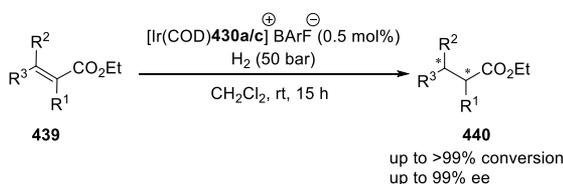
Scheme 141. Asymmetric Isomerization of (*E*)- and (*Z*)-Trisubstituted Allylic Alcohols



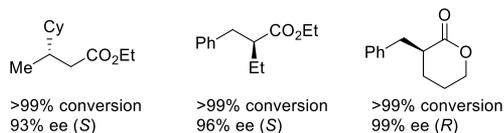
ligand 430b was successfully employed in the isomerization of a broad range of primary allylic alcohols. The yield of product was significantly impacted by the size of the substituent on the allyl alcohols. (*E*)-Cinnamyl alcohols with Cy and $i\text{Pr}$ substituents reacted smoothly (86% yield, >99% ee and 88% yield, >99% ee). For ethyl and methyl substituents, the enantioselectivities were only marginally affected (97% ee and 91% ee), but the aldehyde product was recovered in poor yields (21% and <5%). Compared to the (*E*)-trisubstituted allylic alcohols, the catalytic system was less sensitive to steric effects in the isomerization of (*Z*)-trisubstituted allylic alcohols.

Later in 2012, the same catalytic system was extended to the asymmetric hydrogenation of α,β -unsaturated esters (439) (Scheme 142).¹⁵⁶ A wide variety of ester substrates (439) with both aromatic and aliphatic substituents on the prochiral

Scheme 142. Asymmetric Hydrogenation of α,β -Unsaturated Esters



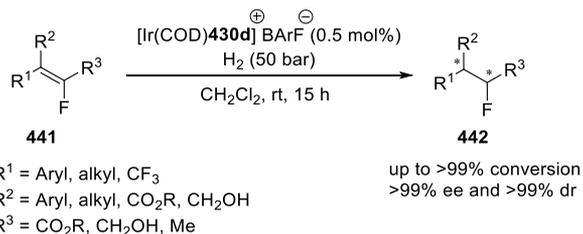
Representative examples



carbon were hydrogenated with excellent enantioselectivities (up to 99%).

More recently, Andersson reported a highly stereoselective synthesis of chiral fluorine-containing compounds (**442**) with two vicinal stereogenic centers via the asymmetric hydrogenation of tetra-substituted vinyl fluorides (**441**) (Scheme 143).¹⁵⁷ The Ir complex of the newly developed ligand (**430d**)

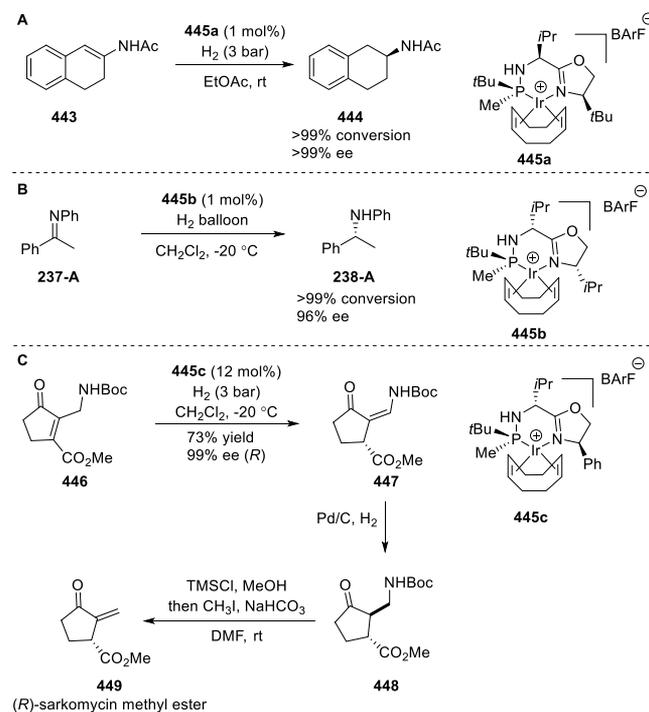
Scheme 143. Asymmetric Hydrogenation of Tetra-Substituted Vinyl Fluorides



was determined to be the most effective catalyst. Several aromatic, aliphatic, and heterocyclic substrates with a variety of functional groups were tolerated to provide chiral fluoroalkanes in excellent yield, diastereoselectivity, and enantioselectivity. Moreover, this catalytic hydrogenation system substantially overcomes the problem of defluorination.

Riera and Verdager developed a novel ligand, MaxPHOX (**430e–g**), which contains three stereogenic centers that can be introduced from three separate and simple building blocks. Initially, Ir-complexes of MaxPHOX-**445a** were applied in the asymmetric hydrogenation of cyclic enamides derived from α - and β -tetralones (**443**) (Scheme 144A).^{158,159} The enantioselectivities observed with Ir-MaxPHOX were much better than those with Ru and Rh catalysts. It was noticed that the enantioselectivity was pressure dependent as reducing the hydrogen pressure to 3 bar increased the enantioselectivity. The X-ray crystallographic study of Ir-**445a** complex showed that the six-membered metallacycle adopts a boat-like conformation. The phosphorus atom and the bulky *t*-butyl group on the oxazoline ring are *syn* to each other on the same face of the metallacycle. In addition to this the catalytic activity observed in coordinating solvents like EtOAc and MeOH suggested bidentate binding of the substrate to the cationic Ir-**445a** complex. It was believed that the directing amide group binds to an axial position away from the bulky *t*-butyl group, while the alkene binds equatorially *trans* to phosphorus. Finally, the asymmetric induction dependence on the hydro-

Scheme 144. Ir-MaxPHOX Catalyzed Asymmetric Hydrogenation



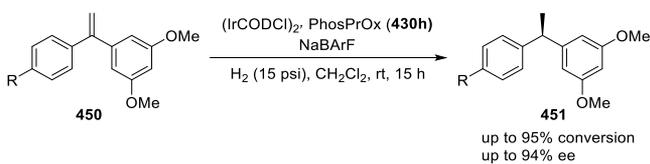
gen pressure indicated that hydrogen is involved in the enantioselectivity-determining step.

A further application of Ir-MaxPHOX-**445b** complexes was shown in the asymmetric hydrogenation of *N*-aryl imines (Scheme 144B).¹⁶⁰ Ir-MaxPHOX-**445b** possessing an *i*Pr group both on the oxazoline ring and in the backbone with a P-stereogenic center was capable of efficient imine hydrogenation. The chirality on phosphorus has a significant impact on the catalyst activity as the non-P-stereogenic equivalent of Ir-MaxPHOX-**445b** gave rise to lower selectivity. Also, the nature of the counterion considerably affects the reaction outcome; smaller counterions (e.g., BF₄) reduced the enantiomeric excess and slowed down the reaction.

Subsequently, the catalytic system was also employed in the synthesis of the antibiotic (*R*)-sarkomycin methyl ester (**449**) (Scheme 144C).¹⁶¹ The key step was an unprecedented asymmetric isomerization of cyclic enone **446** catalyzed by the Ir-MaxPHOX-**445c** complex resulting in the formation of exocyclic enamide in good yield (73%) and excellent enantioselectivity (99% ee). The exocyclic enamide **447** was formed because of stabilization due to the conjugation and formation of a strong intramolecular hydrogen bond. The exclusive formation of the enamide (*Z*)-isomer **447** also supported strong hydrogen bonding stabilization. The exocyclic enamide was subsequently reduced, the amine deprotected followed by spontaneous elimination to provide the desired antibiotic **449** in 45% yield and 98% ee.

In 2013, Sigman developed a novel phosphoramidite ligand, Phos-PrOx (**430h**) and applied it in the Ir-catalyzed asymmetric hydrogenation of 1,1-diaryllkenes (**450**) (Scheme 145).¹⁶² The presence of a coordinating group on the *meta*-position of one of the phenyl rings was essential for the success of the reaction. It was proposed that the 3,5-dimethoxy substitution acts as a directing group by pre-coordinating the substrate alkenes to Ir. This coordination orients one alkene

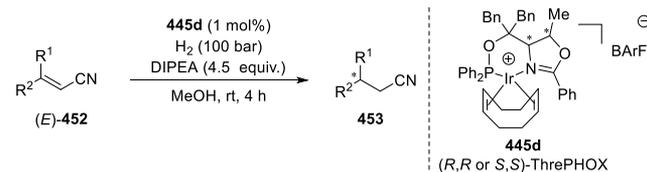
Scheme 145. Ir-Catalyzed Asymmetric Hydrogenation of 1,1-Diaryllalkenes



face toward Ir, poisoning the substrate for subsequent alkene coordination and hydrogenation to deliver 1,1-diarylmethines in moderate to good levels of enantioselectivity.

Pfaltz developed the first Ir-catalyzed asymmetric hydrogenation of α,β -unsaturated nitriles (**452**) using the chiral *P,N*-ligand, ThrePHOX (**430i**) and *N,N*-diisopropylethylamine (DIPEA) (Scheme 146).¹⁶³ The Ir-**430i** complex (**445d**) was

Scheme 146. Ir-Catalyzed Asymmetric Hydrogenation of α,β -Unsaturated Nitriles



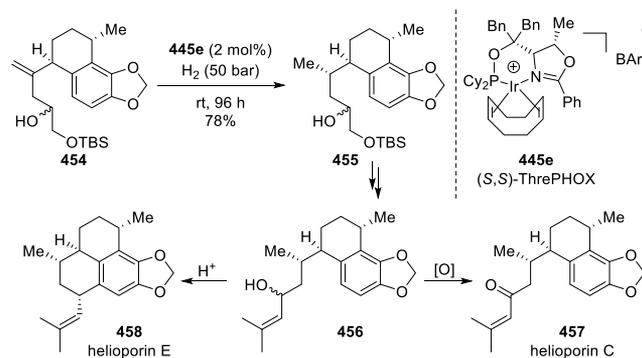
Representative examples

- $R^1 = \text{Me}$; $R^2 = \text{C}_6\text{H}_5$; >99% conversion, 95% ee
- $R^1 = \text{Me}$; $R^2 = \text{C}_6\text{H}_5$; 67% conversion, 25% ee with (*Z*)-alkene
- $R^1 = \text{Me}$; $R^2 = 2\text{-MeC}_6\text{H}_4$; 96% conversion, 78% ee
- $R^1 = \text{Me}$; $R^2 = 4\text{-MeC}_6\text{H}_4$; >99% conversion, 95% ee
- $R^1 = \text{Et}$; $R^2 = \text{C}_6\text{H}_5$; >99% conversion, 98% ee
- $R^1 = \text{CH}_2\text{-CH}(\text{Me})_2$; $R^2 = \text{C}_6\text{H}_5$; >99% conversion, 96% ee

inactive without the addition of DIPEA. Slight variation in the ligand structure, changing the double bond geometry from *trans* to *cis* and the amount of DIPEA used all had a strong impact on the reactivity and selectivity of hydrogenation. Alkenes lacking a conjugated cyano group did not react in the present system which rendered the possibility of selectively reducing the cyano-substituted C=C bond of an α,β -unsaturated nitrile, while leaving the less electrophilic C=C bonds intact. The authors proposed the generation of a reactive neutral Ir(I) monohydride *via* base-mediated deprotonation of an Ir-dihydride complex due to its pronounced Brønsted acidity. The newly generated neutral Ir(I) monohydride is expected to be less electrophilic which means easy release of nitrile from the Ir-metal center, thus opening the free coordination site required for the hydrogenation reaction. Also, the hydride of neutral Ir (I) monohydride would be more nucleophilic than hydrides in a cationic dihydride complex, thus aiding hydride transfer to the electrophilic C=C bond of the α,β -unsaturated nitrile.

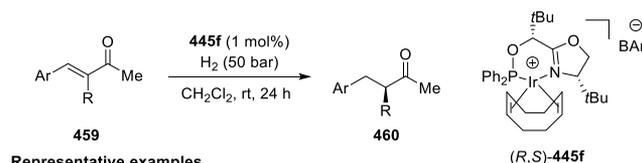
The application of the ThrePHOX ligand (**430j**) developed by Pfaltz was demonstrated by Schmalz in a short total synthesis of helioporins C (**457**) and E (**458**) (Scheme 147).¹⁶⁴ The Ir-catalyzed asymmetric hydrogenation of the exocyclic double bond was established for setting up a homobenzylic stereocenter in a highly diastereoselective manner. The hydrogenated product after subsequent desilylation, oxidative cleavage and vinyl Grignard addition afforded the allylic alcohol **456**. This allylic alcohol underwent oxidation to afford helioporins C (**457**) and acid-catalyzed cyclization to give rise to helioporins E (**458**).

Scheme 147. Total Synthesis of Helioporins C and E



Kazmaier described a new efficient *P,N*-ligand **430k** for Ir-catalyzed asymmetric hydrogenations of β -arylated α,β -unsaturated ketones (**459**) (Scheme 148).¹⁶⁵ By using Ir-

Scheme 148. Ir-Catalyzed Asymmetric Hydrogenations of β -Arylated α,β -Unsaturated Ketones



Representative examples

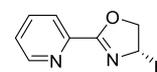
- $\text{Ph-CH}_2\text{-CH}_2\text{-C(=O)Me}$: >99% conversion, >99% ee
- $\text{Ph-CH}_2\text{-CH(Et)-C(=O)Me}$: >99% conversion, >99% ee
- $\text{Ar-CH}_2\text{-CH}_2\text{-C(=O)Me}$ (Ar = 4-MeOC₆H₄): >99% conversion, >99% ee
- Cyclic ketone: >99% conversion, 99% ee

complex (**445f**) derived from ligand **430k**, various linear as well as cyclic α,β -unsaturated ketone substrates were hydrogenated successfully to the corresponding ketones (**460**) in excellent yields (>99%) and enantioselectivities (>99% ee).

To conclude this section, iridium complexes of PHOX ligands (**430a–k**) with phosphorus bonded to *N*- and *O*-atoms have been mainly employed in asymmetric alkene hydrogenation.

2.2. Mono(oxazoline) *N,N*-Ligands

Mono(oxazoline) bidentate *N,N*-ligands are also widely used in asymmetric catalysis. PyOx **461**, which contains a pyridine-oxazoline backbone is the most used ligand in this class (Figure 6). These ligand class will not be discussed here since Yang and Zhang recently reviewed the area since Brunner's original synthesis in 1986.^{166,167}



461

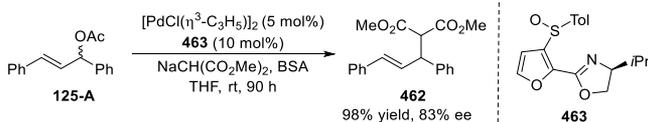
Figure 6. PyOx ligand.

2.3. Mono(oxazoline) *N,S*-Ligands

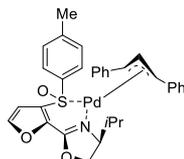
In 2008 Arai developed a series of novel chiral (sulfinyl)furyl oxazoline-containing ligands **463** and applied them in the Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate **125-A**. After optimization, which included changing the solvent from dichloromethane to THF, it was shown that the

product **462** was formed in up to 98% yield and 83% *ee*. It is thought that the oxazoline nitrogen acts as a π -donor while the sulfur is a π -acceptor leading to the reactive intermediate shown (Scheme 149).¹⁶⁸

Scheme 149. Pd-Catalyzed Allylic Alkylation with (Sulfinyl)furyl Oxazoline Ligand

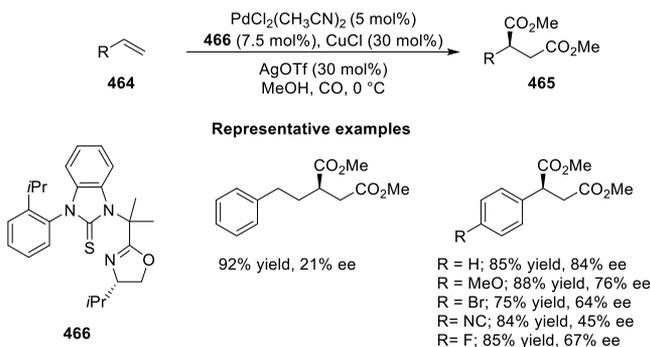


Stereochemical model



In 2010 Huang reported the synthesis of axially chiral thiourea-oxazoline ligands in the Pd-catalyzed enantioselective bis(methoxycarbonylation) of styrenes **464**. When applied in this catalytic transformation ligand **466** afforded the product **465** in up to 85% yield and 84% *ee* (Scheme 150). A variety of

Scheme 150. Pd-Catalyzed Esterification of Styrenes

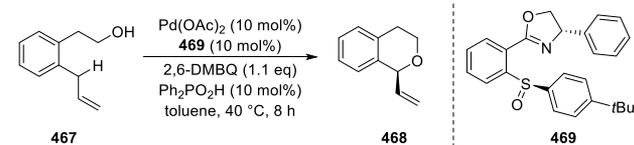


electronically different styrenes **464** were successfully transformed to the product **465**, although when nonstyrenyl alkenes were used, the enantioselectivity dropped dramatically to 21% *ee* although still in 92% yield.¹⁶⁹

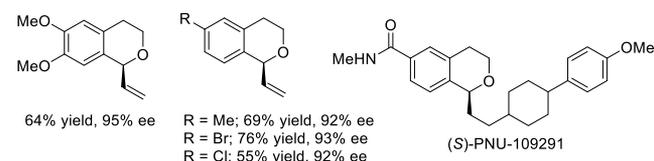
In 2016 White developed a novel set of aryl sulfoxide-oxazoline ligands **469** and applied them in the Pd-catalyzed synthesis of isochroman motifs **468**. A series of oxazoline substituents were screened and the ligand containing the phenyl group gave rise to the desired product in up to 64% yield and 95% *ee* (Scheme 151). The substrate scope included a range of electronically diverse isochroman motifs with 92% *ee* being the lowest obtained for all substrates. This methodology was subsequently applied in the synthesis of PNU-109291 a potent 5HT_{1D} agonist avoiding the costly chiral resolution used in its previous synthesis.¹⁷⁰ In a subsequent publication White further explored the ligand scaffolds performance in the Pd-catalyzed asymmetric allylic alkylation of pyrazole-5-ones.¹⁷¹

Han reported the asymmetric intramolecular allylation of aryl ureas **470** to indolines **471** using a novel sulfoxide-oxazoline ligand **472**. A variety of dienes **116** were applied in this transformation with all substituents furnishing the products **471** in a range of 80 to 90% *ee* with yields proving

Scheme 151. Pd-Catalyzed Synthesis of Isochroman Motifs

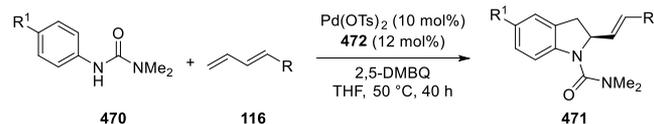


Representative examples

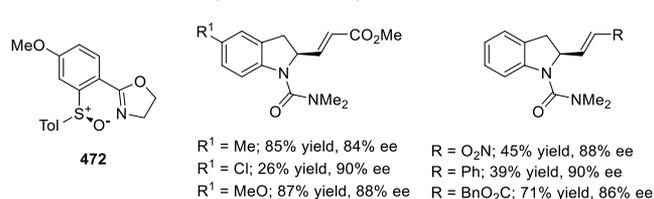


highly variable on the substrate used. Interestingly, this ligand does not possess a chiral oxazoline motif and instead relies on asymmetric induction from the chiral sulfoxide unit. When initial conditions were screened the BOX ligand **600c** afforded the product in only trace amounts. In the initial screen, benzoquinone was used as the oxidant furnishing the product in 77% yield and 85% *ee*, and when 2,5-dimethylquinone 2,5-(DMBQ) was used it improved the results moderately to 79% yield and 88% *ee* (Scheme 152).¹⁷²

Scheme 152. Pd-Catalyzed Asymmetric Intramolecular Allylation of Aryl Ureas



Representative examples



Interestingly, the mono(oxazoline) *N,S*-ligands mentioned in this section (Figure 7) are all used in Pd-catalyzed

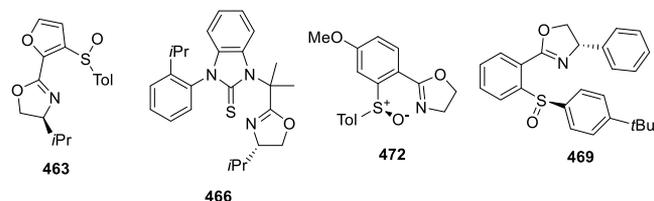


Figure 7. Summary of mono(oxazoline) *N,S*-ligands.

asymmetric reactions with unsaturated systems. While the chemistry is synthetically useful it appears this class of ligand is currently limited in their application. Utilizing these ligands in a wider range of chemistry with inexpensive metals could further develop this area greatly.

2.4. Mono(oxazoline) *N,O*-Ligands

N,O-Ferrocenyloxazoline ligands (*R_p*)- and (*S_p*)-**473a** were originally synthesized by Bolm in 1997 (Figure 8).¹⁷³ Since

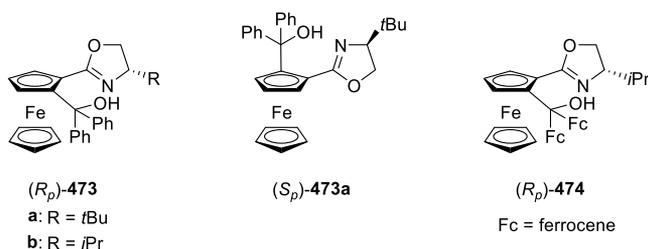


Figure 8. *N,O*-Ferrocenyloxazoline ligands 473 and 474.

then, Butenschön has described the synthesis of (*R_p*)-473b and triferrocenylmethane 474 and applied ligands (*R_p*)-473a–b and 474 in the diethylzinc addition to aromatic and alkenyl aldehydes, achieving enantioselectivities of up to 97% *ee*.¹⁷⁴

In almost all of the examples reported, triferrocenylmethane 474 gave the best enantioselectivity. To exemplify, the results of each ligand in the diethylzinc addition to benzaldehyde 475 are summarized in Table 1. The reaction with Bolm's *t*Bu-473a

Table 1. Comparison of Bolm and Butenschön's *N,O*-Ferrocenyloxazoline Ligands in Asymmetric Diethylzinc Addition to Benzaldehyde 475

entry	ligand	yield 478 (%)	% <i>ee</i>
1	(<i>R_p</i>)-473a	83	93
2	(<i>R_p</i>)-473b	97	83
3	(<i>R_p</i>)-474	95	97

afforded the chiral alcohol 476 in a higher enantiomeric excess (93% *ee*) than Butenschön's *i*Pr-473b (83% *ee*), but Butenschön's triferrocenyl *i*Pr-474 gave the best result (97% *ee*). The increased steric bulk beside the alcohol moiety counteracts the decrease in steric bulk going from *t*Bu to *i*Pr on the oxazoline.

More recently, Guiry has studied the *gem*-dimethyl effect in these *N,O*-ferrocenyloxazoline ligand systems, describing the synthesis of ligands (*R_p*)- and (*S_p*)-479a–b and (*R_p*)-480, applying them in the diethyl- and diphenylzinc addition to aromatic and aliphatic aldehydes 479, with enantiomeric excesses up to >99% (Scheme 153).¹⁷⁵

The results of the diethylzinc additions to benzaldehyde 475 with each ligand are summarized in Table 2. In the case of benzaldehyde, the triferrocenylmethane ligand (480) performed best, giving the chiral alcohol 476 in 93% *ee* (entry 5). However, for different aldehydes, different ligands performed better. This study shows that the *gem*-dimethyl effect can be applied to ligands of this class to reach similar levels of enantioselectivity that can be achieved with less economical *t*Bu-ligands, with (*R_p*)-479a giving the chiral alcohol 476 in 88% *ee* (compared to 93% *ee*) (entry 1). Second, trisubstituted ferrocene derivatives (479b) perform worse than the corresponding disubstituted ferrocene derivatives, with (*R_p*)-479b giving the chiral alcohol 478 in 82% *ee* (entry 3). Finally, in this chiral ligand scaffold, planar chirality has a dominant effect over the stereoselectivity induced, with the (*S_p*)-ligands giving lower levels of enantioselectivity in the diethylzinc additions, while reversing the enantioselectivity in the diphenylzinc additions (entries 2 and 4).

Scheme 153. Application of Guiry's *gem*-Dimethyl *N,O*-Ferrocenyloxazoline Ligands in Diethylzinc Addition to Various Aldehydes 477

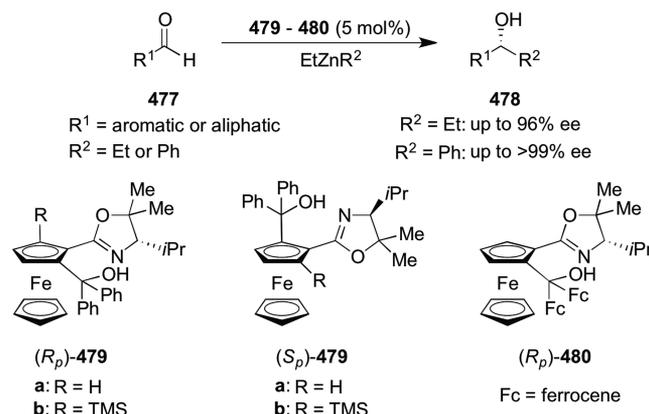


Table 2. Comparison of Guiry's *gem*-Dimethyl *N,O*-Ferrocenyloxazoline Ligands in Asymmetric Diethylzinc Addition to Benzaldehyde 475

entry	ligand	yield 478 (%)	% <i>ee</i>
1	(<i>R_p</i>)-479a	93	88
2	(<i>S_p</i>)-479a	32	33
3	(<i>R_p</i>)-479b	54	82
4	(<i>S_p</i>)-479b	11	–5
5	(<i>R_p</i>)-480	79	93

Xiao and Chen reported the synthesis of *N,O*-ligand 481 bearing a phenyl group at the C-1 position of the oxazoline and an ester at the C-4 stereocenter (Figure 9).

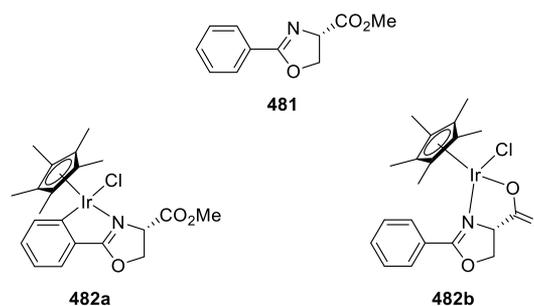
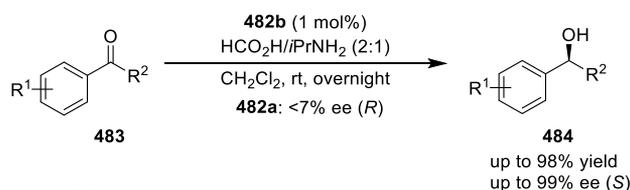


Figure 9. Xiao and Chen's *N,O*-ligand 481 and Ir(481)Cp*Cl 482a and 482b.

They applied this ligand in the asymmetric transfer hydrogenation of aryl ketones 483, having prepared both the *N,C*- and *N,O*-chelated Ir complexes 482a and 482b. It was observed that 482a did not induce appreciable levels of enantioselectivity in this reaction, while the reaction with 482b gave the corresponding secondary alcohols 484 in up to 98% yield and with up to >99% *ee* (Scheme 154).¹⁷⁶

A plausible transition state 485 for this process was proposed in which the hydride is delivered to the *Re*-face of the ketone, with the ammonium cation H-bonding to the *N,O*-ligand and the ketone (Figure 10).

Scheme 154. Ir-Complex 482b-Catalyzed Asymmetric Transfer Hydrogenation of Aryl Ketones 483



Representative examples

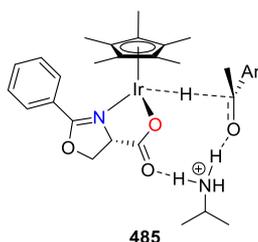
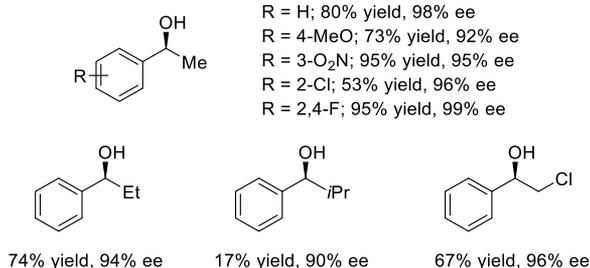


Figure 10. Plausible transition state for the asymmetric transfer hydrogenation of ketones 483 with Ir-complex 482b.

In recent years, Wang has significantly contributed to the development of *N,O*-analogues of PHOX-type ligands, describing the synthesis of Box–OH ligands 486 – 488 and their application in various enantioselective Mg(II)-catalyzed transformations (Figure 11).

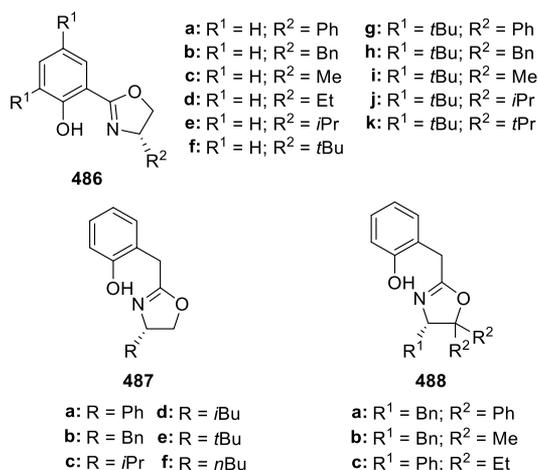
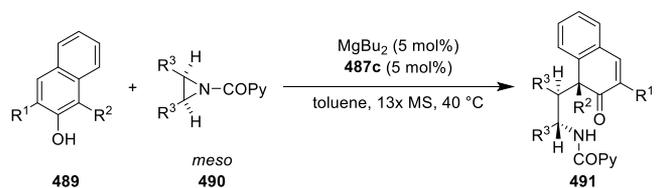


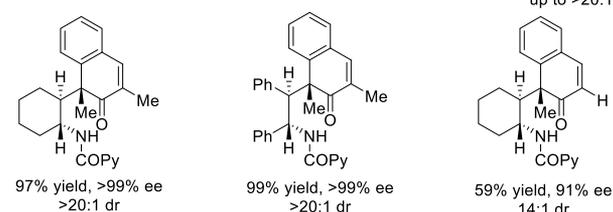
Figure 11. Box–OH ligands 486–488.

Wang first utilized the Box–OH ligands in the Mg-catalyzed asymmetric dearomatization of β -naphthols 489 with *meso*-aziridines 490. Following optimization, ligand 487c was applied in the synthesis of a range of ring-opened products 491 bearing three contiguous stereocenters in up to 99% yield, with up to >20:1 dr and >99% ee (Scheme 155). Ligands of the type 487, with a methylene spacer between the phenol and the

Scheme 155. MgBu₂/487c-Catalyzed Asymmetric Dearomatization of β -Naphthols 489 with *meso*-Aziridines 490



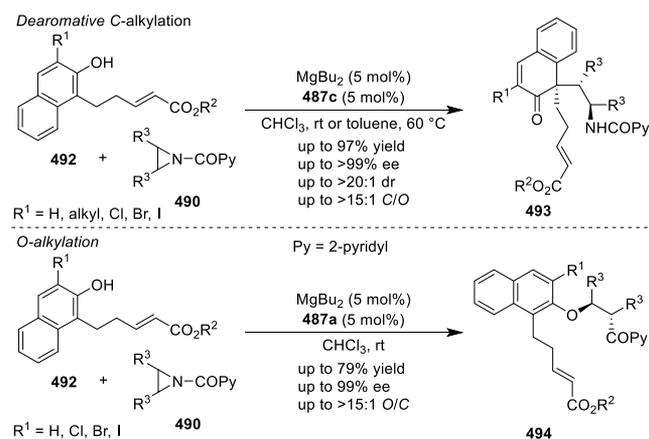
Representative examples



oxazoline, performed better than ligands 486 without the spacer. Changes to the β -naphthols 489 or the *meso*-aziridines 490 did not have a significant effect on the outcome of the reactions, all of which proceeded with excellent levels of enantioselectivity (all but one example >97% ee).¹⁷⁷

Wang further developed Box–OH/Mg-mediated transformations of naphthols with aziridines, describing two distinct processes for the dearomatization or *O*-alkylation of naphthols 492. The *i*Pr-487c/MgBu₂-catalyzed reaction of 492 with aziridines 490 gives access to the dearomatized products 493 in up to 97% yield, with up to >20:1 dr and >99% ee (Scheme 156). Conducting the reaction of C3-H and C3-halogenated

Scheme 156. MgBu₂/487c-Catalyzed Asymmetric Dearomatization and MgBu₂/487a-Catalyzed Asymmetric *O*-Alkylation of Naphthols 494

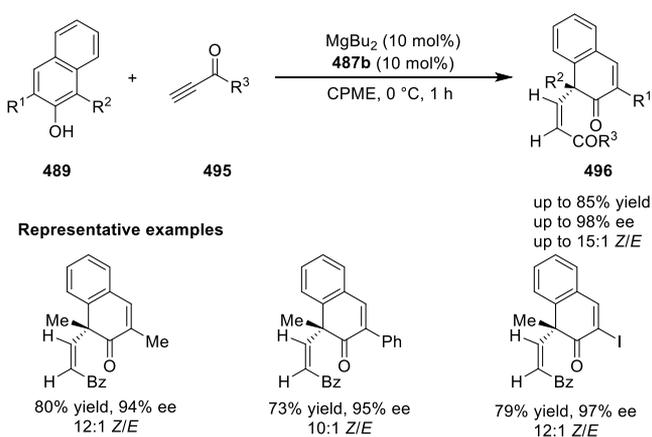


naphthols 492 in the presence of Ph-487a (in place of 487c) gives access to the *O*-alkylated products 494 in up to 79% yield and with up to 99% ee. So far there is no concrete explanation for the remarkable chemoselectivity observed in these processes. The reaction is certainly substrate dependent as the nature of R¹ has the largest effect on chemoselectivity. The ligand plays an important role, and the authors suggest this could be due to π – π or π –anion interactions in the transition state of the reaction with ligand Ph-487a. Finally, the presence of a long alkyl chain at C-1 is essential for *O*-

alkylation to occur, and the nature of this alkyl chain has a slight effect over the *C/O* ratio (the catenulate ester appears to be optimal).¹⁷⁸

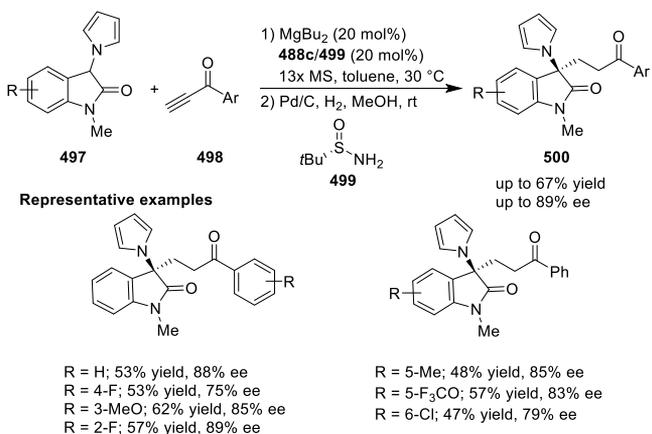
Wang has also reported the **487b**/Mg-catalyzed dearomative conjugate addition of naphthols **489** to alkynyl ketones **495** to give the corresponding alkenes **496** in up to 85% yield, with up to 15:1 *Z/E* selectivity and up to 98% *ee*, using cyclopentyl methyl ether (CPME) as the solvent (Scheme 157).¹⁷⁹ Later, the scope of this reaction was extended to dialkyl acetylenedicarboxylates.¹⁸⁰

Scheme 157. MgBu₂/487b-Catalyzed Dearomative Conjugate Addition of Naphthols **489** to Alkynyl Ketones **495**



Wang extended the Box–OH/Mg-catalyzed conjugate addition reaction to include C3-pyrrolyl-oxindoles **497** with alkynyl ketones **498**. By developing a **499/488c** bis-ligand system, a range of oxindoles **500**, bearing quaternary stereocenters were accessed via the Mg-catalyzed process, followed by reduction of the alkene with Pd/C and H₂ in up to 67% yield and with up to 89% *ee* (Scheme 158). The reaction with sulfoxide **409** as a coligand only slightly improved the enantioselectivity of the process, compared to the reaction with just **488c**, under the exact same reaction conditions (without molecular sieves). The authors did not report the result of the reaction with just ligand **488c** under the final optimized

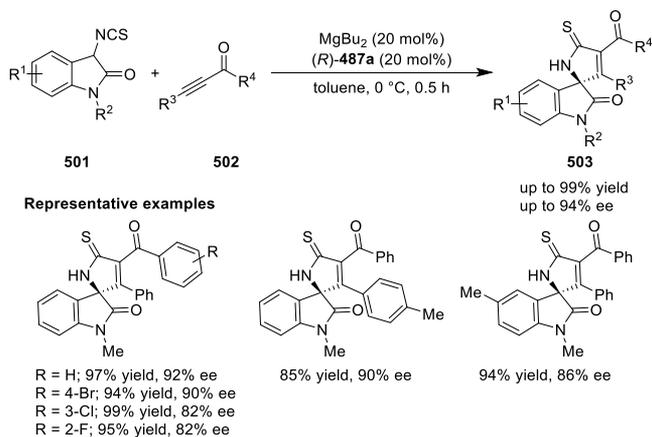
Scheme 158. MgBu₂/488b-Catalyzed Dearomative Conjugate Addition of Oxindoles **497** to Alkynyl Ketones **498**



conditions (including molecular sieves). The best *E/Z* selectivity achieved during optimization, without the reduction of the double bond, was 3:1.¹⁸¹

Wang has also applied Box–OH/Mg-catalysts in the asymmetric [3 + 2] cyclization of 3-isothiocyanato oxindoles **501** with alkynyl ketones **502**. Utilizing (*R*)-**Ph-487a** as the chiral ligand, a range of polycyclic oxindoles **503** were synthesized in up to 99% yield and with up to 94% *ee* (Scheme 159).¹⁸²

Scheme 159. MgBu₂/487a-Catalyzed Asymmetric [3 + 2] Cyclization of 3-Isothiocyanato Oxindoles **501** with Alkynyl Ketones **502**



Overall, mono(oxazoline) *N,O*-ligands have been applied in a very limited range of asymmetric transformations in the past decade. In particular, they have been successfully applied in the asymmetric alkyl or aryl zinc addition to aldehydes, and in asymmetric Mg-catalyzed addition reactions to alkynyl ketones.

2.5. Miscellaneous Mono(oxazoline) Ligands

2.5.1. Mono(oxazoline)-Sulfonamide Ligands. Kishi and co-workers reported a library of chiral sulfonamide ligands (Figure 12) and they were successfully employed in the enantioselective Cr-catalyzed allylation, propargylation and vinylation of aldehydes, a reaction famously known as the Nozaki-Hiyama-Kishi (NHK) reaction.

In 2004, Kishi developed a novel Cr-catalyzed enantioselective allylation of aldehydes using chiral sulfonamide ligands **504–507** (Scheme 160).¹⁸³ A Cr-**504–507** complex gen-

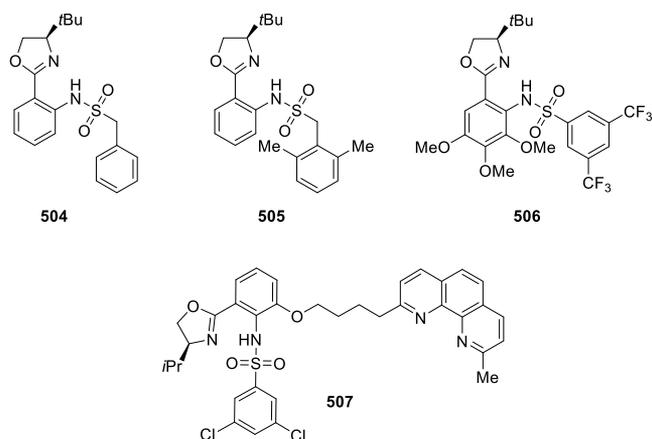
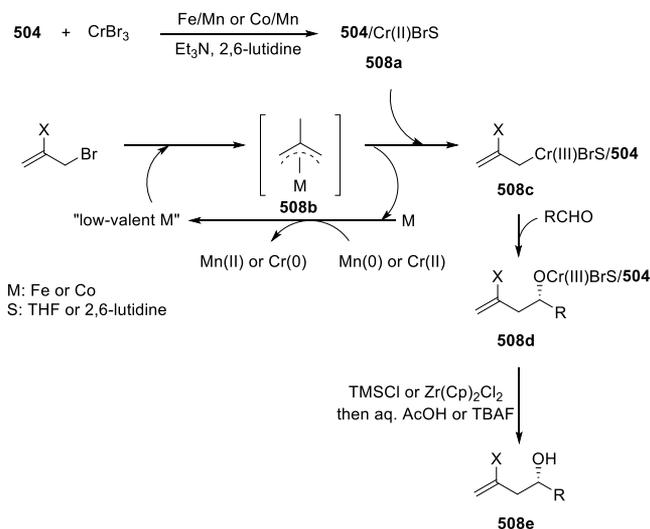


Figure 12. Chiral sulfonamide ligands.

Scheme 160. Proposed Mechanism for Cr-Catalyzed Allylation of Aldehydes

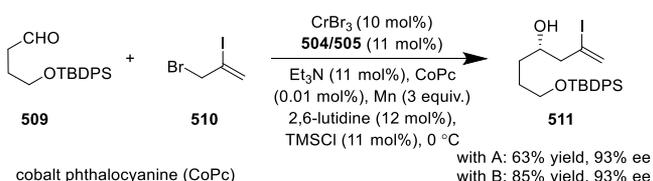


erated from a sulfonamide **504**–**507** and $\text{CrCl}_3/\text{CrBr}_3$ in the presence of Et_3N and Mn as a reducing agent of Cr and TMSCl or $\text{Zr}(\text{Cp})_2\text{Cl}_2$ as a Cr alkoxide dissociating reagent. TMSCl and $\text{Zr}(\text{Cp})_2\text{Cl}_2$ reagents upon hydrolysis breaks complex **508d** to alcohol **508e**. Interestingly, the addition of 2,6-lutidine was found to improve asymmetric inductions significantly by acting as an acid scavenger. Low valent Co phthalocyanine (CoPc) or $\text{Fe}(\text{TMHD})_3$ (iron tris(2,2,6,6-tetramethyl-3,5-heptanedione)) were used as an activator since they facilitate radical formation from allyl halides. The proposed mechanism for the Cr-catalyzed allylation of aldehydes is depicted in Scheme 160. The initial reaction between Cr(III) and chiral sulfonamide **504** in the presence of Et_3N , 2,6-lutidine, Co/Fe and Mn generates Cr(II)-complex **508a**. Metalloallyl species (**508b**), formed from the allyl bromide and Co/Fe, undergoes transmetalation with Cr(II)-complex (**508a**) to generate the Cr(III)-allyl complex **508c**. This complex would undergo the addition to aldehydes through a six-membered transition state to form complex **508d** which further reacts with TMSCl or $\text{Zr}(\text{Cp})_2\text{Cl}_2$ to form the alcohol product **508e**.

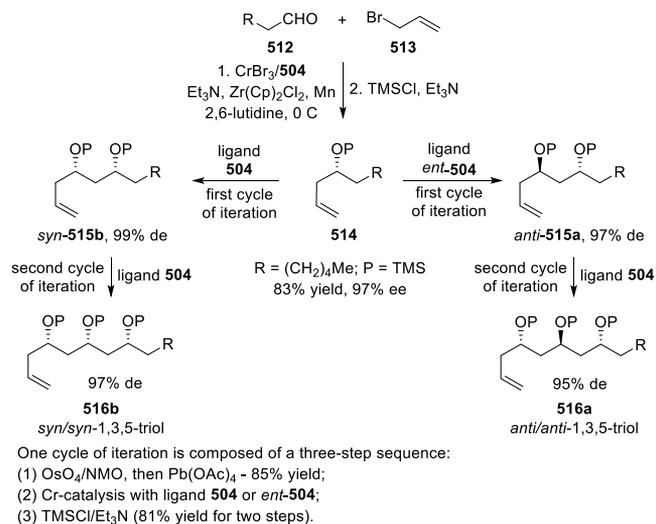
The Cr-complex of ligand **504/505** was applied in the synthesis of chiral alcohol **511** (93% *ee*), a key building block in the halichondrin (a polyether macrolide) synthesis (Scheme 161).¹⁸⁴ Ligand **505** exhibited exceptional crystallinity compared to ligand **504** and therefore it was easier to recover when used on a large scale reaction.

Furthermore, iterative use of Cr(III)/**504**-catalyzed asymmetric allylation of aldehyde **512** provided an easy access to stereocontrolled 1,3-polyols, *syn/syn*- and *anti/anti*-1,3,5-triols (**516a–b**) (Scheme 162).¹⁸⁵ One iteration cycle is composed of a three-step sequence: (i) oxidative cleavage of the olefin to

Scheme 161. Synthesis of Chiral Alcohol 511



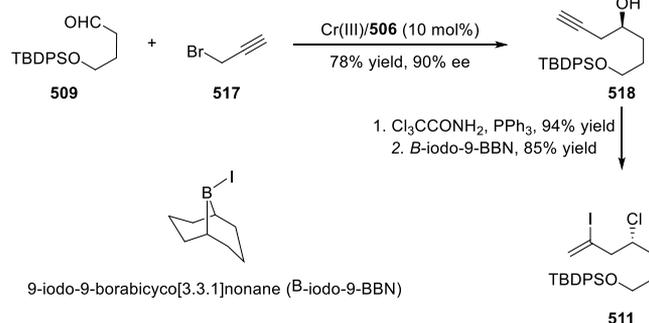
Scheme 162. Iterative Asymmetric Allylation



form an aldehyde; (ii) catalytic asymmetric allylation; and (iii) protection of the resultant alcohol.

In 2009, an asymmetric propargylation of aldehydes was developed by using Cr(III) bromide and (*R*)-sulfonamide **506** (Scheme 163).¹⁸⁶ An optically pure homopropargyl alcohol **518** was obtained in 78% yield with 90% *ee*. Alcohol **518** was further converted to **511**, a building block of halichondrin and E7389.

Scheme 163. Asymmetric Propargylation of Aldehyde

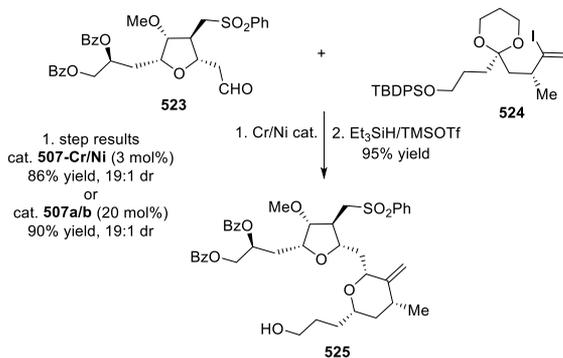
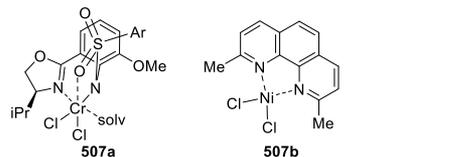
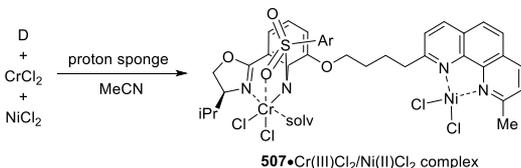
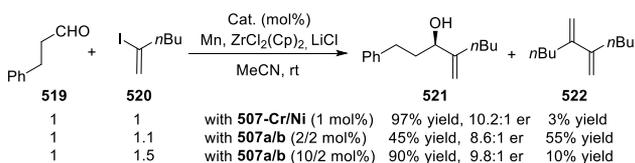


Cr catalysts derived from different chiral sulfonamides were effectively utilized by Kishi to couple various aldehydes with allyl and vinyl halides to construct diverse C–C bonds during their halichondrin synthesis.^{187–189}

In 2009, Kishi designed tethered ligand **507** which then was used to prepare heterobimetallic catalysts with Cr and Ni coordinated to the sulfonamide and phenanthroline moieties, respectively. The Ni/Cr heterobimetallic catalysts performed exceptionally well in the catalytic asymmetric vinylation of aldehydes (**519**) (Scheme 164).¹⁹⁰ The catalyst highlights include low catalytic loading (1 mol%), the formation of a negligible amount of dimer **522**, a byproduct formed through the alkenyl Ni species, use of a 1:1 molar ratio of coupling partners aldehyde **519** and vinyl iodide **520**, the asymmetric induction was similar to that obtained in the coupling with the Cr/**507a** and Ni/**507b**.

The application of this new catalyst was again demonstrated in C–C bond-forming reactions from the synthesis of halichondrin/E7389. The coupling between polyfunctional

Scheme 164. Asymmetric Vinylation of Aldehydes



aldehyde **523** (1.0 equiv) and vinyl iodide **524** (1.2 equiv) in the presence of Cr/Ni catalyst **507** (3 mol%) furnished the desired allylic alcohol in 86% yield with a 19:1 dr whereas the Cr-**507a**/Ni-**507b** catalyst (20 mol%) delivered allylic alcohol **525** in 90% yield with a 19:1 dr.

Overall, chiral monooxazoline sulfonamide ligands have found major success in Cr- and Ni-catalyzed allylation, vinylation, and propargylation of aldehydes. The major challenge remains the extension of this methodology to ketones.

2.5.2. Tridentate Mono(oxazoline) Ligands. This section summarizes the progress made in the design and application of tridentate mono(oxazoline) ligands in metal-catalyzed asymmetric catalysis.

A variety of tridentate iminopyridine oxazoline (IPO) ligands (**526**) (Figure 13) have been applied in asymmetric catalytic transformations.

Huang described the synthesis of novel IPO ligands **526a–c** and applied them in the asymmetric Co-catalyzed hydroboration of 1,1-disubstituted aryl alkenes **527**. Following optimization, a range of alkenes **527** were successfully

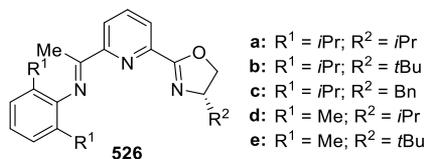
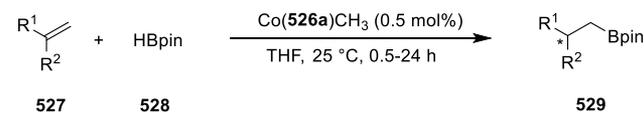


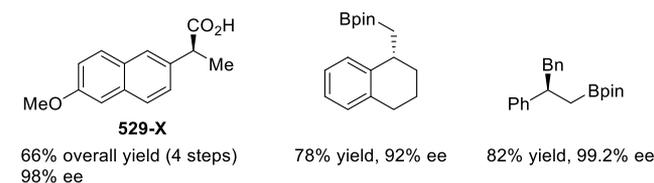
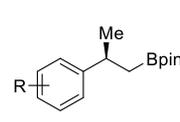
Figure 13. Tridentate iminopyridine oxazoline (IPO) ligands.

subjected to the hydroboration catalyzed by the Co(**526a**)CH₃ complex to give the enantioenriched products **529** in high yields up to 98% and with excellent enantioselectivities up to 99.5% ee (Scheme 165). This methodology was applied to the enantioselective synthesis of Naproxen **529-X** in four synthetic steps, in 66% overall yield and with 98% ee.¹⁹¹

Scheme 165. Asymmetric Co-Catalyzed Hydroboration of 1,1-Disubstituted Aryl Alkenes

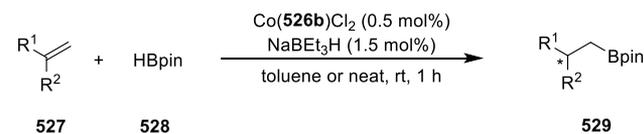


Representative examples

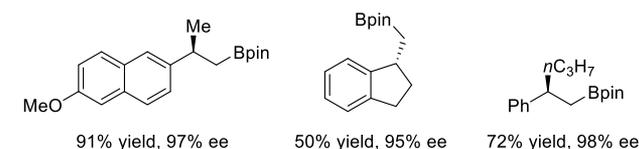
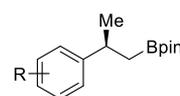


Lu independently reported the application of the same IPO ligands in a very similar Co-catalyzed hydroboration of 1,1-disubstituted aryl alkenes **527** (Scheme 166). In this case, the

Scheme 166. Hydroboration of 1,1-Disubstituted Aryl Alkenes



Representative examples

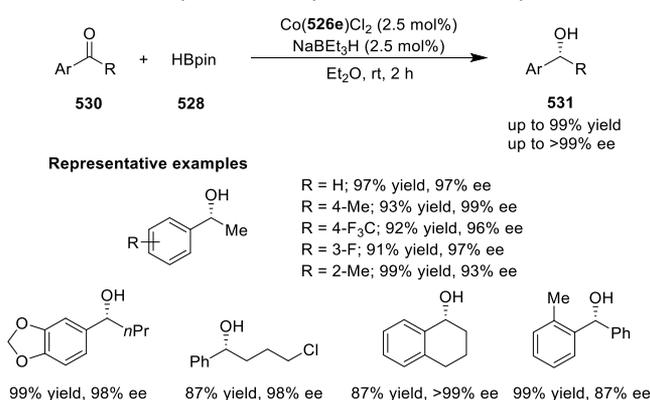


optimized conditions for the hydroboration utilized Co(**526b**)Cl₂ as the catalyst to give the enantioenriched products **529** in up to 96% yield and with up to 99% ee, with very similar results to Huang. Interestingly, this catalyst was tested by Huang to give the model product in 91% ee, compared to Lu's 98% ee. Both groups used similar reaction conditions during their optimization studies (including the addition of NaBEt₃H); however, Lu's reaction conditions were much more concentrated (5.0 M in toluene, or neat) than Huang's (0.25 M in THF), leading to different levels of enantioselectivity. Huang excluded NaBEt₃H from the reaction mixture and used the Co-CH₃ complex (in place of the CoCl₂ complex) as the catalyst in their final optimized reaction

conditions.¹⁹² Lu subsequently described a Bn-IPO Fe(**526c**)-Cl₂-catalyzed hydroboration of 1,1-disubstituted alkenes with very similar results, giving the enantioenriched products in up to 97% *ee*.¹⁹³

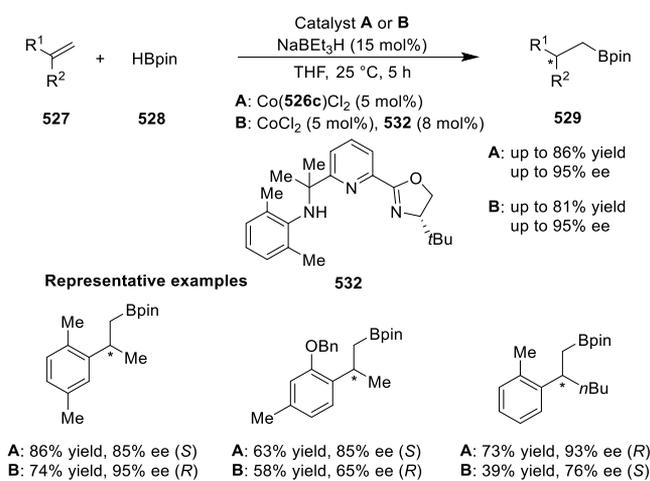
Lu has also applied IPO ligands in the Co(**526e**)-Cl₂-catalyzed hydroboration of aryl ketones **530** to give the enantioenriched alcohols **531** in moderate to high yields up to 99% and with excellent enantioselectivities up to >99% *ee* (Scheme 167). The reaction also works with the IPO-FeCl₂ complexes, but with lower levels of enantioselectivity.¹⁹⁴

Scheme 167. Asymmetric Hydroboration of Aryl Ketones



Lu has further expanded on the Co-catalyzed asymmetric hydroboration of 1,1-disubstituted aryl alkenes **527**, reporting a dual stereocontrolled reaction to give access to both enantiomers of the products **529**. Utilizing Bn-IPO ligand **526c**, the enantioenriched products **529** were accessed in up to 86% yield and with up to 95% *ee* (Scheme 168). Under the

Scheme 168. Asymmetric Hydroboration of 1,1-Disubstituted Aryl Alkenes

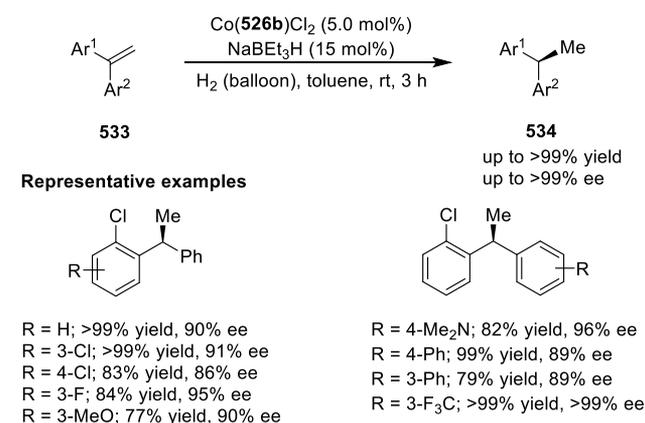


same reaction conditions, but with novel aminopyridine oxazoline (APO) ligand **532** (8 mol%) and CoCl₂ (5 mol%) as the catalytic system, the opposite enantiomers of the products **529** were obtained in up to 81% yield and with up to 95% *ee*. While the IPO system gave higher yields across the board, both the IPO and APO systems gave better levels of enantioselectivity with different substrates. Preliminary deuterium labeling experiments suggested that the reaction with the IPO ligand operated under a different mechanism than the

APO ligand, and this could explain the stereochemical outcomes of the two reactions.¹⁹⁵

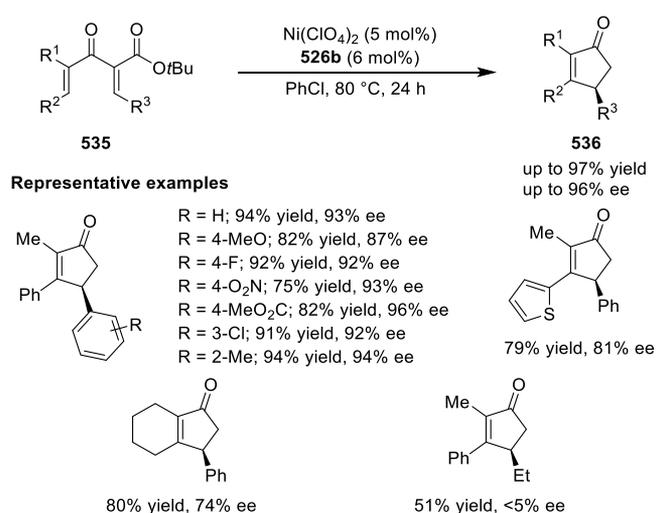
Co(**526b**)-Cl₂ has also been used by Lu in the asymmetric hydrogenation of 1,1-diarylethenes **533**. A range of enantioenriched diarylethane derivatives **534** were accessed in up to >99% yield and with up to >99% *ee* (Scheme 169). In all examples, one of the two aryl groups of the substrates **533** had an *ortho*-substituent.¹⁹⁶

Scheme 169. Asymmetric Hydrogenation of 1,1-Diarylethenes



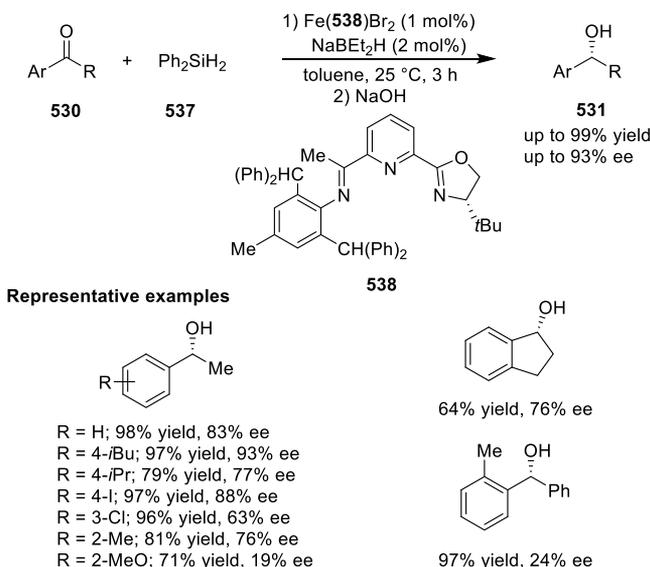
Lu has also reported a sequential Ni-catalyzed asymmetric Nazarov cyclization/decarboxylation of divinylketones **535** bearing a *t*Bu-ester group to give enantioenriched cyclopentanones **536** in up to 97% yield and with up to 96% *ee* (Scheme 170). The reaction tolerated a range of electronically and sterically different aryl groups at R² and R³, although aliphatic groups at R³ were not tolerated.¹⁹⁷

Scheme 170. Ni-Catalyzed Asymmetric Nazarov Cyclization/Decarboxylation



Huang has reported a highly hindered IPO ligand **538** for use in the Fe-catalyzed hydrosilylation of aryl ketones **530** (Scheme 171). The hindered Fe(**538**)-Br₂ catalyst showed high activity for accessing a range of chiral secondary alcohols **531** in up to 99% yield and with moderate to high enantioselectivities up to 93% *ee*.¹⁹⁸

Scheme 171. Fe-Catalyzed Hydrosilylation of Aryl Ketones



Lu later described derivatives of IPO ligands **538**, **539a**, and **539b** (Figure 14), for the Co- and Fe-catalyzed hydrosilylation of alkenes, respectively.

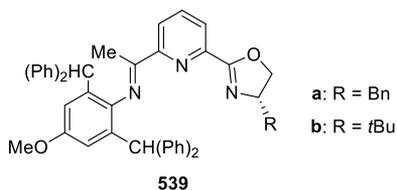


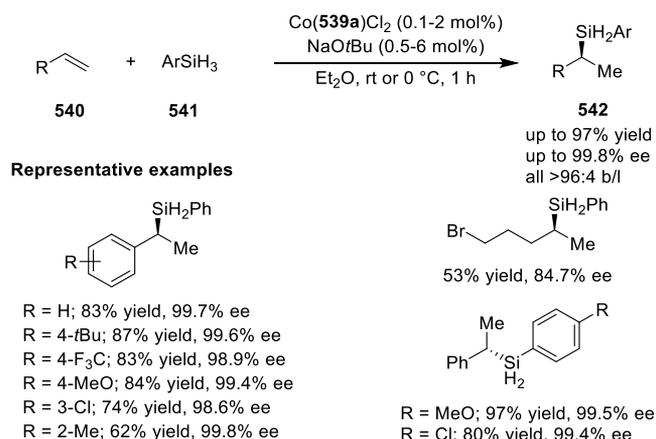
Figure 14. IPO ligands **539a**–**b**.

First, Lu developed the Co-catalyzed hydrosilylation of alkenes with phenylsilane **541**. During optimization, they found that the sterically hindered ligand **539a** performed better than the less hindered ligands **526a** and **526d**, giving the model product in 98.5% ee under those conditions, compared to 72% ee (**526a**) and 88% ee (**526d**). Under optimized conditions with Bn-IPO **539a** as the chiral ligand, a range of silylated products **542** were synthesized in up to 97% yield, with >96:4 b/l and with excellent levels of enantioselectivities up to 99.8% ee (Scheme 172). Styrenes were hydrosilylated with excellent levels of enantioselectivity while aliphatic alkenes gave <88% ee.¹⁹⁹

Lu subsequently developed the Fe(**539b**)Cl₂-catalyzed hydrosilylation of aliphatic alkenes **540** under similar reaction conditions to the previous Co-catalyzed report (ligand **539a** was not reported). A range of silylated products were isolated in up to 97% yield, with >96:4 b/l and with excellent levels of enantioselectivities up to 99.8% ee (Scheme 173). These reports offer complementary systems, with the same family of chiral ligands, for the enantioselective hydrosilylation of styrenes and aliphatic alkenes in similarly high stereoselectivities.²⁰⁰

Other unsymmetrical tridentate pyridine-oxazoline-containing ligands have been applied in asymmetric catalytic transformations. Yu has described the design of C₁-symmetric benzimidazole-pyridyl oxazoline ligands **543a** and **543b** (Figure 15).

Scheme 172. Co-Catalyzed Hydrosilylation of Alkenes with Phenylsilane



Scheme 173. Fe-Catalyzed Hydrosilylation of Aliphatic Alkenes

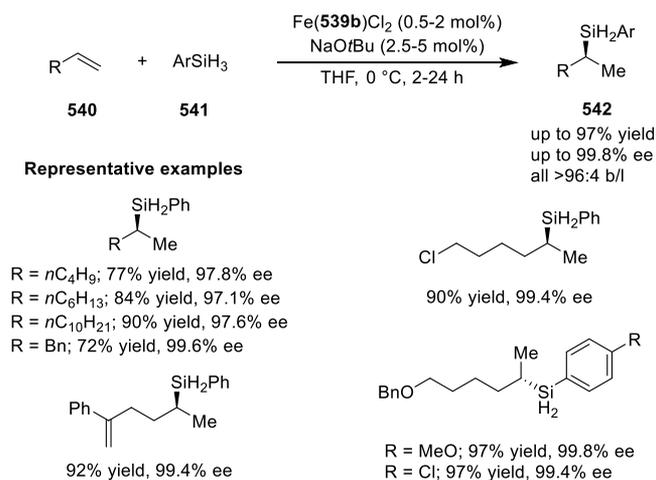


Figure 15. C₁-symmetric benzimidazole-pyridyl oxazoline ligands.

Yu observed that the Ru-complex Ru(**543b**)(PPh₃)Cl₂ was a highly active catalyst for the asymmetric transfer hydrogenation of ketones **544**, giving the corresponding chiral alcohols in up to >99% yield and with up to 97% ee (Scheme 174).²⁰¹

Wang and Shi have reported the synthesis of novel Schiff base oxazoline-containing ligands **546**–**548** (Figure 16) and their applications in the asymmetric α -chlorination of β -keto esters. The denticity of the ligands was not determined, but the *ortho*-hydroxy groups were observed to be essential for generating products with appreciable levels of enantioselectivity.

The results of a screen of ligands **546**–**548** in the enantioselective Cu-catalyzed α -chlorination of β -keto ester **549** are summarized in Table 3. The reaction with bulkier *i*Pr-oxazoline ligand **546**, which bears no substitution on the *ortho*-phenol, gave the chlorinated product **550** with only 47% ee (entry 1). The reaction with Ph-oxazoline *ortho*-naphthol **547**

Scheme 174. Asymmetric Transfer Hydrogenation of Ketones

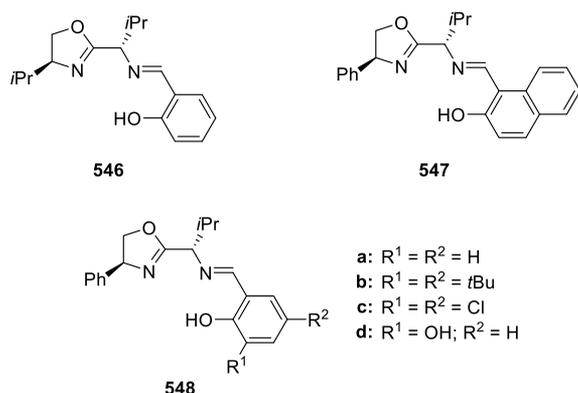
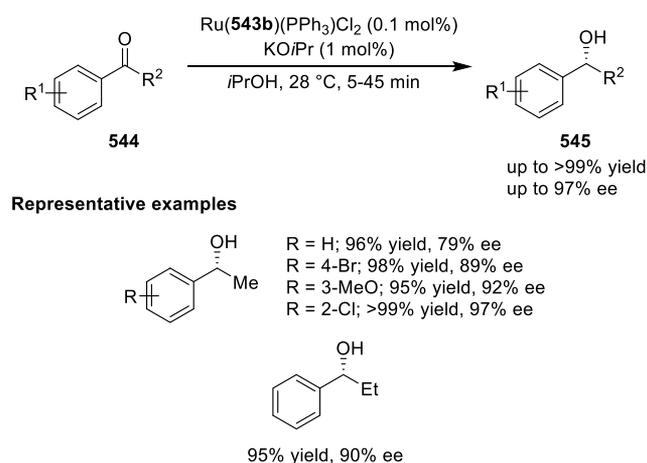
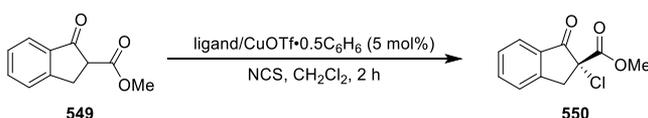


Figure 16. Novel Schiff base oxazoline-containing ligands.

Table 3. Enantioselective Cu-Catalyzed α -Chlorination of β -Keto Ester



entry	ligand	temp (°C)	yield (%)	% ee
1	546	rt	99	47
2	547	rt	99	78
3	548a	rt	99	78
4	548b	rt	95	50
5	548c	rt	99	54
6	548d	rt	99	68
7	548a	0	99	83
8	548a	-20	99	72
9	548a	-78	99	6

gave **550** in 99% yield and with a much improved 78% ee. A screen of other Ph-oxazoline ligands **548a–d** showed that ligand **548a**, with no substitution on the *ortho*-phenol, gave **550** in 99% yield and with 78% ee (entries 3–6). A temperature screen was conducted in the reaction with ligand **548a** (entries 7–9). The reaction conducted at 0 °C gave **550** with the highest level of enantioselectivity of 83% ee (entry 7).²⁰²

2.5.3. Mono(oxazoline) Carbene Ligands. In the past decade, limited progress has been made in the design and

application of mixed oxazoline-carbene ligands in asymmetric catalysis.

Burgess has applied the Ir-complex **551** (Figure 17) in the asymmetric catalytic hydrogenation of vinyl ethers.

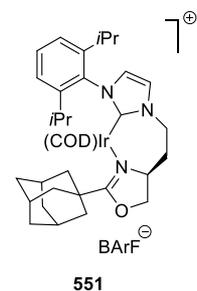
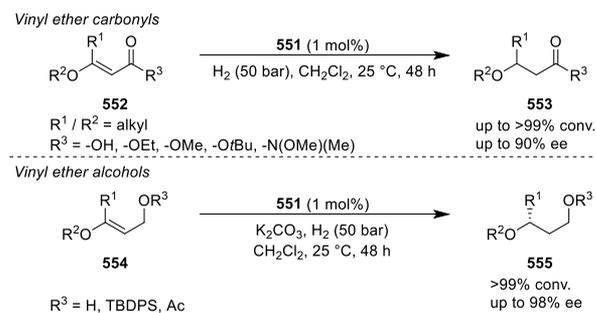


Figure 17. Mixed oxazoline-carbene ligands.

Under optimized conditions, vinyl ether esters **552** were successfully hydrogenated, under 50 bar of H₂, to give the corresponding chiral esters **553** with up to >99% conversion and with mostly moderate to good enantioselectivities of up to 90% ee (Scheme 175). Ir-complex **551** was then applied in the

Scheme 175. Asymmetric Hydrogenation of Vinyl Ether Alcohols



asymmetric hydrogenation of vinyl ether alcohols with better results, under slightly altered reaction conditions. The chiral alcohols **555** were formed with >99% conversion and with very high enantioselectivities of up to 98% ee.²⁰³

Ito and Nishiyama reported a set of mixed carbene-oxazoline Rh- and Ru-complexes **556–559** (Figure 18), which are analogous to PheBOX complexes (covered in section 2.5.4). The applications of the Rh-complexes in asymmetric conjugate reduction and the Ru-complexes in the asymmetric catalytic hydrogenation and asymmetric transfer hydrogenation of ketones, led to low or moderate enantioselectivities of the isolated products in all cases.

For example, the asymmetric transfer hydrogenation of 9-acetylanthracene was conducted with **558a–c** and **559b** as the catalysts (Table 4). Interestingly, the reactions with Ru-catalysts **558a**, **558b**, and **559b** selectively formed secondary alcohols **561a** and **561b** in which the ketone and part of the anthracene ring are reduced (entries 1–3). The reaction with **559b** gave the alcohol **561a** with the highest stereoselectivity of 60% ee. Achiral Ru-catalyst **558c** gave remarkable selectivity in the formation of **561a**. These results suggest that further development of these mixed-carbene-oxazoline systems could be useful for the selective reduction of extended aromatic-ring-systems.²⁰⁴

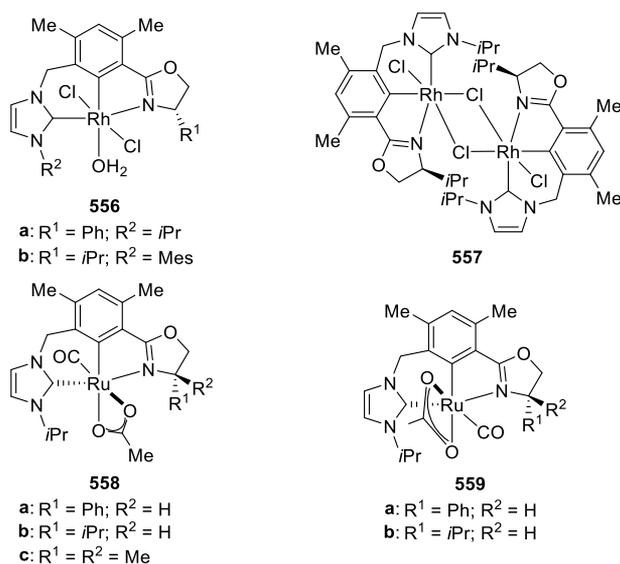
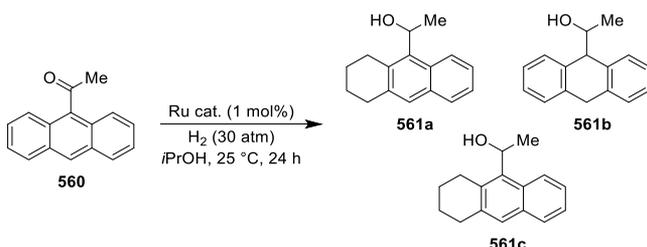


Figure 18. Mixed carbene-oxazoline Rh- and Ru-complexes.

Table 4. Asymmetric Transfer Hydrogenation of 9-Acetylanthracene



entry	cat	yield (%)	561a/b/c	% ee (561a)	% ee (561b)
1	558a	99	60:40:0	9 (R)	18 (R)
2	558b	99	51:49:0	31 (R)	5 (R)
3	559b	97	60:40:0	60 (R)	28 (R)
4	558c	90	93:<1:7		

Wang and Shi have applied Pd-complex **562** (Figure 19), bearing an axially chiral mixed carbene-oxazoline ligand, in an asymmetric allylic arylation for the kinetic resolution of Morita-Baylis-Hillman (MBH) adducts **563**.

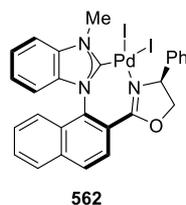
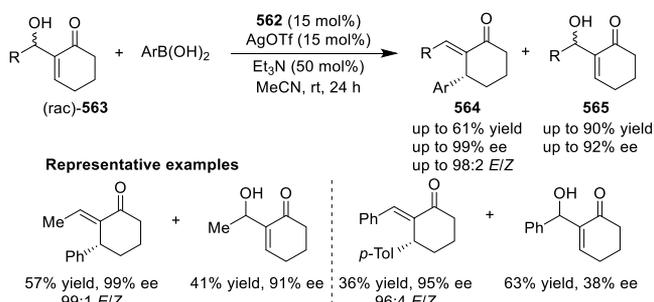


Figure 19. Axially chiral mixed carbene-oxazoline ligand.

Reacting racemic MBH adducts **563** with aryl boronic acids in the presence of **562**, the corresponding arylated products **564** were isolated in up to 61% yield, with up to 99:1 *E/Z* selectivity and >99% *ee* (Scheme 176). The enantioenriched alcohols **565** were recovered in up to 37% yield and with the best enantioselectivity of 92% *ee*. This process is clearly a better method for synthesizing the arylated products **564** enantioselectively than it is for resolving the MBH adducts **563**.²⁰⁵

Scheme 176. Kinetic Resolution of Morita–Baylis–Hillman (MBH) Adducts



Ma and Jiang have independently developed novel planar chiral mixed carbene-oxazoline ligands for use in asymmetric catalysis (Figure 20). Jiang has reported the ferrocene-based

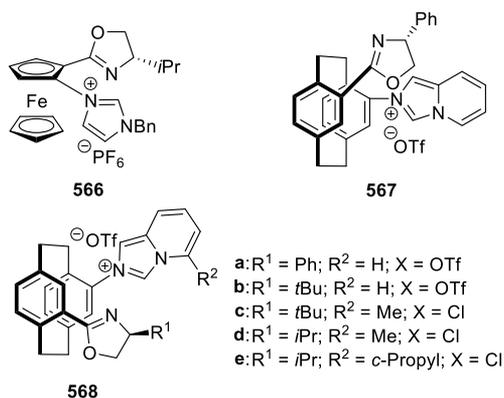


Figure 20. Novel planar chiral mixed carbene-oxazoline ligands.

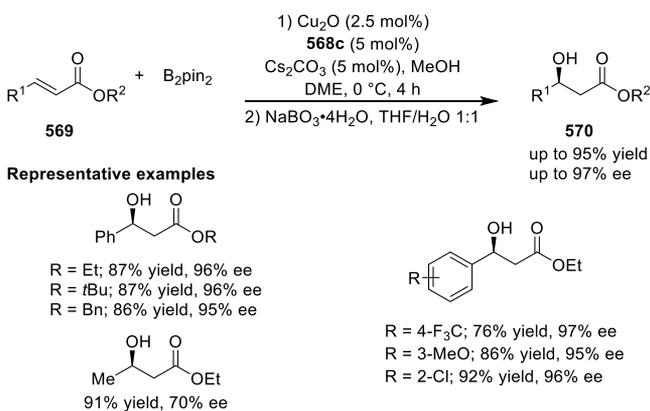
ligand precursor **566**, while Ma has reported the cyclophane-based ligand precursors like **567** and **568**. Jiang has applied the Rh^I(**566**)(cod) complex in the asymmetric hydrosilylation of ketones, obtaining only low to moderate enantioselectivities of 39–56% *ee*.²⁰⁶

In Ma's initial report, the cyclophane-containing ligands were applied in the Cu-catalyzed conjugate borylation of α,β -unsaturated ketones, with the products isolated with up to 84% *ee* when ligand precursor *t*Bu-**568b** was used.²⁰⁷ The pseudo-*ortho*-cyclophanes **568** generally perform better than the pseudo-*geminal*-cyclophanes, like **567** in Ma's reports. Ma extended the substrates from α,β -unsaturated ketones to α,β -unsaturated esters in the conjugate borylation of **569**. Under optimized conditions, a range of esters **569** were borylated with B₂pin₂, utilizing Cu₂O/*t*Bu-**568c** as the catalytic system, followed by treatment with sodium perborate, to yield the corresponding chiral alcohols **570**. The enantioenriched products **570** were generated in up to 95% yield and with high enantioselectivities up to 97% *ee* (almost all examples >90% *ee*) (Scheme 177).²⁰⁸

Ma has also developed a Cu₂O/*i*Pr-**568d**-catalyzed 1,2-silylation of *N*-tosylaldimines **571**, generating the silylated amines **573** in up to 98% yield and with excellent enantioselectivities of up to 97% *ee* (Scheme 178).²⁰⁹

2.5.4. Ruthenium(II)/Phenylloxazoline (Ru(II)-Pheox). Iwasaa designed and synthesized novel chiral Ru(II)/phenylloxazoline (Ru(II)-Pheox) complexes (Figure 21).²¹⁰ This catalyst system showed excellent reactivity and enantioselectivity in inter- and intramolecular cyclopropanation reactions.

Scheme 177. Cu-Catalyzed Conjugate Borylation of α,β -Unsaturated Esters



Scheme 178. 1,2-Silylation of *N*-Tosylaldimines

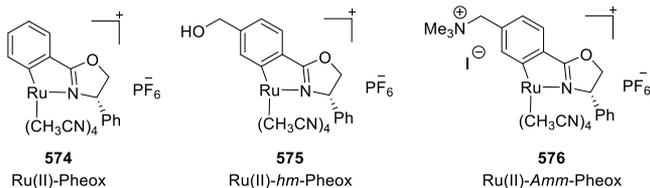
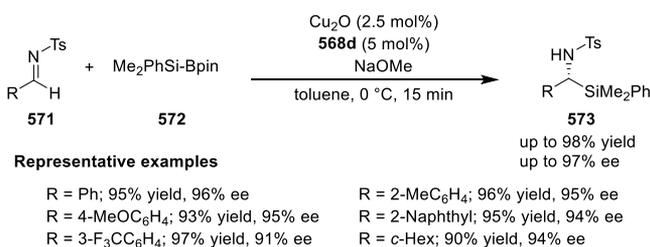
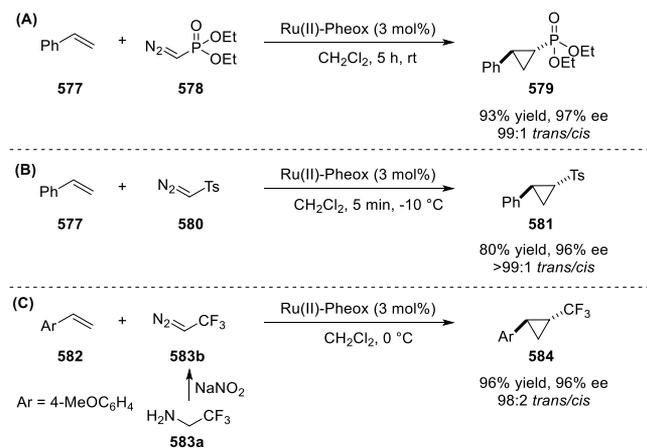


Figure 21. Chiral Ru(II)/phenyloxazoline (Ru(II)-Pheox) complexes.

Iwasaa employed Ru(II)-Pheox complex (**574**) for the highly stereoselective cyclopropanation of alkenes (**577**) with various diazo precursors (**578/580/583a**) (Scheme 179A–C).^{211–213} The asymmetric cyclopropanation between diethyl diazomethylphosphonate (**578**) and a series of alkenes including styrene derivatives, α,β -unsaturated esters, ketones,

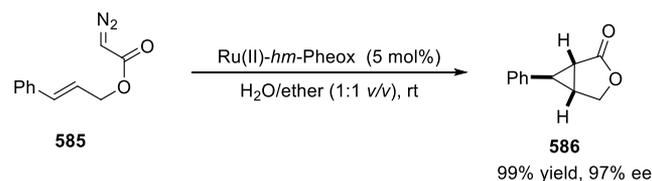
Scheme 179. Highly Stereoselective Cyclopropanation of Alkenes with Various Diazo Precursors



and amides was carried out to provide the corresponding cyclopropylphosphonate products (**579**) in high yields and with excellent diastereoselectivity (up to 99:1 dr) and enantioselectivity (up to 97% ee) (Scheme 179A).²¹¹ Similarly, diazosulfones (**580**) reacted with various alkenes including vinyl ethers, vinyl amines, and vinyl carbamates to furnish chiral cyclopropyl sulfones (**581**) in high yields (up to 80%) with excellent *trans*-selectivity and enantioselectivity (up to 96% ee) (Scheme 179B).²¹² An asymmetric synthesis of various trifluoromethyl cyclopropanes (**584**) was achieved in high yields with excellent diastereoselectivity (up to 98:2 dr) and enantioselectivity (up to 96% ee) by reacting *in situ* generated CF₃CHN₂ (**583b**) with a range of alkenes including vinyl ferrocene, vinyl ethers, vinyl amines, vinyl carbamates, and dienes (Scheme 179 C).²¹³

In 2012, Iwasaa described the highly enantioselective intramolecular cyclopropanation of *trans*-allylic diazoacetates (**585**) and alkenyl diazoketones using a water-soluble Ru(II)/hydroxymethyl (phenyl)oxazoline catalyst, Ru(II)-*hm*-Pheox (**575**) (Scheme 180).²¹⁴ The polar protic functionality of the

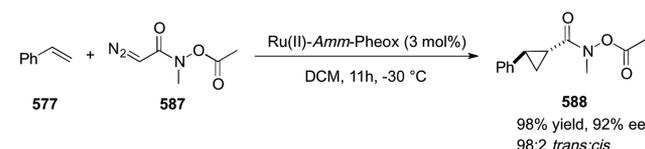
Scheme 180. Enantioselective Intramolecular Cyclopropanation



Ru catalyst was vital to give rise to high yields, due to its ability to form strong hydrogen bonds with water. The catalyst could be reused at least five times without substantial decline in reactivity or enantioselectivity.

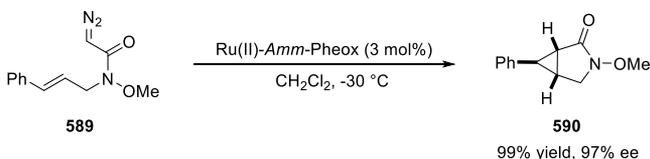
Later in 2016, chiral Ru(II)-*Amm*-Pheox complex (**576**) containing an internal quaternary ammonium unit was first employed in the stereoselective intermolecular cyclopropanation of diazo Weinreb amides (**587**) with alkenes (**577**) to furnish the corresponding chiral cyclopropyl Weinreb amides (**588**) in high yields (up to 98%) with excellent diastereoselectivities (up to 98:2 dr) and enantioselectivities (up to 92% ee) (Scheme 181).²¹⁵ Additionally, the use of acetoxy-functionalized diazoacetamide (AMD) as the carbene source was found to be crucial for the high *trans*-selectivity of the cyclopropanation.

Scheme 181. Enantioselective Intermolecular Cyclopropanation of Alkenes with Diazo Weinreb Amides



In subsequent studies, the intramolecular stereoselective cyclopropanation of a series of *trans*-allylic diazo Weinreb amide derivatives (**589**) was developed using the chiral Ru(II)-*Amm*-Pheox catalyst (**576**) to afford the corresponding chiral bicyclic cyclopropyl products (**590**) in excellent yields (up to 99%) with excellent enantioselectivity (up to 97% ee) (Scheme 182).²¹⁶

Scheme 182. Enantioselective Intramolecular Cyclopropanation of *trans*-Allylic Diazo Weinreb Amide Derivatives



Overall, chiral Ru(II)-Pheox complexes have found their applications in inter and intramolecular asymmetric cyclopropanation reactions between various alkenes with diazo derivatives.

2.5.5. Cobalt Oxazoline Palladacycle (COP). The enantioselective chiral cobalt oxazoline palladacycle (COP) catalyst (**591/592**) (Figure 22) was first reported by Richards

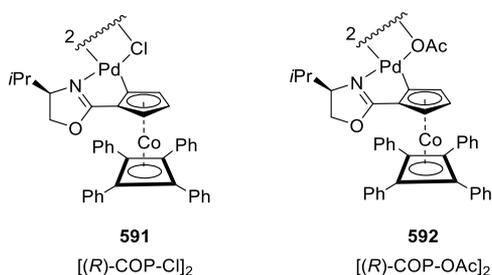
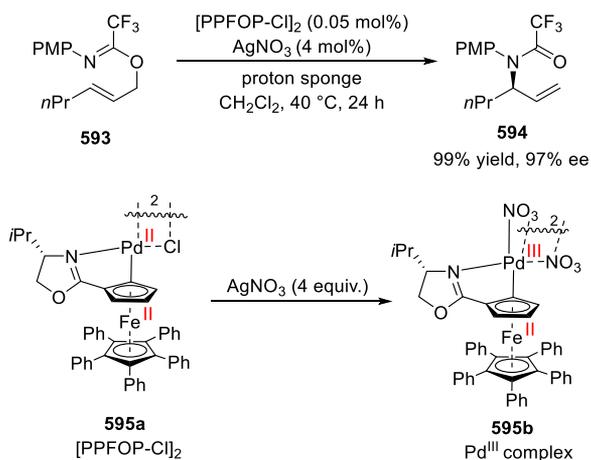


Figure 22. COP catalysts.

and Overman in 2003 for the enantioselective rearrangement of allylic *N*-arylimidates.²¹⁷ A detailed review on Pd(II)-catalyzed enantioselective reactions using the COP catalyst was published by Overman in 2016.²¹⁸

2.5.6. Pentaphenylferrocene Oxazoline Palladacycle [PPFOP]. Peters reported^{219,220} the novel Pd(III)-catalyst (**595b**) for the asymmetric rearrangement of allylic trifluoroacetimidates (**593**) (Scheme 183). Various spectroscopic and electrochemical methods demonstrated that the Pd-catalyst (**595b**) unexpectedly had an activated oxidized form of a Pd(III) center bound to a ferrocene core which remained unchanged (Fe(II)) during the oxidative addition. The dimeric paramagnetic ferrocene-derived palladacycle (**595b**) contains

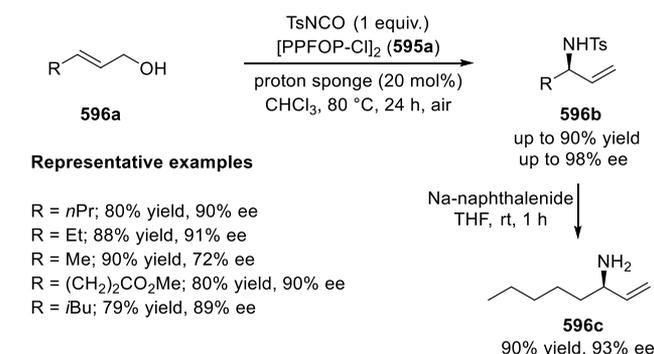
Scheme 183. Novel Pd(III)-Catalyst for Asymmetric Rearrangement of Allylic Trifluoroacetimidates



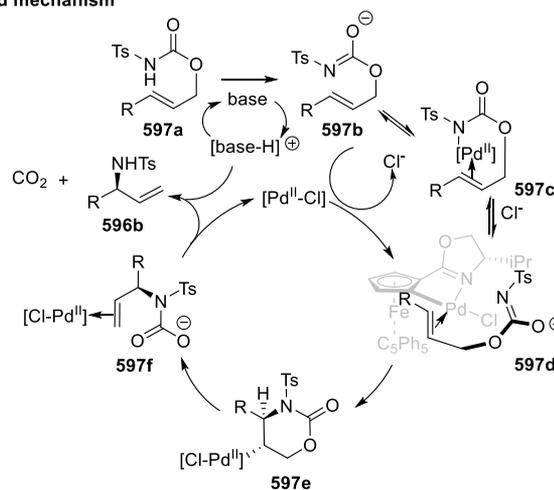
two Pd(III) centers without involving a Pd–Pd bond. The Pd(III)-catalyst was formed by activating the diamagnetic dimeric chloride-bridged pentaphenylferrocene oxazoline palladacycle precatalyst, [PPFOP-Cl]₂ (**595a**), by treatment with AgNO₃ (4 equiv). Two equivalents of the AgNO₃ were required for a Cl-counterion exchange while another 2 equiv oxidized the complex to deliver the dark red-brown paramagnetic species (**595b**). Pd-complex (**595b**) was found to be the most efficient enantioselective catalyst for the rearrangement of allylic trifluoroacetimidates in terms of catalyst TON, scope and enantioselectivity. Previously it was assumed that the reaction between [PPFOP-Cl]₂ and AgNO₃ resulted in the oxidation of Fe(II) to Fe(III) in a ferrocenium core which would decrease the electron density of the Pd(III) center thus generating a more Lewis acidic Pd(III) center.²¹⁹

Peters reported the regio- and enantioselective synthesis of sulfonyl-protected chiral allylic amines (**596b**) from achiral allylic alcohols (**596a**) by using a catalytic ferrocene palladacycle, [PPFOP-Cl]₂ (**595a**) and a tertiary amine (proton sponge -1,8-bis(*N,N*-dimethylamino)naphthalene) (Scheme 184).^{221,222} This reaction was highly step-economic and

Scheme 184. Regio- and Enantioselective Synthesis of Sulfonyl-Protected Chiral Allylic Amines



Proposed mechanism



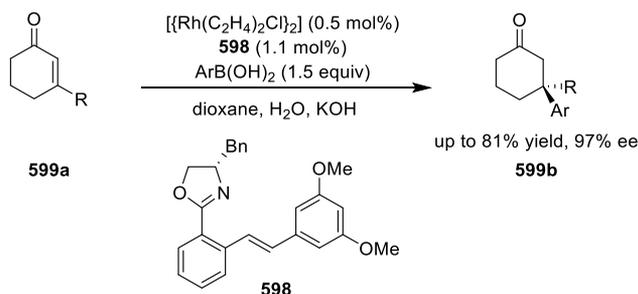
proceeded with no inert-gas atmosphere or catalyst activation by a silver salt. The preference for the branched allylic product was due to the Pd(II)-catalyzed cyclization-induced decarboxylative [3,3]-rearrangement of *in situ*-generated allylic carbamate intermediates. The allylic alcohol with an aliphatic group formed products in good to high yields and with high regio- and enantioselectivity whereas aromatic substituents were not well tolerated. The proposed mechanism of the

Pd(II)/base-catalyzed decarboxylative allylic carbamate **597a** rearrangement is shown in Scheme 184. The deprotonated carbamate **597b** reacts with ferrocene palladacycle **595a** to form a chelate complex **597c**, the resting state, in which both the olefin and the anionic carbamate moiety are coordinated to the Pd center thus replacing the anionic ligand, Cl. Further dissociation of the carbamate N-atom in complex **597c**, which might be triggered by the reversible recoordination of the anionic ligand, Cl, generates complex **597d** which subsequently undergoes outer-sphere attack of the nucleophilic deprotonated N-center to the coordinated olefin to form intermediate **597e**. The cyclic aminopalladated intermediate **597e** featuring a σ -alkyl-Pd bond undergoes a ring-opening and β -hydride elimination to form the deprotonated carbaminoic acid derivative **597f**. Decomplexation, decarboxylation, and protonation of **597f** leads to the formation of *N*-sulfonylated allylic amine **596b** and regenerates the Pd(II) and base catalysts for the next turnovers.

To conclude this section, chiral PPFOP ligands are successfully applied in the synthesis of chiral allyl amines via the asymmetric [3,3] rearrangement of allylic amides.

2.5.7. Olefin-mono(oxazoline) Ligands. In 2010, Glorius developed the η^2 -binding ligand OlefOx **598** and applied it in the conjugate addition of aryl boronic acids to cyclohexanones **599a** (Scheme 185). The ligand **598** had a

Scheme 185. Rhodium Catalyzed Conjugate Addition of Phenylboronic Acids to Cyclohexanones



modular synthesis which allowed for fine-tuning of its structure, furnishing the substituted cyclohexanone product **599b** in up to 97% ee and 81% yield. It was thought that the η^2 -binding mode allowed for alternative coordination geometries to traditional η^1 -oxazoline ligand motifs.²²³

3. BIS(OXAZOLINE) LIGANDS

3.1. Bis(oxazoline) Ligands with One Carbon Separating the Oxazoline Rings

3.1.1. Parent Bis(oxazoline) Ligands with One Carbon Separating the Oxazoline Rings. For C_2 -symmetric bis(oxazoline) ligands, only examples reported after 2010 will be described in this section. For applications of these ligands prior to 2010, see the 2011 review by Desimoni and Jørgensen.²²⁴

Watson has applied **600a** (Figure 23) in the alkylation of benzopyranyl acetals **601** using chiral cuprates (Scheme 186). The reaction proceeded smoothly giving enantiomeric excesses of up to 95% and yields up to 90%. Regarding substrates, the enantioselectivity was enhanced to 95% ee when a methoxy was placed in the 7-position of the chromene acetal. Nonaromatic alkynes were shown to be detrimental to enantioselectivity with results dipping to 70% ee and 49% yield.²²⁵

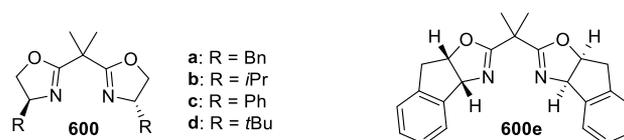
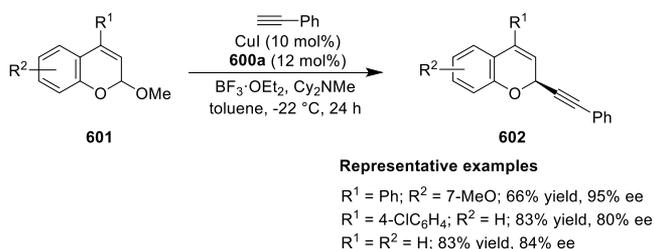


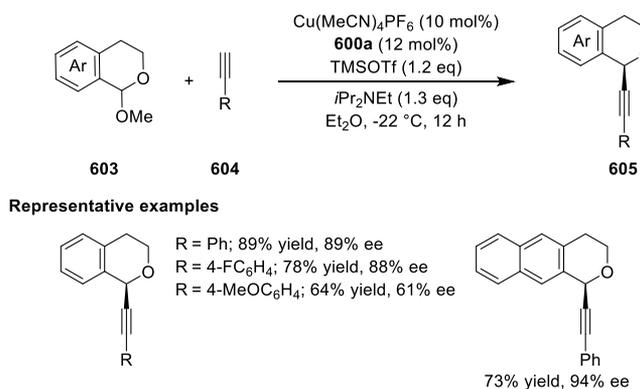
Figure 23. Parent BOX ligands.

Scheme 186. Cu-Catalyzed Asymmetric Alkylation of Benzopyranyl Acetals



Watson developed an asymmetric Cu-catalyzed addition of terminal alkynes **604** to a TMSOTf-generated oxocarbenium ion (Scheme 187). By treating isochroman acetals **603** with

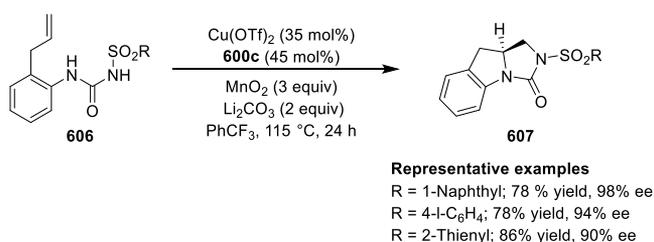
Scheme 187. Cu-Catalyzed Asymmetric Addition of Alkynes



TMSOTf, this generates an oxocarbenium ion that can be attacked by the chiral $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ -**600a** acetylene complex generating the product in up to 94% ee and good yields. It was shown that the *p*-methoxy electron-donating group on the alkyne lowered the enantioselectivity dramatically to 61% ee.²²⁶

Zeng reported the application of **600c** (Figure 23) in the Cu-catalyzed intramolecular cyclization of *N*-alkenylureas **606** (Scheme 188). It allowed for the generation of chiral vicinal diamino bicyclic heterocycles in good yields and high enantioselectivities of up to 98% ee. Substituted aryl and

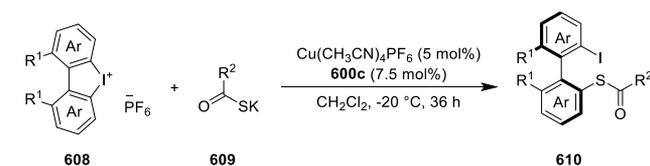
Scheme 188. Cu-Catalyzed Intramolecular Cyclization of *N*-Alkenylureas



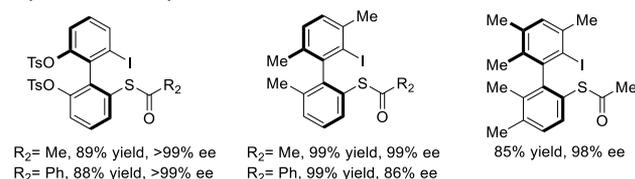
heteroaryl systems were well tolerated with this catalysis with substrates possessing 2-thienyl substituted sulfonyl groups affording the corresponding product in 90% *ee* and 86% yield.²²⁷

Gu utilized Cu complexes of ligand **600c** in the thiolative ring opening of five-membered cyclic diaryliodonium salts **608** in order to synthesize atropisomeric products and various axially chiral P,S ligands (Scheme 189). The best results were

Scheme 189. Cu-Catalyzed Ring Opening of Diaryliodonium Salts



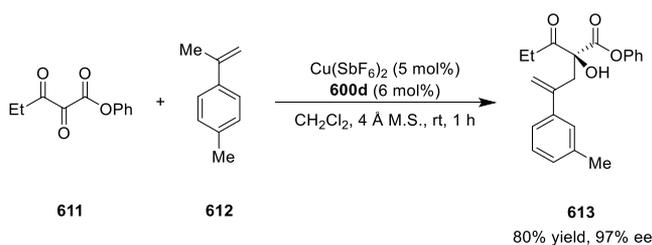
Representative examples



obtained using $\text{Cu}(\text{MeCN})_4\text{PF}_6$ as the Cu(I) source, which provided high yields and enantioselectivities up to >99% *ee*. While most substrates were tolerated, bulky aryl thioates **609** appeared to reduce the enantioselectivity to as low as 86% *ee*.²²⁸

Doyle applied ligand **600d** (Figure 23) in the enantioselective carbonyl-ene reactions of 2,3-diketo esters **611** (Scheme 190). The best results were obtained with $\text{Cu}(\text{SbF}_6)_2$ as the

Scheme 190. Enantioselective Carbonyl-Ene Reaction of 2,3-Diketo Esters

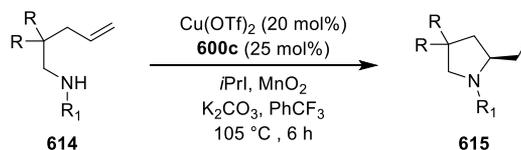


Lewis acid and loadings as little as 1 mol% which furnished yields up to 94% and enantioselectivities up to 97% *ee*. This reaction was also performed on gram-scale while maintaining high yields and excellent enantioselectivities.²²⁹

Chemler applied ligand **600c** in the Cu-catalyzed aminohalogenation/cyclization reaction of 2-allylaniline **614** (Scheme 191). Isopropyl iodide was used as the halide source providing 2-iodomethylindoline products **615** in 93% *ee* and high yields. It was also noted that mesyl-protecting groups were not tolerated in this reaction with enantioselectivities lowered to 43% *ee*.²³⁰

Reiser applied ligand **600b** (Figure 23) in the Cu-catalyzed cyclopropanation of furans **616** in moderate yields and enantioselectivities of up to 83% *ee* (Scheme 192). This protocol was subsequently applied in the synthesis of (–)-paeonilide on a 20 g scale but this methodology was

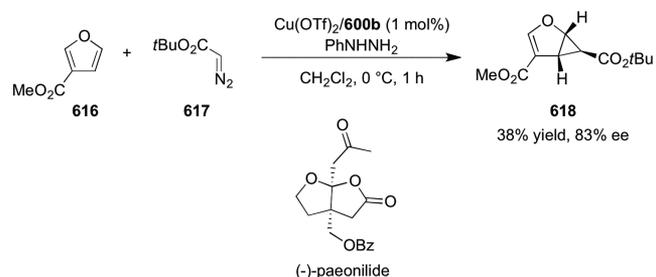
Scheme 191. Cu-Catalyzed Asymmetric Aminohalogenation



Representative examples

R = Me, R₁ = Ts, 81% yield, 88% *ee*
R = Ph, R₁ = Ts, 85% yield, 93% *ee*
R = Me, R₁ = Ms, 78% *ee*, 43% *ee*

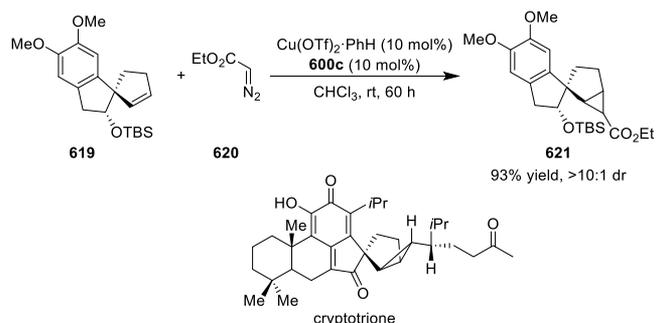
Scheme 192. Cu-Catalyzed Asymmetric Cyclopropanation of Furans



limited by the fact that a second cyclopropanation would occur if it was allowed to run to completion.²³¹

Shi also employed a similar cyclopropanation using a catalyst derived from $(\text{CuOTf})_2\cdot\text{PhH}$ and ligand **600c** achieving 93% yield and a diastereomeric ratio of >10:1 in the synthesis of Cryptotrine (Scheme 193). It was shown that slow addition of ethyl diazoacetate **620** via syringe pump was critical to obtaining the higher yields and enantioselectivities.²³²

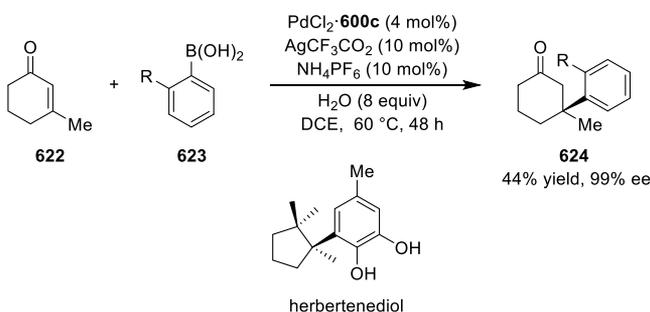
Scheme 193. Cu-Catalyzed Asymmetric Synthesis of Cryptotrine Core



Minnaard developed a Pd-catalyzed Michael addition of boronic acids to β,β -disubstituted cyclic enones **622** using chiral ligand **600c** affording products **624** with up to 99% *ee* (Scheme 194). The moderate yields were attributed to significant protodeboronation of the arylboronic acid. It was shown that larger *ortho*-substituents such as aldehydes, nitro groups, trifluoromethyl groups as well as di-*ortho* substitution were not tolerated on the aryl boronic acid **623**. The developed methodology was then applied in the enantioselective synthesis of sesquiterpenes such as herbertenediol.²³³

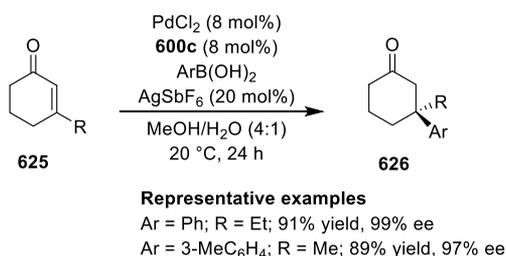
Minnaard detailed an efficient Pd-catalyzed conjugate addition of arylboronic acids to form β -substituted carbocyclic, heterocyclic and acyclic ketones. A $\text{PdCl}_2\text{-600c}$ complex provided the optimal results of up to 91% yield and 99% *ee*;

Scheme 194. Pd-Catalyzed Michael Addition and Synthesis of Herbertenediol



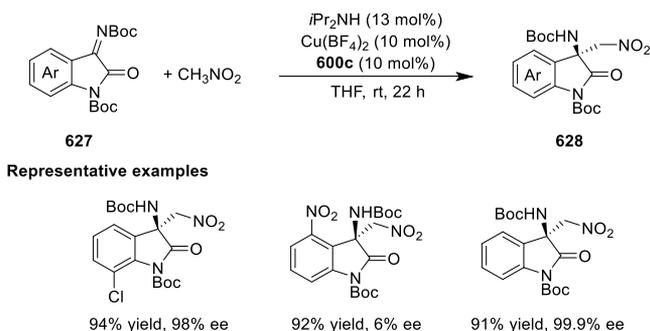
however, the use of AgBF_4 was needed to promote *in situ* dehalogenation to increase the conversion (Scheme 195). It was shown that the enantioselectivities dramatically dropped for acyclic enones with 60% *ee* being the highest reported.²³⁴

Scheme 195. Pd-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids



Pedro applied ligand **600c** in the Cu-catalyzed aza-Henry reaction with isatin *N*-Boc ketimines **627** achieving yields up to 99% and outstanding *ees* of 99.9% (Scheme 196). The reaction

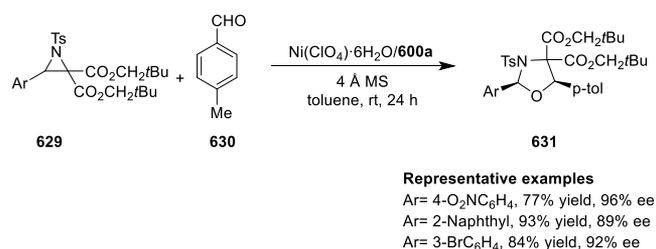
Scheme 196. Cu-Catalyzed Asymmetric Henry Reaction of Isatin *N*-Boc Ketimines



proceeds smoothly with or without protection of the isatin NH. The use of less acidic Cu(II) salts avoided imine hydrolysis but affected the enantioselectivity with CuCl_2 affording the product in 97% yield and 27% *ee*. The best result was obtained with Cu(II) tetrafluoroborate hydrate and ligand **600c**. It was also shown that having a nitro group in the 7-position of the isatin significantly reduced the enantioselectivity to 6% *ee*.²³⁵

Zhang applied ligand **600a** in the Ni-catalyzed cycloaddition of *N*-tosylaziridines **629** leading to very high yields of up to 99% and enantioselectivities up to 96% *ee* (Scheme 197). A variety of aziridines were subjected to the optimized reaction conditions, most of which achieved enantioselectivities of

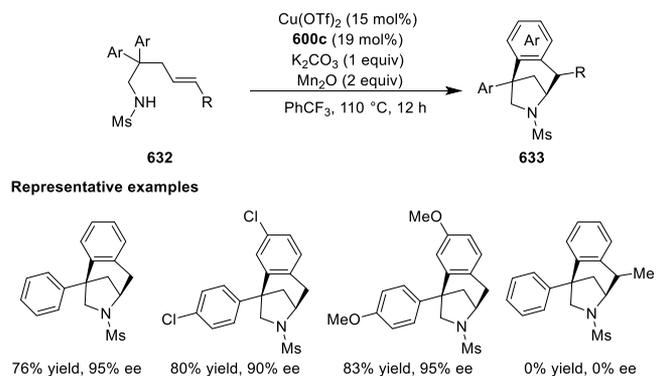
Scheme 197. Ni-Catalyzed Asymmetric Cycloaddition of *N*-Tosylaziridines



greater than 92% *ee*. Naphthyl-substituted aziridines however led to a reduction in enantioselectivity (89% *ee*).²³⁶

Chemler utilized a **600c**-Cu complex in the synthesis of 6-azabicyclo[3.2.1]octanes **633** via an enantioselective alkene carboamination (Scheme 198). This process allowed for the

Scheme 198. Cu-Catalyzed Synthesis of 6-Azabicyclo[3.2.1]octanes

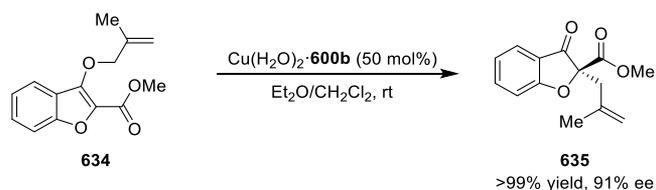


rapid synthesis of bridged bicyclic rings containing nitrogen in good yields and up to 95% *ee*. Two new stereocenters are formed in the reaction, and the C–C bond-forming arene addition is a net C–H functionalization. Electron-donating and withdrawing arenes were tolerated in this reaction. However, this reaction was limited in the substitution of the alkene. If the alkene was 1,1 disubstituted the reaction proceeded smoothly but when 1,2-disubstituted the reaction halted completely, not giving any product.²³⁷

Tang developed an efficient synthesis of dihydrofuran-3-ones **634** and then applied them as substrates in an asymmetric Claisen rearrangement catalyzed by the Cu complex of ligand **600b**. This furnished the corresponding product **635** in quantitative yield and high enantioselectivities up to 91% *ee* (Scheme 199).²³⁸

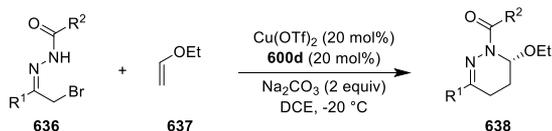
Xiao employed ligand **600d** in the Cu-catalyzed inverse electron-demand hetero-Diels–Alder reaction between α -halo-*N*-acylhydrazones **636** with enol ethers **637**. The reaction

Scheme 199. Cu-Catalyzed Asymmetric Synthesis of Dihydrofuran-3-ones

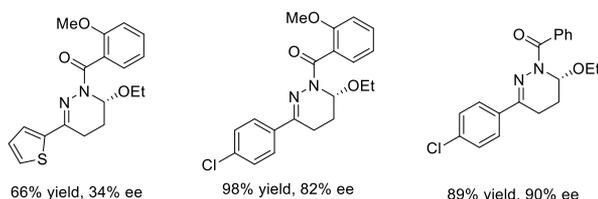


exhibits high enantioselectivity of up to 90% *ee* and provides densely substituted chiral pyridazine derivatives **638** in good yields (Scheme 200). It was shown that ester and thienyl-substituted hydrazones led to a drop in enantioselectivity to 34% *ee*.²³⁹

Scheme 200. Cu-Catalyzed Synthesis of Chiral Pyridazine Derivatives

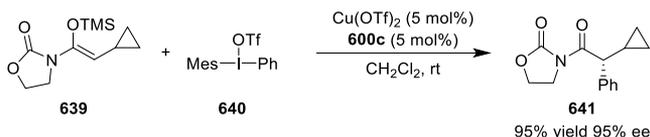


Representative examples



Gaunt applied chiral Cu-(II)-bisoxazoline complexes derived from ligand **600c** in the enantioselective α -arylation of *N*-acyloxazolidinones **639** by diaryliodonium salts **640** (Scheme 201). Cu(II) triflate was used as the Cu source providing the arylated product in up to 95% *ee* in excellent yields under mild conditions.²⁴⁰

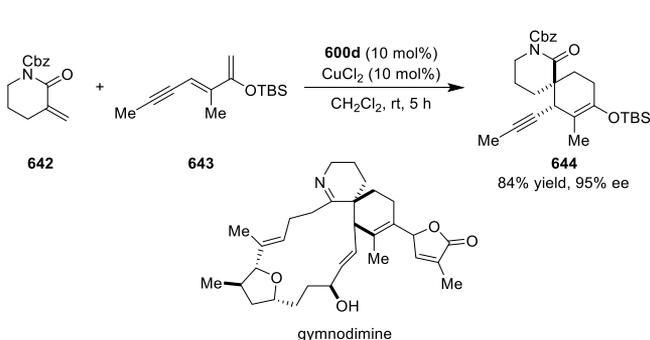
Scheme 201. Cu-Catalyzed Asymmetric α -Arylation of *N*-Acylloxazolidinones



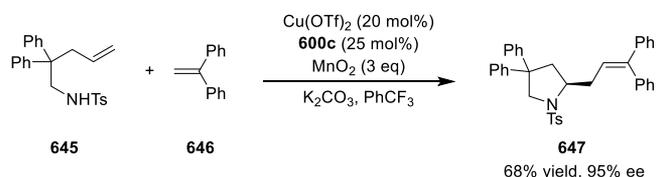
Romo employed a Cu-catalyzed Diels–Alder reaction to synthesize an intermediate of spirocyclic imine marine toxin (–)-Gymnodimine and an unnatural epimer. It provided the spiro lactam product **644** in 84% yield and 95% *ee* (Scheme 202).²⁴¹

Ligand **600c** was applied successfully in the intramolecular amination/Heck-type coupling of γ -alkenylsulfonamides **645** by Chemler. Using $\text{Cu}(\text{OTf})_2$ as the Cu source and **600c** as the ligand, enantioselectivities of up to 95% *ee* and 68% yield were observed for bulky alkenylsulfonamides (Scheme 203).²⁴²

Scheme 202. Cu-Catalyzed Synthesis of Gymnodimine Core

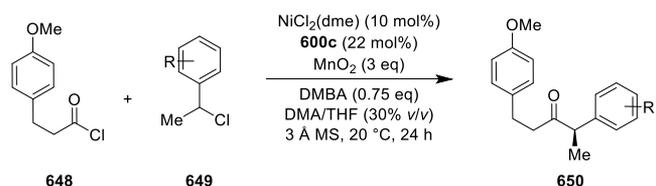


Scheme 203. Cu-Catalyzed Asymmetric Amination of γ -Alkenylsulfonamides



Reisman utilized **600c** in the Ni-catalyzed synthesis of α,α -disubstituted ketones **650** from acyl chlorides **648** and racemic benzyl halides **649** (Scheme 204). The best results were

Scheme 204. Ni-Catalyzed Asymmetric Synthesis of α,α -Disubstituted Ketones



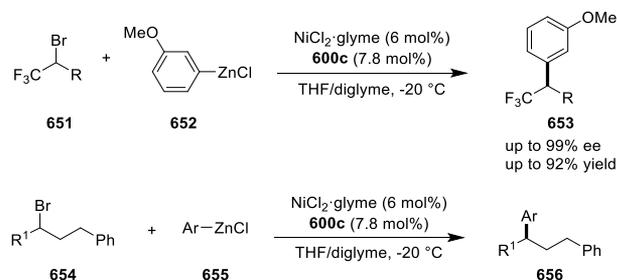
Representative examples

R = H; 79% yield, 93% *ee*
 R = 4-Me; 74% yield, 93% *ee*
 R = 3-Me; 75% yield, 93% *ee*
 R = 2-Me; 35% yield, 72% *ee*
 R = 4-OMe; 56% yield, 86% *ee*
 R = 4-Br; 73% yield, 86% *ee*

obtained by using MnO_2 as a stoichiometric reductant and DMBA (7,12-dimethylbenz[*a*]anthracene) to avoid homocoupling with 79% yield and *ees* up to 93%. A wide variety of substrates with a range of different substitutions were tolerated, however it was shown that *ortho*-substituted benzyl chlorides were poor substrates providing products in only 35% yield and 72% *ee*. It was also noted that an unusual solvent mixture (30% v/v DMA/THF) was needed. It was shown that higher *ees* but poor yields were obtained in THF while homocoupling issues remained when using pure DMA.²⁴³

Fu showed that a catalyst combination of ligand **600c** and bench-stable NiCl_2 -glyme were able to synthesize tertiary stereocenters bearing a CF_3 group in a Negishi arylation reaction in up to 92% yield and 99% *ee* (Scheme 205). It was shown that a variety of functional groups were compatible with the reaction conditions, including silyl ether, primary alkyl chloride, primary alkyl bromide, primary alkyl tosylate, aryl ether, ketone, aryl iodide, carbamate, ester and a furan with all

Scheme 205. Ni-Catalyzed Asymmetric Cross-Electrophile Coupling



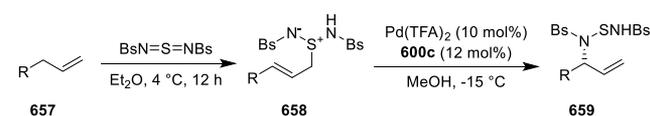
Representative examples

$\text{R}^1 = n\text{-C}_3\text{F}_7$; Ar = 3-OMeC₆H₄; 92% yield, 99% *ee*
 R¹ = CF₂Cl; Ar = 4-OMeC₆H₄; 89% yield, 96% *ee*

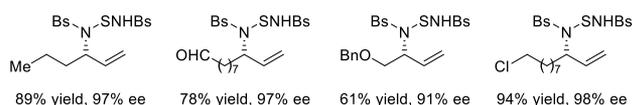
of the above groups maintaining enantioselectivities of greater than 95% *ee*. It was also shown that a range of electron-withdrawing fluorinated groups could be applied to this methodology.²⁴⁴

Tambar developed a novel methodology for the enantioselective allylic amination of terminal olefins **657** by using a Pd(TFA)₂-**600c** catalyst system which promotes the rearrangement of their stable ene-adducts **658** (Scheme 206). This

Scheme 206. Enantioselective Allylic Amination of Terminal Olefins



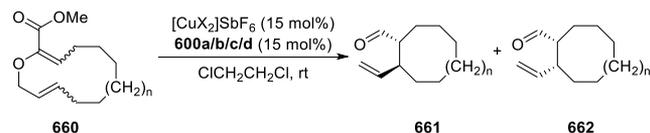
Representative examples



furnished the product **659** in up to 98% *ee* with good to excellent yields. Also notable is the ability to accommodate a wide variety of functional groups, although carboxylic acids and free alcohols were not compatible in this methodology due to competing addition to the ene-adducts.²⁴⁵

Hiersemann reported a Cu-catalyzed [1,6]-transannular Gosteli–Claisen rearrangement of cyclic allyl vinyl ethers **660**. Throughout their study they showed that enantioselectivity and diastereoselectivity varied significantly depending on the ligand system used (Scheme 207). When diastereoselec-

Scheme 207. Cu-Catalyzed [1,6]-Transannular Gosteli–Claisen Rearrangement of Cyclic Allyl Vinyl Ethers



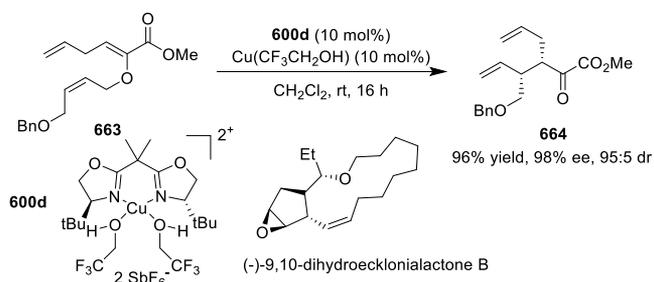
Representative examples

n = 1	n = 7
600c , X ₂ = H ₂ O, 92:8 dr, 13% <i>ee</i>	600c , X ₂ = PhOH, 95:5 dr, 44% <i>ee</i>
600c , X ₂ = PhOH, 92:8 dr, 13% <i>ee</i>	600d , X ₂ = H ₂ O, 95:5 dr, 98% <i>ee</i>
600a , X ₂ = PhOH, 87:13 dr, 70% <i>ee</i>	
600d , X ₂ = H ₂ O, 87:13 dr, 98% <i>ee</i>	
600d , X ₂ = CF ₃ CH ₂ OH, 87:13, 98% <i>ee</i>	
600d , X ₂ = PhOH, 87:13, 98% <i>ee</i>	

tivity was high the enantioselectivity dropped dramatically and *vice versa* when the enantioselectivity was high. For eight-membered ring systems the reaction had outstanding *trans*-selectivity and reached up to 98% *ee* and 87:13 dr with ligand **600d**. This methodology was extended to larger ring systems and displayed a switch to *cis*-selectivity affording the 12-membered ring product in up to 98% *ee* and 95:5 dr once again using chiral ligand **600d**.²⁴⁶

Hiersemann employed a **600d**-Cu(II) complex to prepare a key intermediate in the synthesis of (–)-9,10-dihydroecklonialactone B. This Claisen rearrangement of Gosteli-type allyl vinyl ethers **663** produced the key keto ester **664** in 96% yield, 95:5 dr and 98% *ee* (Scheme 208). It was shown that a modified catalyst-complex using bis(trifluoroethanol) was more effective for the Claisen rearrangement than the traditionally used bis(aqua) Cu(II) complex. This key

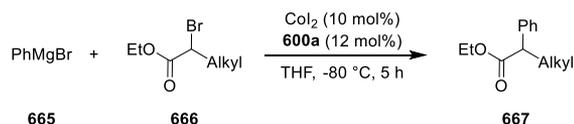
Scheme 208. Cu-Catalyzed Claisen Rearrangement of Gosteli-type Allyl Vinyl Ethers



intermediate was then converted in eight steps to (–)-9,10-dihydroecklonialactone B.²⁴⁷

Walsh reported the asymmetric arylation of α -bromo esters **666** using a CoI₂ and **600a** catalyst complex with up to 96% yield and 97% *ee*. The reaction was tolerant of different cyclic/acyclic and aromatic esters. The scope for the alkyl chain showed tolerance for halides/alkenes/aromatic/heteroaromatic/esters while maintaining excellent enantioselectivities (Scheme 209). Interestingly *iPr*- and cyclopentyl-containing α -

Scheme 209. Co-Catalyzed Asymmetric Arylation of α -Bromo Ketones



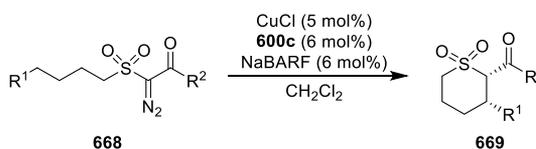
Representative examples

Alkyl = Me; 92% yield, 92% <i>ee</i>	(S)-fenoprofen
Alkyl = <i>iPr</i> ; 82% yield, 23% <i>ee</i>	(S)-ar-turmerone
Alkyl = C ₂ H ₄ Br; 82% yield, 92% <i>ee</i>	
Alkyl = CH ₂ C ₆ H ₅ ; 81% yield, 90% <i>ee</i>	

bromo esters showed a significant drop in *ee*. The scope for the aryl-Grignard reagent **665** showed very little variability in *ee* regardless of sterics or electronics. This methodology was then employed in the synthesis of (S)-fenoprofen and (S)-ar-turmerone without erosion of *ee* in subsequent steps.²⁴⁸

Maguire highlighted the use of CuCl and **600c** as a potent catalyst for intramolecular C–H insertion in the synthesis of a series of thiopyrans **669** (Scheme 210). The optimal catalyst complex in conjunction with NaBARF showed good yields and enantioselectivities of up to 98% *ee*. Interestingly the electron deficient nitrophenyl substrate did not yield any product. It was also shown that these reactions could be completed in

Scheme 210. Cu-Catalyzed Synthesis of Thiopyrans



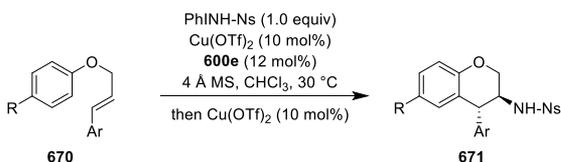
Representative examples

R ¹ = Ph; R ² = OMe; 47% yield, 98% <i>ee</i>
R ¹ = 4-NO ₂ C ₆ H ₄ ; R ² = OMe; no reaction
R ¹ = Octyl; R ² = OBn; 66% yield, 90% <i>ee</i>
R ¹ = Ph; R ² = Ph; 49% yield, 97% <i>ee</i>

significantly less time using microwave heating, but this came with a cost of reduced enantioselectivity. Further detailed investigations were also carried out by Maguire.^{249–252}

Copper triflate and **600e** was utilized in the aziridoarylation of aryl cinnamyl ethers **670** for the synthesis of 3-amino-4-arylchromans **671** (Scheme 211). This one-pot, two-step

Scheme 211. Cu-Catalyzed Asymmetric Aziridoarylation



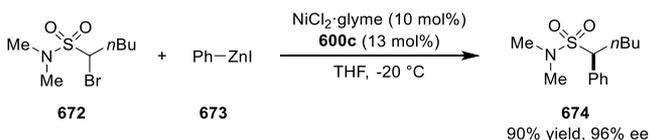
Representative examples

R = Me; Ar = Ph; 48% yield, 95% ee
 R = H; Ar = 4-ClC₆H₄; 28% yield, 83% ee
 R = Me; Ar = 4-MeC₆H₄; 32% yield, 73% ee

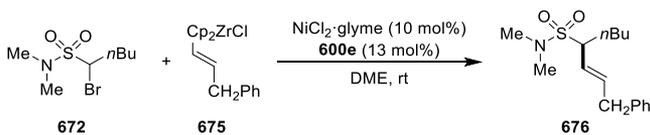
reaction uses the catalyst mixture of **600e** and Cu(OTf)₂ to effect a stereoselective aziridination, following additional Cu(OTf)₂ the arylative ring-opening of the aziridine furnishes substituted chromans in moderate yields and enantioselectivities of up to 95% ee.²⁵³

Fu reported the use of NiCl₂-glyme and ligand **600c** as an effective catalyst for the asymmetric Negishi coupling of sulfonamides and sulfones **672** with organozinc reagents **673** in good yields and reaching up to 96% ee (Scheme 212). A

Scheme 212. Ni-Catalyzed Asymmetric Negishi Coupling of Sulfonamides



90% yield, 96% ee



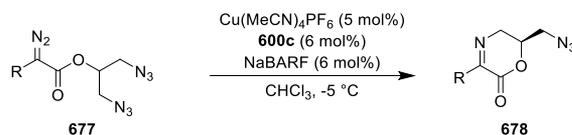
81% yield, 90% ee

wide range of substrates including aromatic, cyclic and acyclic sulfonamides were investigated, although for sulfones there was a more limited scope which proceeded with high enantioselectivity of 90% ee. The alkenylation of α -bromosulfonamides using zirconium reagents **675** as the nucleophile and **600e** as the ligand of choice proceeded in 81% yield and 90% ee.²⁵⁴

Gu developed an enantioselective desymmetrization of 1,3-diazoisopropyl diazo(aryl)acetates **677** catalyzed by a Cu complex with ligand **600c** to furnish imino esters **678** in very high yields and enantioselectivities of up to 97% ee (Scheme 213). The best results were obtained when using the large noncoordinating counterion, NaBARF, which is often employed in these reactions to increase the enantioselectivity. The substituents on the aromatic ring slightly affected the enantioselectivity. The *ortho*-groups showed the largest effect on enantioselectivities with electron-donating groups greatly diminishing the enantioselectivity to 58% ee.²⁵⁵

Waser developed the azidation of β -keto esters **679** and silyl enol ethers using a benziodoxole reagent **680** (Scheme 214).

Scheme 213. Cu-Catalyzed Synthesis of Cyclic Iminoesters

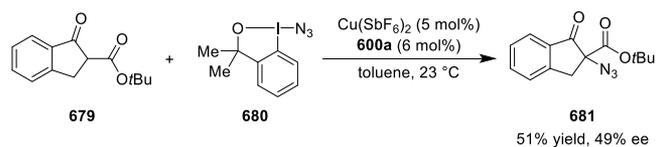


Representative examples

R = C₆H₅; 96% yield, 89% ee
 R = 2-MeOC₆H₄; 99% yield, 58% ee
 R = 2-ClC₆H₄; 98% yield, 97% ee

This methodology was expanded upon but not fully optimized with an initial test reaction using ligand **600a** and a Cu salt showing moderate enantioselectivities of 49% ee.²⁵⁶

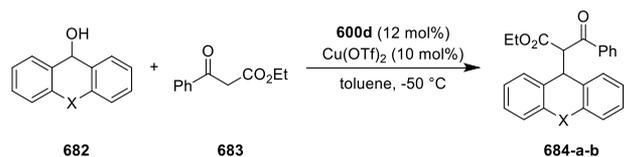
Scheme 214. Cu-Catalyzed Asymmetric Azidation of β -Keto Esters



51% yield, 49% ee

Nájera disclosed a Cu-catalyzed asymmetric alkylation of β -keto esters **683** using ligand **600d** and benzylic alcohols **682** as the alkylating agents (Scheme 215). Xanthidrol and

Scheme 215. Cu-Catalyzed Alkylation of β -Keto Esters



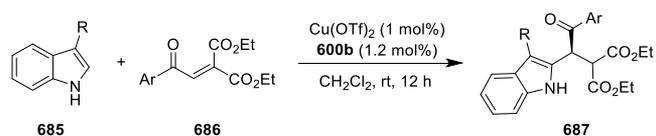
678-a; 82% yield, 80% ee
678-b; 74% yield, 90% ee

thioxanthidrol were the model alkylating reagents while aryl, alkyl and lactone-based β -keto esters were all shown to be good substrates for this reaction, and good yields with enantioselectivities of up to 90% ee were observed.²⁵⁷

Jia performed the asymmetric Friedel–Crafts alkylation of 3-substituted indoles **685** using Cu(OTf)₂ and ligand **600b** as the optimal catalyst and ligand system achieving excellent yields and enantioselectivities of up to 93% ee (Scheme 216). This reaction was performed with α,β -unsaturated esters **686** and was sensitive only to bulky substituents on the indole ring.²⁵⁸

Pan disclosed an asymmetric cyano-trifluoromethylation of styrenes **688** using Togni's reagent **689** as the electrophilic source of CF₃ and **600e** as the chiral ligand (Scheme 217). CuF₂ was shown to be the ideal combination with ligand **600e**

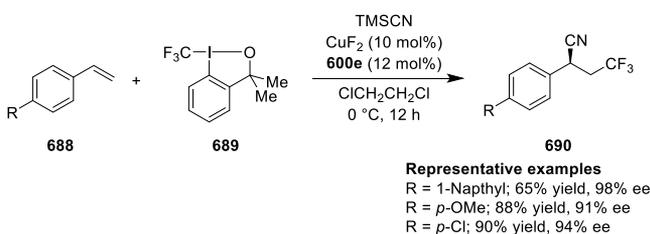
Scheme 216. Cu-Catalyzed Friedel–Crafts Alkylation of Indoles



Representative examples

Ar = Ph; R = Me; 99% yield, 93% ee
 Ar = Ph; R = Bn; 95% yield, 79% ee
 Ar = 2-Naphthyl; R = Me; 98% yield, 90% ee

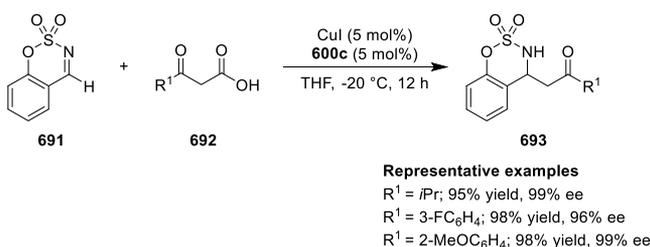
Scheme 217. Cu-Catalyzed Cyano-trifluoromethylation of Styrenes



and the products were formed in good yields and enantioselectivities of up to 98% *ee*. Electron-withdrawing and donating styrenes were tolerated remarkably well with *p*-methoxystyrene giving the lowest yield of 88% with 91% *ee*.²⁵⁹

Ma disclosed a highly enantioselective decarboxylative Mannich reaction of β -ketoacids **692** and cyclic aldimines **691** (Scheme 218). Using ligand **600c** and CuI excellent yields

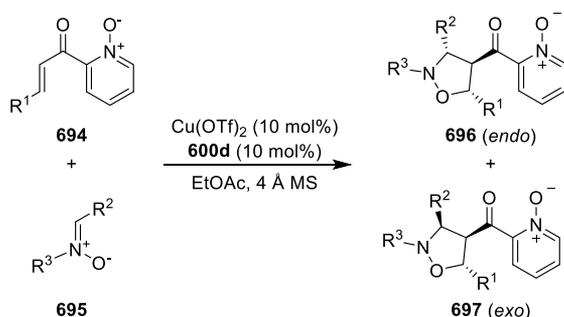
Scheme 218. Cu-Catalyzed Decarboxylative Mannich Reaction



and enantioselectivities of up to 99% *ee* were achieved. No substrate dipped below 90% *ee* with a wide variety of electronically different substrates being tolerated by the reaction conditions.²⁶⁰

Pedro reported the cycloaddition between nitron **695** and 2-alkenyl pyridine *N*-oxides **694** to give the isooxazolidine **696/697** products in high *ee* and *de* (Scheme 219). It was shown that *N*-phenyl nitrones performed much better in catalysis than *N*-methyl or *N*-benzyl nitrones which gave a

Scheme 219. Cu-Catalyzed Cycloaddition of Nitrones and Pyridine *N*-Oxides



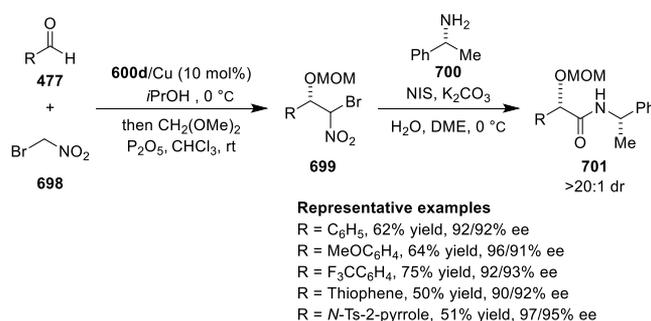
Representative examples

R¹;R²;R³ = Ph; 94% yield, 94:6 *endo:exo*, 95/61% ee
 R¹;R² = Ph; R³ = Me; 59% yield, 66:34 *endo:exo*, 88/78% ee
 R¹;R² = Ph; R³ = Bn; 62% yield, 61:39 *endo:exo*, 80/75% ee
 R¹;R³ = Ph; R² = 4-BrC₆H₄; 81% yield, 91:9 *endo:exo*, 94/45% ee
 R¹;R³ = Ph; R² = 4-O₂NC₆H₄; 36% yield, 94:6 *endo:exo*, 89/79% ee
 R¹ = 4-MeOC₆H₄; R²;R³ = Ph; 69% yield, 93:7 *endo:exo*, 96/nd% ee
 R¹ = 4-BrC₆H₄; R²;R³ = Ph; 82% yield, 90:10 *endo:exo*, 96/22% ee

much higher mixture of *endo:exo*. The nitron derived from *p*-nitrobenzaldehyde formed the product in poor yields although the enantioselectivities remained high at 89% *ee*. The scope for the 2-alkenyl pyridine *N*-oxides was remarkably tolerant of varying electronic properties achieving high *endo:exo* ratios while the enantioselectivities remained high.²⁶¹

Johnston utilized ligand **600d** in a three-step sequence for an umpolung amide synthesis (Scheme 220). Aldehydes **477** were

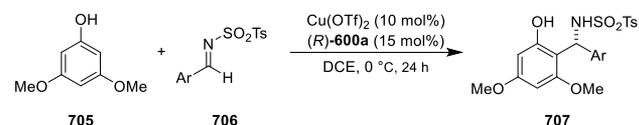
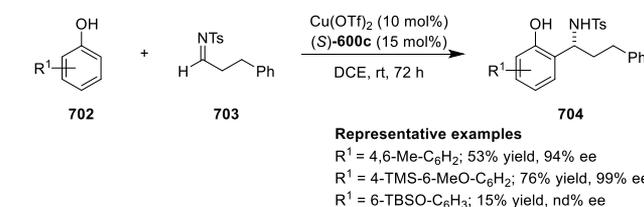
Scheme 220. Cu-Catalyzed Asymmetric Umpolung Amide Synthesis



reacted with bromonitromethane **698** in an enantioselective Henry addition using Cu(II) *ortho*-iodo benzoic acid as the catalyst, followed by MOM protection of the corresponding alcohol. This gave the MOM-protected alcohols **699** in good yields and with high enantioselectivities of up to 99% *ee*. The MOM-protected alcohols **699** were then subjected to the umpolung amide synthesis using enantioenriched (>99% *ee*) α -methyl benzyl amine **700** and these products **701** were used to provide confirmation that the two diastereomers of **699** are homochiral at the benzylic carbon (differing at the nitro- α -carbon) and remained enantioenriched throughout the three-step sequence (Henry/MOM-protection/umpolung amide synthesis).²⁶²

Chemler developed a Cu-catalyzed aza-Friedel–Crafts reaction between phenols **702** and aldimines **703** that provides chiral secondary benzylamines **704** with enantioselectivities up to 99% *ee* using **600c** as the chiral ligand (Scheme 221). With regards to the phenol scope most substrates were well tolerated, however some substrates such as 1,3,5-trimethoxyphenol and 5-OTBS phenol gave poor conversions as low as 15% yield and enantioselectivities of <5% *ee*. When the aryl

Scheme 221. Cu-Catalyzed Asymmetric Aza-Friedel–Crafts Reaction



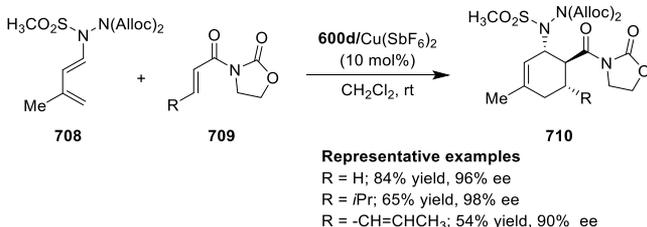
Representative examples

Ar = Piperonal; 78% yield, 97% ee
 Ar = 2-Furan; 96% yield, 91% ee

imine scope was attempted the conditions had to be reoptimized using (*R*)-**600a** as the ligand and lower temperatures to provide better enantioselectivity of up to 97% *ee*.²⁶³

Sorensen reported the asymmetric Diels–Alder cycloaddition of 1-hydrazinodienes **708** and *N*-acryloyl oxazolidinones **709** using ligand **600d** and Cu(SbF₆)₂ as the catalyst complex (Scheme 222). The scope of the reaction was varied

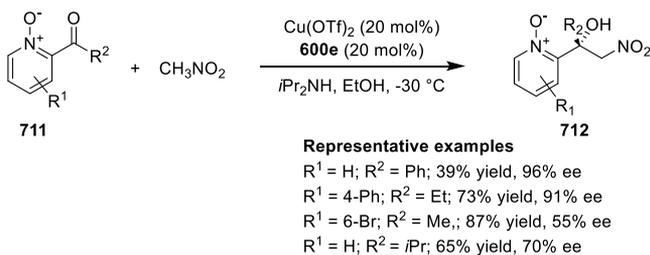
Scheme 222. Cu-Catalyzed Asymmetric Diels–Alder of 1-Hydrazinodienes



and tolerated different substituents on the substituted *N*-acryloyl oxazolidinones and the lowest enantioselectivities were seen when *p*-Cl/Br/CF₃ substituted aryl rings were used all affording 90% *ee*. When changing the 1-hydrazinodienes there was little to no drop in enantioselectivity with 97% *ee* being the lowest recorded.²⁶⁴

An asymmetric addition of nitromethane to 2-acylpyridine *N*-oxides **711** was reported by Pedro in 2014. Using **600e** and Cu(OTf)₂ as the catalyst complex and ethanol as the solvent enantioselectivities up to 96% *ee* were achieved (Scheme 223).

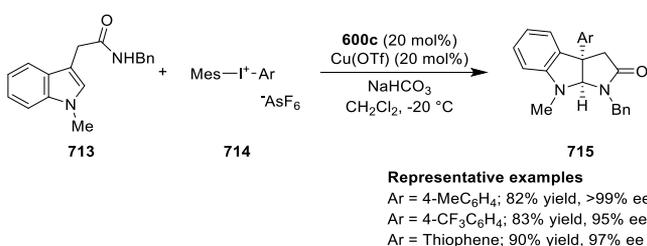
Scheme 223. Cu-Catalyzed Asymmetric Addition to 2-Acylpyridine *N*-Oxides



Ethanol was chosen as the solvent as it stopped competitive background reactions from occurring. Substrates substituted on the 6-position had a disastrous effect on the enantioselectivity which dropped to as low as 48% *ee*.²⁶⁵

MacMillan developed an enantioselective cascade arylation-cyclization using Cu(OTf), **600c** and aryl iodonium salts **714** to synthesize aryl pyrroloindolines **715** (Scheme 224). In

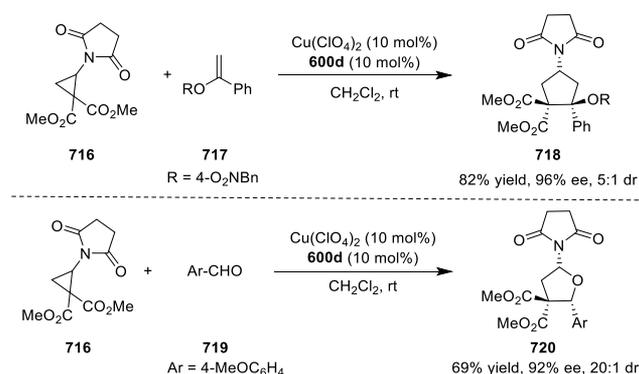
Scheme 224. Copper-Catalyzed Asymmetric Synthesis of Pyrroloindolines



general, the reaction was highly enantioselective with *ee*'s up to >99% *ee*. Unprotected indole starting material has the largest negative impact on the catalytic transformation as enantioselectivity was lowered to 90% *ee*.²⁶⁶

Waser reported a dynamic kinetic asymmetric annulation of aminocyclopropanes **716** with enol ethers **717** and aldehydes furnishing up to 96% *ee* and 92% *ee*, respectively (Scheme 225). The best enantioselectivities were achieved with

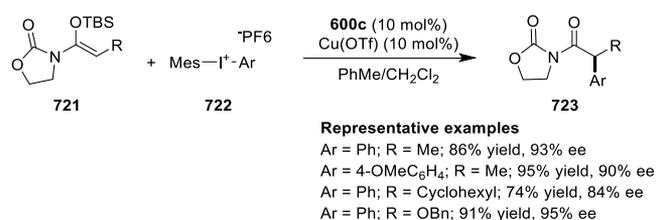
Scheme 225. Dynamic Kinetic Asymmetric Annulation of Aminocyclopropanes



Cu(ClO₄)₂-**600d** as the catalyst system and succinimide as the nitrogen-containing component of the aminocyclopropanes with up to 96% *ee* being obtained. It was also shown that the counterion had a large influence on the *ee*, hexafluoroantimonate led to the highest dr's but when perchlorate was chosen it provided the highest enantioselectivities.²⁶⁷

MacMillan published the enantioselective α -arylation of carbonyls using aryl iodonium salts **722** with ligand **600c** and Cu(OTf) as the active catalyst system (Scheme 226). Using

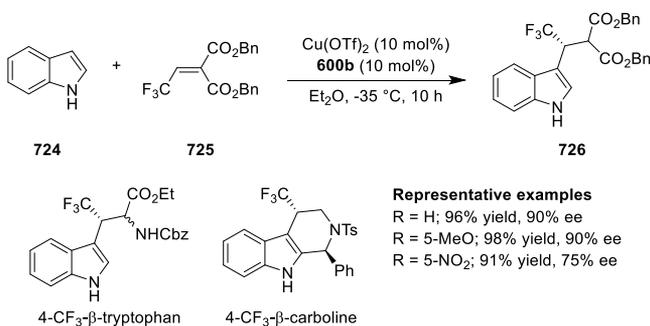
Scheme 226. Cu-Catalyzed Enantioselective α -Arylation of Carbonyls



silyl enol ethers **721** as the silylated nucleophile they attacked the Cu-oxazoline iodonium salt complex to give good yields and enantioselectivities up to 95% *ee*. It was shown that using the PF₆ counterion and a mixed solvent system of toluene/CH₂Cl₂ at 0 °C produced the best yields. A diverse range of aryl and heteroaryl rings were tolerated well in catalysis. As well as this, arenes, olefins, ethers, esters, and carbamates were all tolerated for the silyl enol ether scope.²⁶⁸

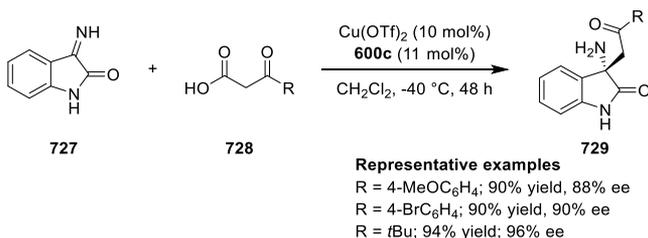
Lu developed a Cu-catalyzed Friedel–Crafts alkylation of indoles **724** with trifluoroethylidene malonates **725** to construct a tertiary stereocenter bearing a trifluoromethyl group (Scheme 227). Using Cu(OTf)₂ and **600b** as the catalyst system excellent conversions and enantioselectivities of up to 90% *ee* were achieved. This protocol was then utilized in the synthesis of β -CF₃-tryptophan and 4-CF₃- β -carboline.²⁶⁹

Scheme 227. Cu-Catalyzed Friedel–Crafts Alkylation of Indoles



Ohshima reported an enantioselective decarboxylative Mannich-type reaction of unprotected isatin-derived ketimines **727** (Scheme 228). By utilizing a β-keto acid **728** as the

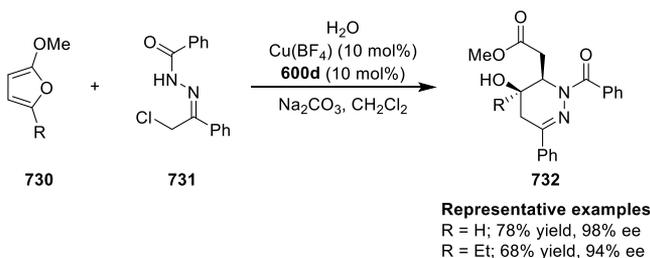
Scheme 228. Cu-Catalyzed Enantioselective Decarboxylative Mannich Reaction of Unprotected Isatin-Derived Ketimines



nucleophile this led to an irreversible decarboxylation addition process. Using Cu(OTf)₂ and **600c** as the ligand the desired product was formed in up to 96% ee and very high yields (of up to 90%). With regards to the β-keto acids this reaction was also tolerant of heteroaryl systems such as furan/thiophene and naphthyl with good enantioselectivities (85–92% ee) being obtained.²⁷⁰

Wang disclosed a multicomponent cascade inverse Aza-Diels–Alder/nucleophilic addition/ring-opening reaction using 2-methoxyfurans **730** as dienophiles (Scheme 229). This reaction was envisaged to synthesize a bicyclic

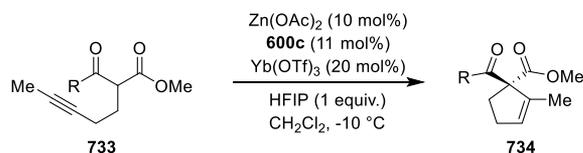
Scheme 229. Cu-Catalyzed Inverse Aza-Diels–Alder Cascade Reaction



heterocycle, but water does a nucleophilic addition following a ring opening leading instead to a series of tetrahydropyridazine derivatives **732**. With this methodology in place a series of substituted tetrahydropyridazines were synthesized. Electron-donating and electron-withdrawing groups were all well tolerated with enantioselectivities in the 92–98% ee range for this Cu-catalyzed process.²⁷¹

Shibata developed a Zn(OAc)₂/Yb(OTf)₃ cocatalyst system to induce an intramolecular 5-*endo-dig* cyclization of β-keto esters **733** and alkynes to produce enantioenriched cyclopentene products of type **734** (Scheme 230). The best results

Scheme 230. Dual-Catalytic Asymmetric Cyclization



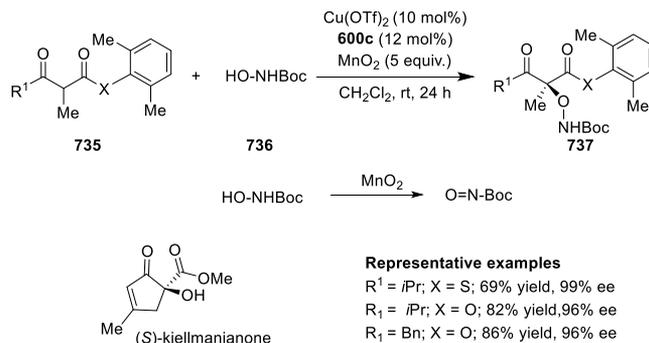
Representative examples

R = Ph; 70% yield, 90% ee
 R = Me; 91% yield, 21% ee
 R = 2-BrC₆H₄; 93% yield, 98% ee
 R = 2-MeOC₆H₄; 99% yield, 94% ee

were achieved using **600c** as the ligand and 1 equiv of hexafluoroisopropanol (HFIP). It was proposed that the effect of HFIP was to improve catalytic turnover by releasing the products from the catalytic cycle or assist initial enolization. It was believed that the generally high ees were due to the π–π stacking interactions of aromatic ketones with the phenyl groups of the ligand **600c**. This hypothesis was backed up by the fact that the reaction with nonaromatic ketones led to poor enantioselectivities as low as 21% ee.²⁷²

Yamamoto reported an asymmetric synthesis of α-hydroxy-β-keto esters **737** in a Cu-catalyzed *O*-nitrosocarbonyl aldol reaction (Scheme 231). Using ligand **600c** and Cu(OTf)₂ as

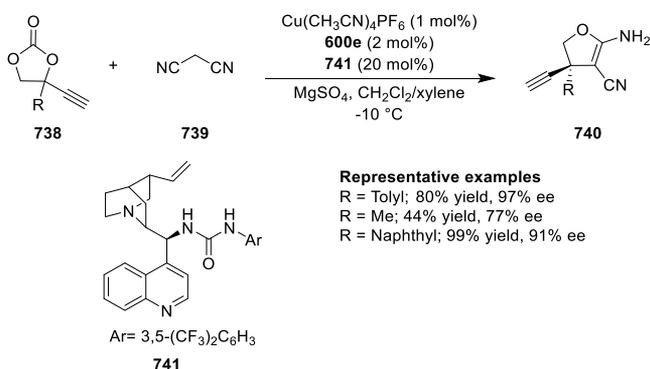
Scheme 231. Cu-Catalyzed Asymmetric Nitrosocarbonyl Aldol Reaction



the catalyst complex high levels of enantioselectivities up to 99% ee were observed. MnO₂ was chosen as the oxidizing reagent as it was found to be a mild method for the generation of nitrosocarbonyl compounds which avoided overoxidation of the products. This catalysis was shown to be particularly flexible as both oxo-ester and thioesters **735** can be tolerated while retaining high levels of enantioselectivity. This methodology was then applied to the synthesis of antibacterial agent (*S*)-Kjellmanianone.²⁷³

Song used ligand **600e** and Cu(CH₃CN)₄PF₆ in combination with cinchona alkaloid **74** to promote a [3 + 2] cycloaddition reaction of ethynylethylene carbonates **738** and malononitrile **739** (Scheme 232). This system relied on cinchona alkaloid **741** for activation of the malononitrile and a Cu-mediated decarboxylation of a carbonate followed by a cycloaddition. The ligand **600e** was not fully responsible for enantioselectivity as the choice of alkaloid was also shown to

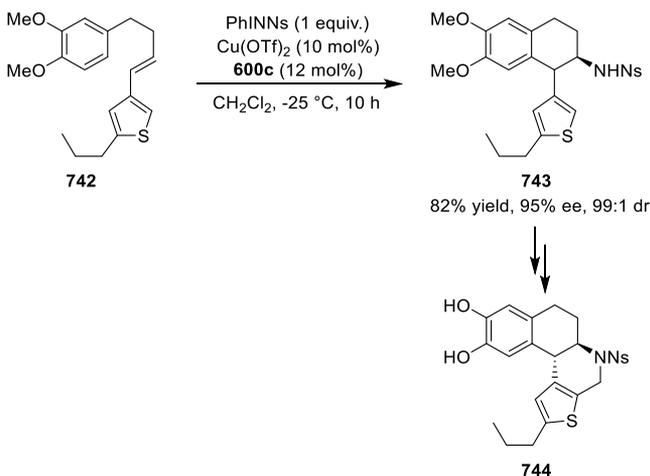
Scheme 232. Bicatalytic [3 + 2] Cycloaddition Reaction of Ethynylethylene Carbonates



have an impact on the enantioselectivity. Good yields and enantioselectivities up to 97% *ee* were achieved using this copper/organocatalytic system.²⁷⁴

Bar utilized a one-pot aziridination/Friedel–Crafts cyclization in the synthesis of dopamine D1 agonist A-86929 **744** (Scheme 233). Using ligand **600c** in combination with

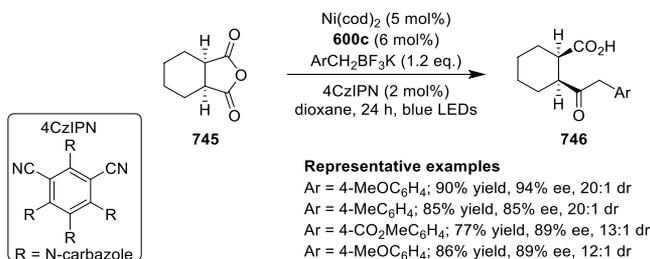
Scheme 233. Cu-Catalyzed Asymmetric Synthesis of Dopamine D1 Agonist



Cu(OTf)₂ it was shown to be an effective catalyst for the asymmetric aziridination and subsequent Friedel–Crafts cyclization. This provided the key intermediate in good yields, > 99:1 dr and 95% *ee*.²⁷⁵

Doyle and Rovis reported a dual Ni- and photoredox-catalyzed enantioselective desymmetrization of cyclic *meso*-anhydrides **745** (Scheme 234). Using **600c**, Ni(cod)₂ and

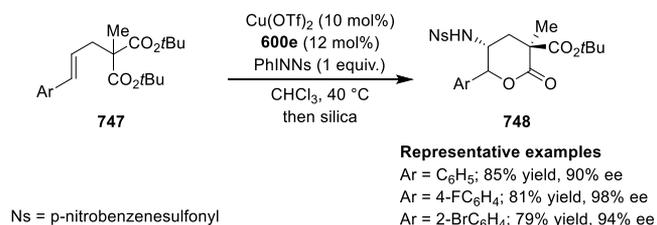
Scheme 234. Ni-Catalyzed Asymmetric Desymmetrisation of Cyclic *meso*-Anhydrides



photocatalyst 4CzIPN, enantioselectivities up to 94% *ee* were achieved, with dr values of >20:1. A range of electrophiles were tested such as cyclopentyl, cyclobutyl and cyclopropyl succinic anhydrides, all of which were suitable. However, anhydrides bearing β -substitution provided moderate enantioselectivities of 36% *ee*. Both electron-deficient and electron-neutral trifluoroborates reacted smoothly. Some *ortho*-substituted nucleophiles led to a lower diastereoselectivity of 6:1 dr.²⁷⁶

Aziz developed an asymmetric aminolactonization of 1,2-disubstituted alkenoic acid ester **747** via an aziridination-cyclization reaction protocol (Scheme 235). Using Cu(OTf)₂

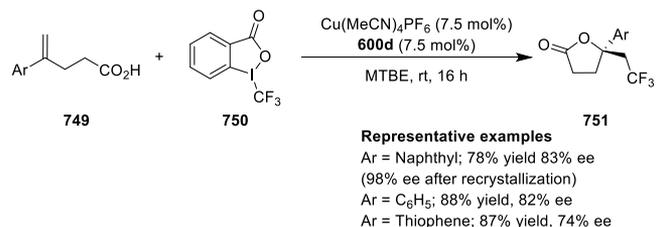
Scheme 235. Cu-Catalyzed Asymmetric Aminolactonization



and ligand **600e** the aziridination proceeds smoothly and upon treatment with additional Cu(OTf)₂ or silica gel the aziridine successfully cyclizes to produce the desired aminolactone **748** in up to 98% *ee*.²⁷⁷

Buchwald developed an efficient Cu-catalyzed synthesis of enantioenriched CF₃-containing lactones **751** (Scheme 236).

Scheme 236. Cu-Catalyzed Synthesis of Enantioenriched CF₃-Containing Lactones

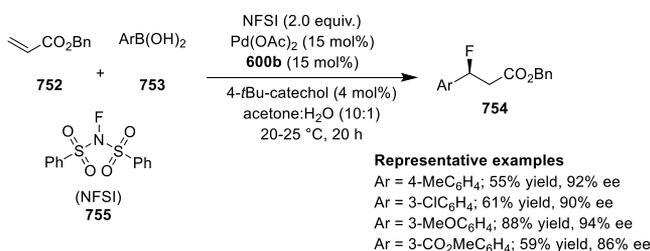


Using **600d** as the chiral ligand and [Cu(MeCN)₄]PF₆ as the Cu source enantioselectivities up to 98% *ee* after recrystallization were achieved in good yields. Togni's reagent **750** proved to be a competent radical coupling reagent which promoted an asymmetric cyclization. Mechanistic studies supported a redox radical addition mechanism. This reaction showed a good functional group compatibility with a variety of aryl and heteroaryl systems being tolerated.²⁷⁸

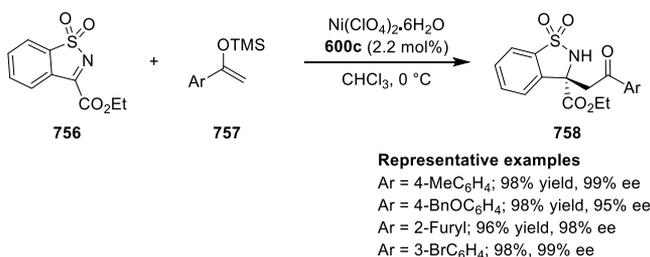
Fustero and Toste documented a three-component coupling of deactivated alkenes **752**, aryl boronic acids **753** and *N*-fluorobenzenesulfonamide **755** (Scheme 237). This asymmetric Pd-catalyzed functionalization of α,β -unsaturated systems afforded good yields and high enantioselectivities using a Pd(OAc)₂ and ligand **600b** catalyst system. The reaction goes through a high-valent Pd(IV) intermediate. This methodology is amenable to a wide range of aryl boronic acids without a large drop in enantioselectivity (84–94% *ee*).²⁷⁹

Fu reported an asymmetric Mukaiyama–Mannich reaction of cyclic *N*-sulfonyl α -ketiminoesters **756** and silyl enol ethers **757** which synthesized a range of sultams **758** (Scheme 238). The Ni(ClO₄)₂·6H₂O-**600c** complex promoted the reaction very efficiently, giving the desired product in good yields and

Scheme 237. Pd-Catalyzed Three-Component Coupling of Deactivated Alkenes



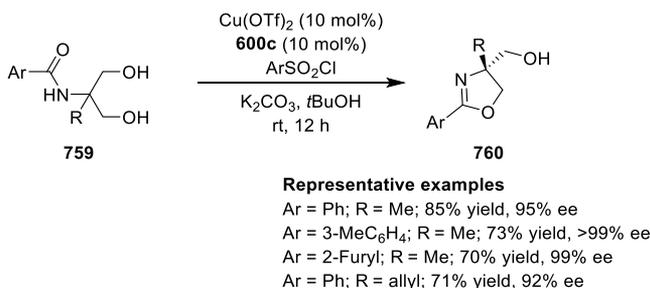
Scheme 238. Ni-Catalyzed Asymmetric Synthesis of Benzosultam



up to 99% ee. The reaction appeared to tolerate most substitution on the *N*-sulfonyl α -ketiminoester substrates in high enantioselectivities. Silyl enol ethers furnished high levels of enantioselectivity regardless of the aromatic/heteroaromatic group attached (97–99% ee). However, the α -difluorinated acetophenone derived silyl enol ether gave the corresponding benzosultam **758** in only 21% yield with a 30% ee value.²⁸⁰

Onomura developed a catalytic synthesis of chiral oxazoline derivatives **760** via asymmetric desymmetrization of 1,3-diols **759** (Scheme 239). This method employed Cu(OTf)₂ and

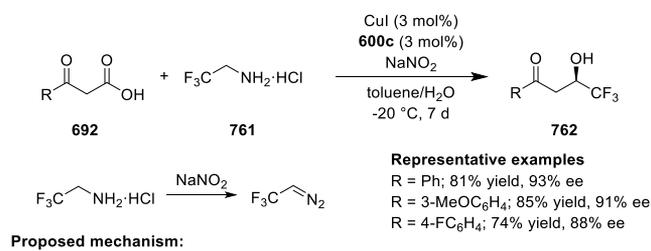
Scheme 239. Cu-Catalyzed Synthesis of Chiral Oxazoline Derivatives



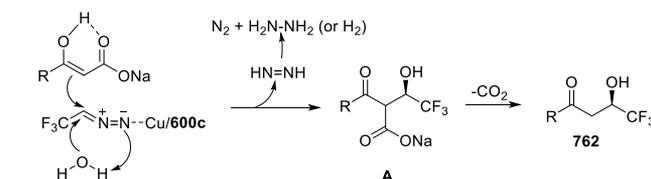
ligand **600c** in *t*-butanol affording good yields and enantioselectivities of up to >99% ee. For the substrate scope of 2-(*N*-acylamino)-1,3-propanediols, the enantioselectivity remained high regardless of the electronic nature of Ar be it aryl or heteroaryl (87–99% ee). When investigating the R substituents the enantioselectivities remained high (89–97% ee) but the yields were lowered (20–71% yield).²⁸¹

Ma reported a novel Cu-catalyzed one-pot cross-coupling of β -ketoacids **692** with *in situ* generated trifluorodiazoethane **761** to access trifluoromethylated aldol products **762** (Scheme 240).²⁸² Initially the reaction was examined racemically with CuI being the best Lewis acid to promote the formation of the aldol product **762**. To move to an asymmetric system the reaction had to be reoptimized with the temperature being

Scheme 240. Cu-Catalyzed Denitrogenative-Decarboxylative Coupling



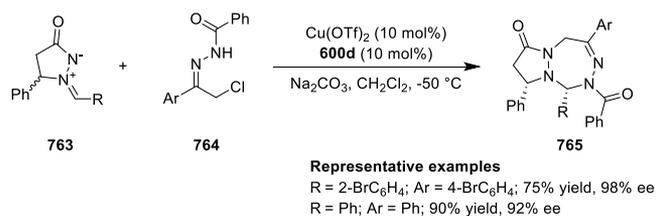
Proposed mechanism:



lowered and the reaction time extended. Ligand **600c** was shown to be optimal giving up to 93% ee in good yields. The proposed reaction mechanism involves nucleophilic attack of the enol form of the ketoacid to activated trifluorodiazoethane and simultaneous termination with water to form intermediate **A** with the release of diazene which rapidly undergoes a disproportionation reaction to form nitrogen gas and hydrazine (or H₂). Finally, decarboxylation leads to trifluoromethylated aldol product **762**.

Wang described an asymmetric 1,3-dipolar [3 + 4] cycloaddition of azomethine imines **763** and azoalkanes **764** (Scheme 241). Using **600d** as the ligand and Cu(OTf)₂ as the

Scheme 241. Cu-Catalyzed Cycloaddition of Azomethine Imines

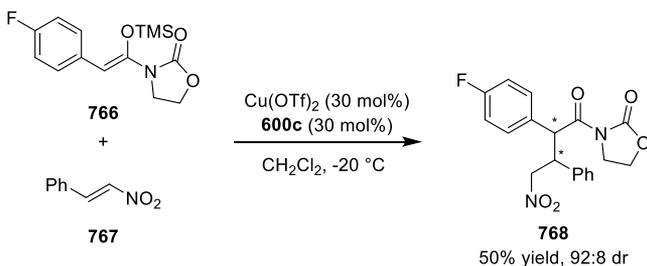
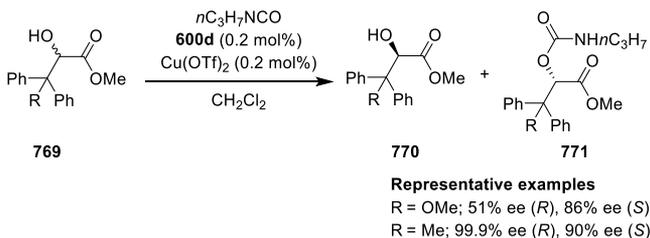


metal, enantioselectivities up to 98% ee were obtained in good yields. Azomethine imines **763** bearing electron-donating, electron-neutral or electron-withdrawing groups at *para*-, *meta*-, or *ortho*-positions of the aryl ring were well tolerated, giving the corresponding products in up to 90% yield and 98% ee. Naphthyl, heteroaromatic, and alkyl azomethine imines were also tolerated with up to 92% yield and 96% ee. Unfortunately, only racemic product was obtained when an alkyl-substituted hydrazone was employed.²⁸³

Sen detailed a diversity orientated synthesis (DOS) strategy toward the synthesis of optically active quinolizidinones, piperidinones, and pyrrolidinones. Ligand **600c** was applied in the Cu-catalyzed asymmetric Michael reaction of a silyl keteneimide **766** and nitrostyrene **767** to generate valuable intermediates in high diastereomeric ratios and good yields (Scheme 242).²⁸⁴

Ohkuma performed a kinetic resolution of sterically hindered racemic α -tert-alkyl- α -hydroxy esters **769** via an enantiomer-selective carbamoylation reaction (Scheme 243). Using ligand **600d** and Cu(OTf)₂ as the catalyst and carrying out the reaction at 0 °C enantioselectivities up to >99.9% ee

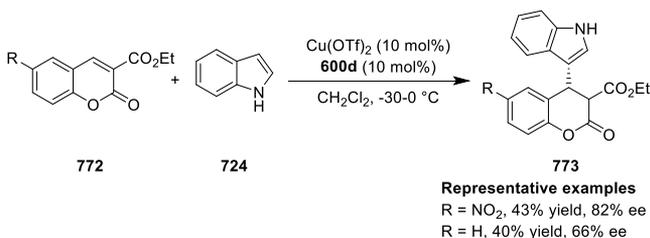
Scheme 242. Cu-Catalyzed Asymmetric Michael Reaction

Scheme 243. Cu-Catalyzed Kinetic Resolution of α -Tert-alkyl- α -hydroxy Esters

and selectivity factors of up to 261 were achieved. The racemic α -tert-alkyl- α -hydroxy esters **769** reacted smoothly with 0.5 equiv of isocyanate to give the enriched starting-material **770** and carbamate **771**, respectively. Regarding substrates, most were tolerated to give high selectivity and enantioselectivity. However, it was shown that replacing the β -methyl group with a β -methoxy group had a coordinative interaction with the catalyst and this reduced the enantioselectivity to as low as 51% ee.²⁸⁵

Beletskaya reported an asymmetric Friedel–Crafts reaction of indoles **724** with coumarin-3-carbonylates **772** in good yields and enantioselectivities (Scheme 244). Using ligand

Scheme 244. Cu-Catalyzed Asymmetric Friedel–Craft Alkylation of Coumarin-3-carbonylates

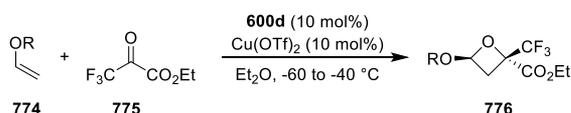


600d and Cu(OTf)₂ up to 82% ee and good yields were achieved. Groups with contrasting electronics in the 5-position of indole did not influence the yield or enantioselectivity, but the introduction of a methoxy group in the 4-position halted the reaction. Electron-withdrawing groups in the 5-position of coumarin greatly increased the enantioselectivities up to 82% ee.²⁸⁶

Mikami carried out an enantioselective Cu-catalyzed [2 + 2] cycloaddition of silyl enol ethers **774** with trifluoropyruvate **775** in the synthesis of oxetane derivatives **776** (Scheme 245). Using **600d** as the ligand and Cu(OTf)₂ as the catalyst, excellent *cis/trans* ratios and enantioselectivities up to >99% ee were achieved.²⁸⁷

As shown above parent BOX ligands have been widely applied in asymmetric catalysis to great success. While there

Scheme 245. Cu-Catalyzed Asymmetric Synthesis of Oxetane Derivatives

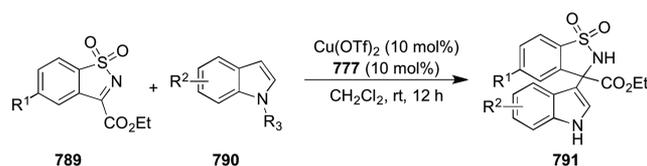


Representative examples

R = TIPS; 99:1 *cis:trans*, >99% ee
R = TBS; 82:12 *cis:trans*, 98% ee
R = TBDPS; 97:3 *cis:trans*, 99% ee

are few shortcomings for parent BOX ligands in catalysis, structural modifications are used to modulate the bite angles, electronics and sterics of ligands to gain enhanced activity.

3.1.2. Bis(oxazoline) Ligand with Modified Oxazoline Ring Substitution. Jia reported the construction of cyclic indolyl α -amino esters *via* a Cu-catalyzed asymmetric Friedel–Crafts alkylation reaction (Scheme 246). Using **777** as the

Scheme 246. Cu-Catalyzed Friedel–Crafts Alkylation of Indoles and *N*-Sulfonyl Ketimino Esters

Representative examples

R¹ = R² = H; 96% yield, 99% ee
R¹ = H, R² = 5-OMe; 97% yield, 83% ee

ligand (Figure 24) and Cu(OTf)₂ as the Lewis acid excellent yields and up to 99% ee were furnished. A range of *N*-sulfonyl ketimino ester derivatives **789** and indoles **790** reacted smoothly to give the product in up to 96% yield and >99% ee. This process was then extended to pyrrole and *N,N*-dimethylaniline while maintaining enantioselectivities up to 98% ee. At the same time indole substrates were very well tolerated with only 5-methoxyindole causing a drop in enantioselectivity to 83% ee.²⁸⁸

Jia once again utilized **777** as the ligand but this time in the Ni-catalyzed Friedel–Crafts alkylation of indoles **792** with β -CF₃- β -disubstituted nitroalkenes **793** to produce trifluoromethylated all-carbon quaternary stereocenters with enantioselectivities up to 97% ee and good yields (Scheme 247A). Most nitroalkenes furnished the products **784** in 88–97% ee while benzyl substituted nitroalkenes provided the corresponding product in 78% yield and 33% ee. For the indole substrate scope a range of electron-donating and -withdrawing substrates were proven successful (90–97% ee), only methyl substitution in the 1- and 2-positions provided poor results with trace amounts of product being formed.²⁸⁹

This methodology was extended to nitroacrylates **795** and indoles **724** garnering access to β -2,2-amino acid derivatives **796** in excellent yields and enantioselectivities up to 97% ee (Scheme 247B). In this case the nitroacrylate scope was very tolerant with different electronic patterns being widely accepted while maintaining high enantioselectivities (88–97% ee). The substitution on the indole ring had a much larger effect on the enantioselectivity. Substrates with 2-Me, 1-Me or 1-allyl all proved to be challenging substrates with enantioselectivities dropping as low as 54% ee.²⁹⁰

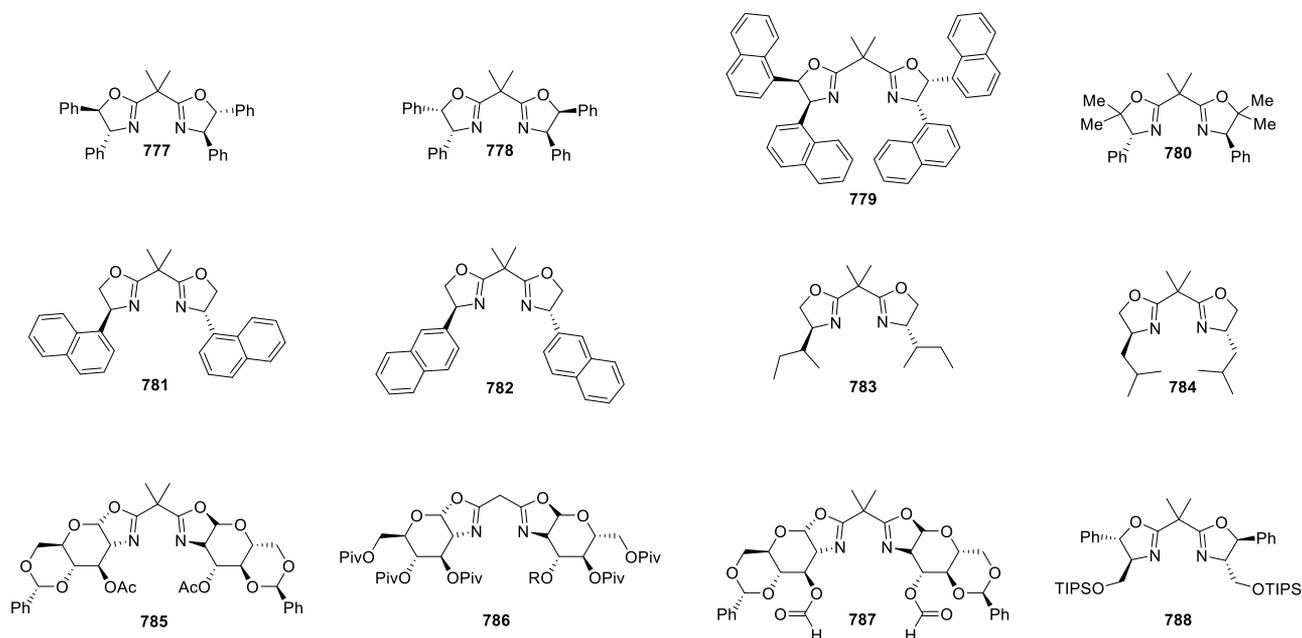
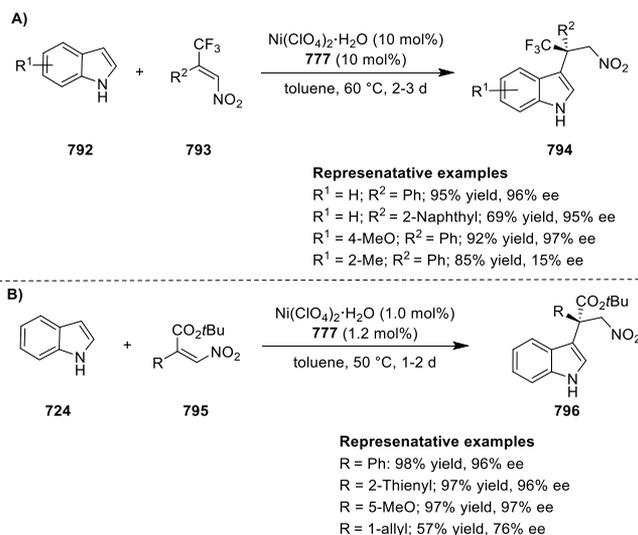


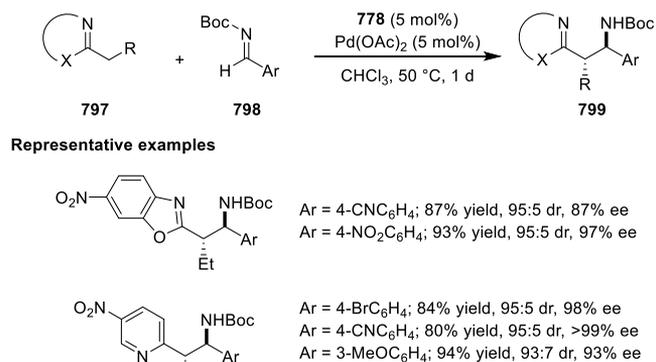
Figure 24. Summary of Bis(oxazoline) ligands with modified oxazoline ring substitution.

Scheme 247. Ni-Catalyzed Asymmetric Friedel–Crafts of Indoles and β -CF₃- β -Disubstituted Nitroalkenes



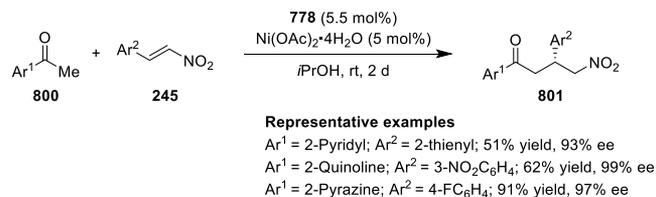
Lam reported the use of **778** in a Pd-catalyzed asymmetric addition of alkylazaarenes **798** to *N*-Boc aldimines **797** to produce Boc-protected α -stereogenic amines **799** (Scheme 248). Addition of the nitro group was integral to activating the alkylazaarenes **797** such as nitrobenzoxazoles and 3-nitropyridines were shown to be appropriate starting materials. A range of electron-donating and withdrawing groups were well tolerated in the optimized conditions achieving good yields, diastereomeric ratios and enantioselectivities (up to 95:5 dr and >99% ee). However, moving the nitro groups to the 4-position of the nitrobenzoxazole was shown to be disastrous for reactivity and enantioselectivity due to co-ordination of Pd and the nitro group furnishing the product in 38% yield, 18% ee and 83:17 dr. Nitroalkenes **245** were shown to be good substrates with similarly impressive enantioselectivities being achieved of up to >99% ee and 95:5 dr.²⁹¹

Scheme 248. Pd-Catalyzed Asymmetric Addition to *N*-Boc Aldimines



In a follow up publication by Lam, the scope of nitroalkenes **245** was investigated extensively, affording good yields and enantioselectivities up to 99% ee (Scheme 249). Regarding the

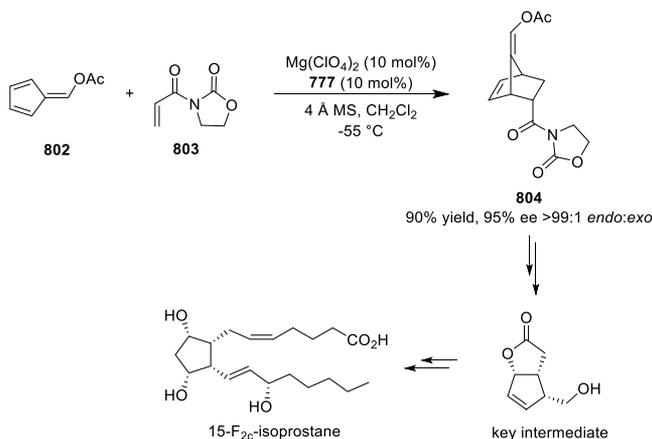
Scheme 249. Ni-Catalyzed Asymmetric Friedel–Crafts Alkylation between Nitrostyrenes and Aryl Ketones



2-acetylazaarenes **800** scope, substrates containing quinoline, pyrazine, thiazole, benzothiazole, or *N*-methylimidazole all reacted smoothly to produce the desired product **801** in yields up to 95% and with high levels of enantioselectivity (up to 99%). It was also shown that β -alkyl-substituted nitroalkenes were not optimal substrates even after reoptimization with enantioselectivities reaching a maximum of 82% ee.²⁹²

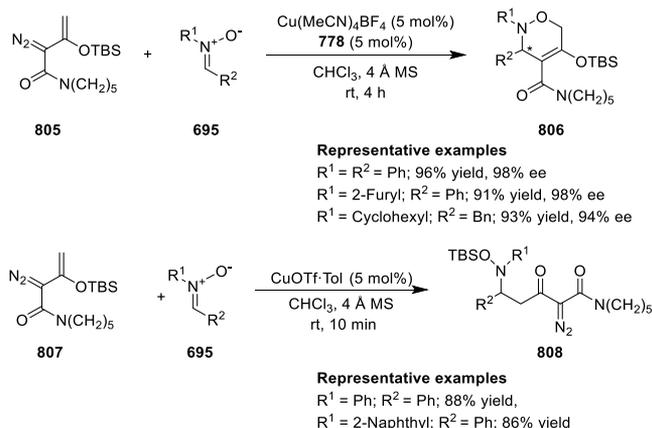
Zanoni performed an enantioselective Mg-catalyzed Diels–Alder cycloaddition of acetoxyfulvene **802** and 3-acryloyl-1,3-oxazolidin-2-one **803**. The resulting cycloadduct **804** was further transformed into a key building block for the formal synthesis of isoprostanoids (Scheme 250). Using Mg(ClO₄)₂ and **777** the cycloadduct product was isolated in 95% *ee* and with an *endo/exo* ratio of >99:1.²⁹³

Scheme 250. Mg-Catalyzed Asymmetric Synthesis of 15-F_{2c}-Isoprostane Intermediate



Doyle reported a catalyst divergent reaction of enoldiazoacetamides **805** with nitrones **695** (Scheme 251). When using

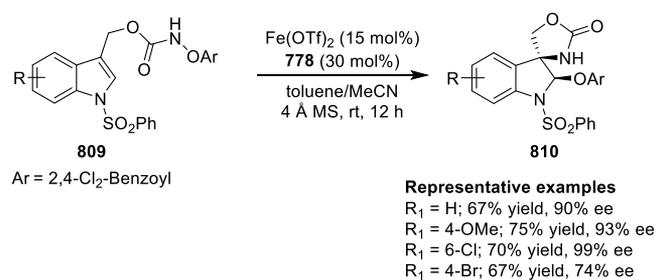
Scheme 251. Cu-Catalyzed Asymmetric Enoldiazoacetamide Cyclization



the achiral catalyst of Cu(OTf).Tol, the Mannich addition products **808** were observed in up to 98% yield. However, when using Cu(MeCN)₄BF₄ a [3 + 3] cyclization product was observed. Exploiting this catalyst system using **778** as the ligand enantioselectivities up to 98% *ee* were obtained with excellent yields. Regarding the substrate scope a range of aryl, heteroaryl and bulky alkyl substrates were tolerated with enantioselectivities and yields remaining high throughout (94–98% *ee*).²⁹⁴

Xu developed an Fe-catalyzed asymmetric intramolecular aminohydroxylation of indoles **809** using Fe(OTf)₂ and ligand **778** achieving up to 99% *ee* and >20:1 *dr* (Scheme 252). A scope of substituted indoles was attempted, and all were shown to be excellent substrates. Electron donating groups and electron withdrawing groups in the 5-, 6-, and 7-positions were

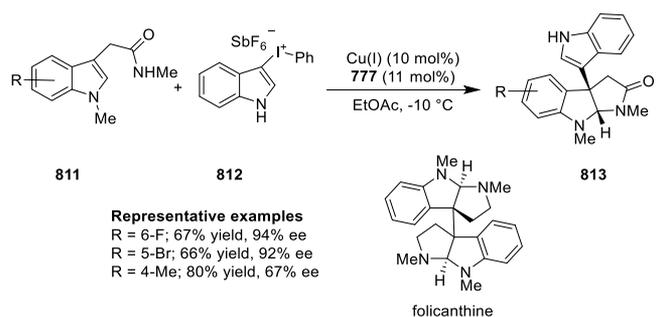
Scheme 252. Fe-Catalyzed Asymmetric Intramolecular Aminohydroxylation



well tolerated (86–99% *ee*), although 4-bromo-substituted indole caused a substantial drop in enantioselectivity to 74% *ee* and moderate yields.²⁹⁵

You reported the asymmetric dearomatization of indole acetamides **811** with 3-indolylphenyliodonium salts **812** catalyzed by a Cu(I) **777** complex (Scheme 253). This

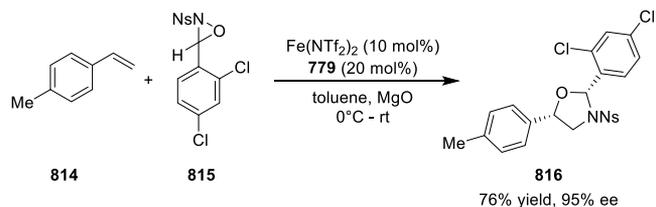
Scheme 253. Formal Synthesis of Folicanthine



process was then applied by carrying out the formal synthesis of folicanthine. Using [Cu(CH₃CN)₄PF₆] and ligand **777** in ethyl acetate enantioselectivities up to 94% *ee* were achieved with good yields. Electron-withdrawing groups were well tolerated regardless of the position with the 6-fluoro substrate giving 94% *ee*. It was also shown that placing a methyl group in the 4- and 5-positions led to products formed in 67% *ee* and 82% *ee*, respectively.²⁹⁶

Yoon applied ligand **779** in the Fe-catalyzed aminohydroxylation of alkenes **814** using oxaziridines **815** (Scheme 254). Using Fe(NTf₂)₂ and ligand **779** enantioselectivities up to

Scheme 254. Fe-Catalyzed Aminohydroxylation of Alkenes

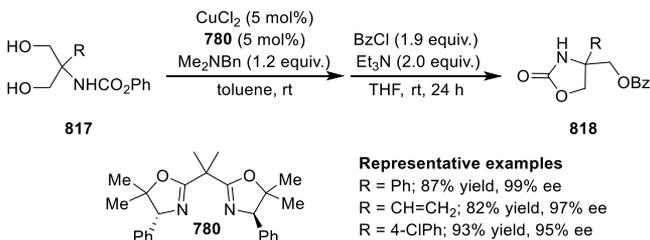


95% *ee* and 76% yield were obtained. A variety of aryl alkenes were tested in the reaction providing high enantioselectivities throughout with *p*-bromostyrene giving 63% yield and 85% *ee* as the lowest enantioselectivity. It was also shown that aliphatic alkenes and *trans*- β -methylstyrene were not tolerated in this reaction providing no product whatsoever.²⁹⁷

Kang reported the dual-functional Cu-catalyzed desymmetrization and subsequent kinetic resolution of serinols **817** to

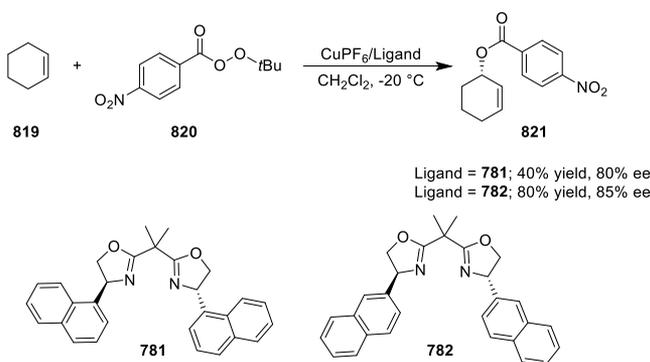
produce enantioenriched oxazolidinones (Scheme 255). Using ligand **780** and a CuCl₂ complex enantioselectivities were high across the board tolerating a range of alkyl, aryl and alkenes (94–99% *ee*).²⁹⁸

Scheme 255. Cu-Catalyzed Synthesis of Chiral Oxazolidinones



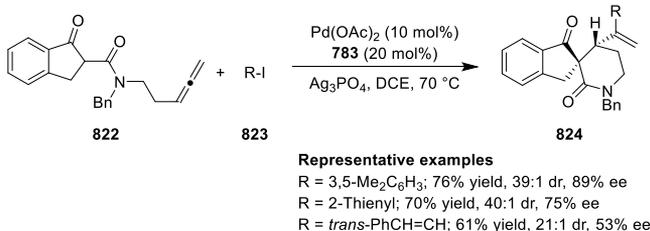
Andrus and Zhou prepared two regioisomers of naphthyl-substituted BOX ligands (**781** and **782**) and screened them in the allylic oxidation of cyclohexene **819** (Scheme 256). Using ligand **781** and CuPF₆ the corresponding product was isolated in 40% yield and 80% *ee*, while use of ligand **782** gave the product in 80% yield and 85% *ee*.²⁹⁹

Scheme 256. Cu-Catalyzed Allylic Oxidation of Cyclohexene



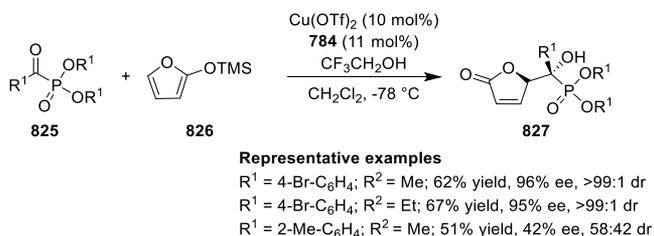
Dixon reported a Pd-catalyzed arylyative and vinylyative allene carbocyclization cascade. Using silver phosphate and a Pd(OAc)₂, **783** (*s*-butyl-substituted BOX ligand), the allene-linked ketoamide **822** pro-nucleophile and aryl iodides **823** were cyclized in good yields and up to 39:1 dr and 89% *ee* (Scheme 257). While a range of substituted aryl and *cis*-styrenyl iodides were well tolerated, *trans*-styrenyl iodides were shown to cause a large drop in enantioselectivity to 61% yield, 21:1 dr, 53% *ee*.³⁰⁰

Scheme 257. Pd-Catalyzed Asymmetric Carbocyclization Cascade



Miao developed an asymmetric Cu-catalyzed vinylogous Mukaiyama aldol reaction of α -keto phosphonates **825** and 2-TMSO furan **826** (Scheme 258). Using the ligand **784** with

Scheme 258. Cu-Catalyzed Asymmetric Mukaiyama Aldol Reaction of α -Keto Phosphonates



Cu(OTf)₂ and 2,2,2-trifluoroethanol as an additive, the aldol products **827** were obtained in enantioselectivities up to 96% *ee* and diastereoselectivities up to 99:1 dr. It was shown that the size of the phosphonate ester **825** group had little to no effect on the enantioselectivity or diastereoselectivity as both the methyl and ethyl esters gave the same results (95% *ee* and >99:1 dr). Electron-withdrawing and electron-donating groups were shown to have no effect on the results all giving enantioselectivities in the range of 94–98% *ee*. However, phosphonates that possessed an *ortho*-methyl substituent were less reactive giving enantioselectivities as low as 42% *ee* and diastereoselectivities as low as 58:42 dr.³⁰¹

3.1.2.1. Bis(oxazoline) Ligands with Glucose Derived Oxazoline Ring Substitution. Boysen developed a series of glucose-derived ligands (Figure 25) and applied them in Cu-

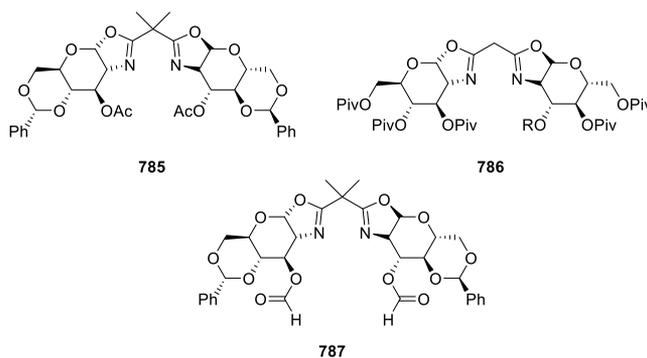
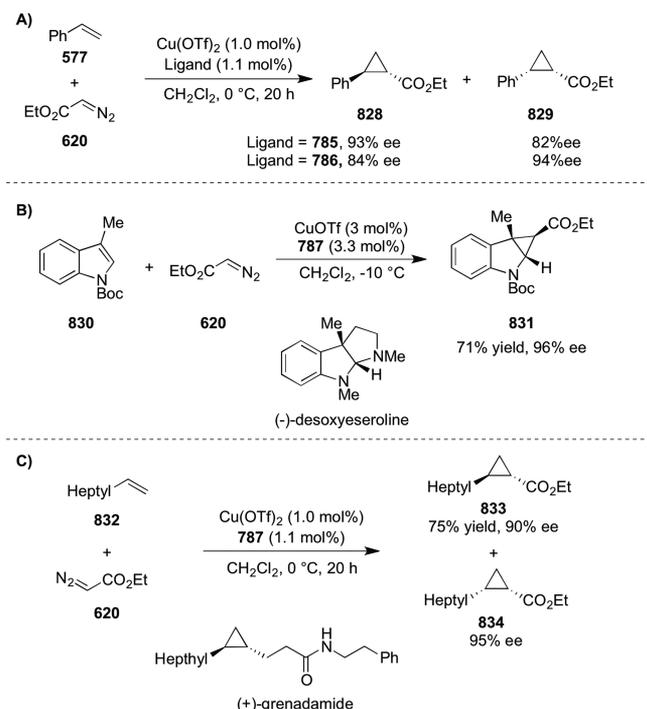
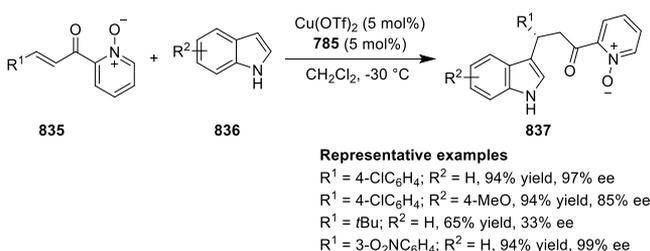


Figure 25. Glucose-derived BOX ligands.

catalyzed cyclopropanations. Initially both ligands **785** and **786** were applied in the cyclopropanation of styrene **577** giving up to 93% *ee* for the *trans*-product **828** and 94% *ee* for the *cis*-product **829**, respectively (Scheme 259A).³⁰² Following on from this initial report, ligand **785** was subsequently applied in the cyclopropanation of **830** affording the product in up to 71% yield and 96% *ee* (Scheme 259B). The subsequent product was then applied in the synthesis of (–)-desoxyseroline. A similar strategy was employed using ligand **787** to provide intermediate **833** in 75% yield and 90% *ee* in the synthesis of (+)-grenadamide (Scheme 259C).^{303,304}

Reddy reported the use of ligand **785** in the Cu-catalyzed asymmetric Friedel–Crafts reaction of 2-enoylpyridine-*N*-oxides **835** with indoles **836** (Scheme 260). Using ligand **785** and Cu(OTf)₂ enantioselectivities up to 99% *ee* were obtained in excellent yields. The indole substitution pattern had a large influence on the enantioselectivity, for example,

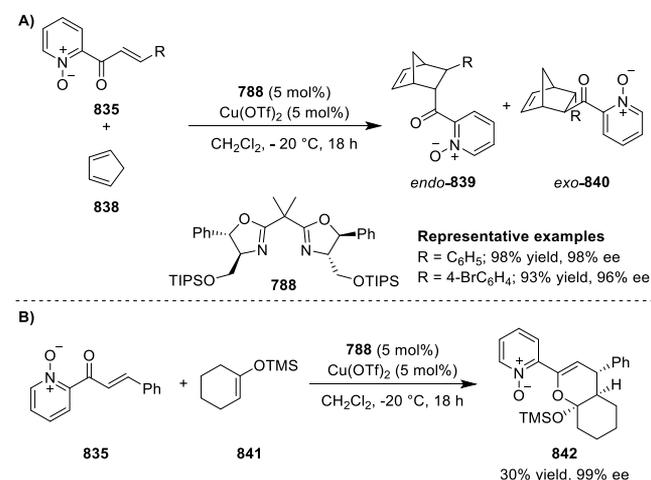
Scheme 259. Cu-Catalyzed Asymmetric Cyclopropanation

Scheme 260. Cu-Catalyzed Asymmetric Friedel–Crafts Reaction of 2-Enolpyridine-*N*-oxides

when the electron-donating 4-methoxyindole was used the enantioselectivity dropped to 85% *ee* although the yield was still high at 94%. For the 2-enolpyridine-*N*-oxide substrate scope it was shown the aryl and heteroaryl were suitable substrates with the enantioselectivities remaining high at 90–99% *ee*. When alkyl substituents were tested the enantioselectivity dropped dramatically with *t*-butyl affording the product in 65% yield and 33% *ee*, while the cyclohexyl-containing substrate did not give rise to product.³⁰⁵

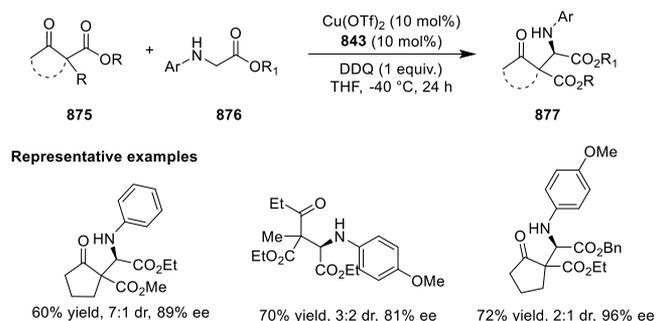
3.1.2.2. Bis(oxazoline) Ligands with Silyl-Protected Oxazoline Ring Substitution. Desimoni and Faita disclosed the Cu-catalyzed cycloaddition of 2-alkenolpyridine-*N*-oxides **835** and dienes **838** (Scheme 261A). Using ligand **788** and $\text{Cu}(\text{OTf})_2$ excellent enantioselectivities up to 98% *ee* and *endo:exo* ratios up to 99:1 were observed for the products **839/840**. Electron-withdrawing arylidenepyridine-*N*-oxides were also attempted and showed to have no effect on the enantioselectivity. In a subsequent publication, ligand **788** was applied in the cycloaddition between enol silyl ethers **841** and 2-alkenolpyridine-*N*-oxides **835** forming products **842** in poor yield (30%) and with high enantioselectivity (99% *ee*) (Scheme 261B).^{306,307}

The BOX ligands with modified oxazoline ring substitutions are widely applied in Lewis acid catalysis to great affect as

Scheme 261. Cu-Catalyzed Cycloaddition of 2-Alkenolpyridine-*N*-oxides and Dienes/Enol Silyl Ethers

shown above. While many of the modifications rely on costly non-natural amino alcohols more cost-effective ligands have been developed using carbohydrates for their chiral information.

3.1.3. Bis(oxazoline) Ligands with Backbone Modifications. Wang reported the Cu-catalyzed asymmetric cross coupling of α -substituted- β -keto esters **875** with *N*-substituted glycine esters **876** (Scheme 262). Using a $\text{Cu}(\text{OTf})_2$ and

Scheme 262. Cu-Catalyzed Asymmetric Coupling of α -Substituted- β -keto Esters and Glycine Esters

ligand **843** complex (Figure 26) gave the product **877** in good yields and up to 96% *ee* in a 2:1 dr. A variety of α -substituted- β -keto esters **875** were screened affording the products **877** in up to 72% yield and 96% *ee*. Acyclic α -substituted- β -keto esters however led to a drop in enantioselectivity as low as 81% *ee* in a 3:2 dr.³⁰⁸

Wang developed a Ni-catalyzed asymmetric amination of 3-bromooxindoles **879** with indolines **878** (Scheme 263), a synthetic methodology that was then applied in the formal synthesis of Psychotrimine (Figure 27). Using ligand **843** and $\text{Ni}(\text{OAc})_2$ as the optimized catalyst complex enantioselectivities up to 96% *ee* were obtained. Indolines and oxindoles with a variety of halides in the 4-, 5-, and 6-positions afforded the product in high enantioselectivities (86–96% *ee*). However, placing electron-donating substituents (methyl or methoxy) in the 5-position led to a significant drop in the enantioselectivity, to 61% *ee* and 74% *ee*, respectively.³⁰⁹

Yoon applied ligand **850** in the Fe-catalyzed kinetic resolution of *N*-sulfonyl oxaziridines **881** achieving up to

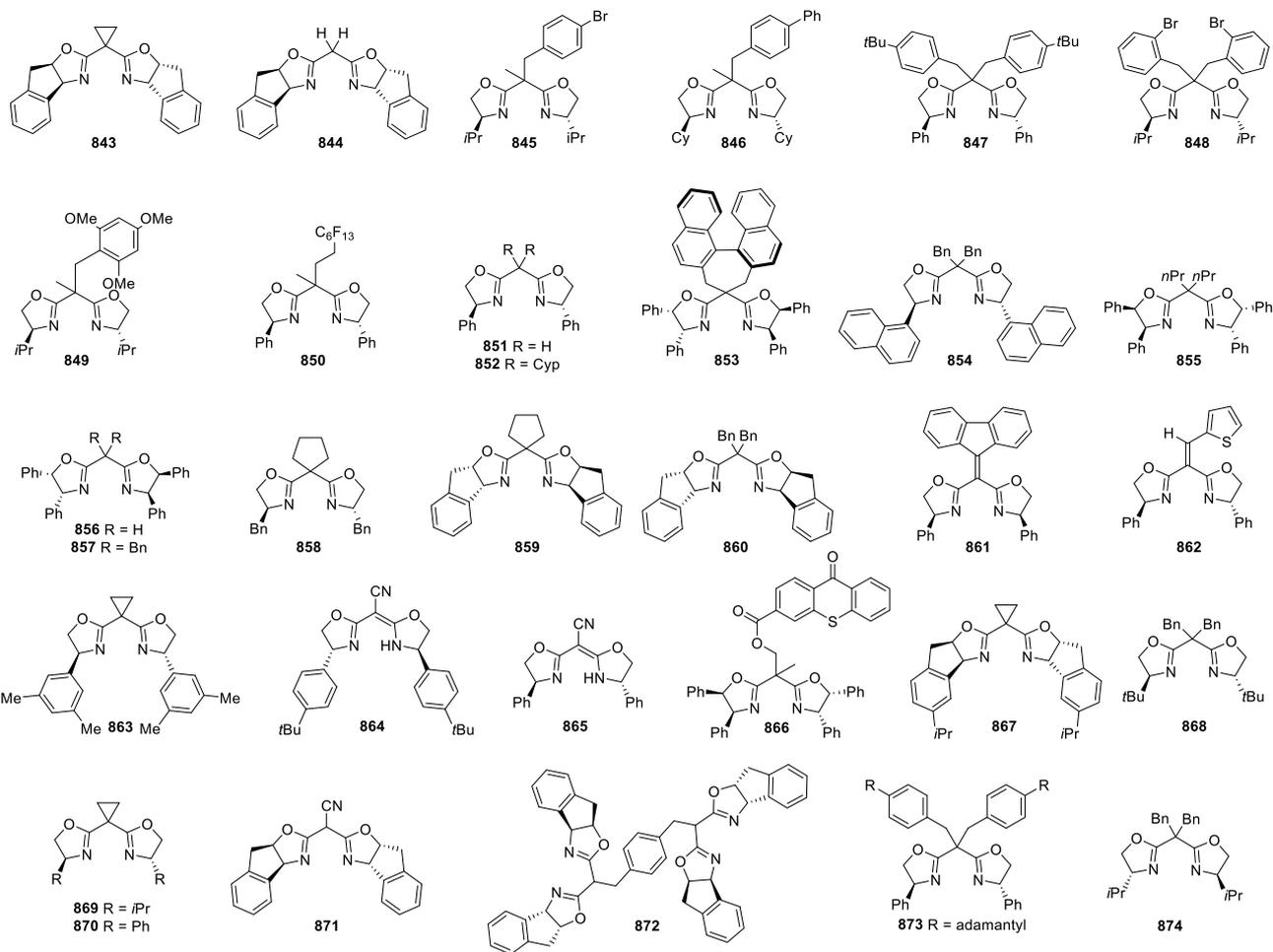
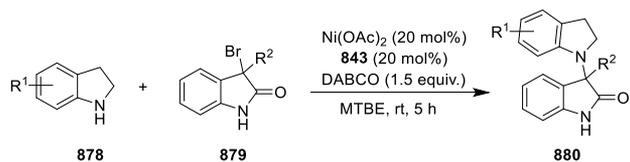


Figure 26. BOX ligand with backbone modifications.

Scheme 263. Ni-Catalyzed Asymmetric Amination of 3-Bromooxindoles



Representative examples

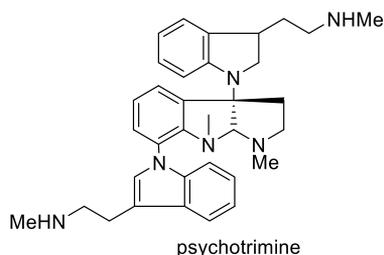
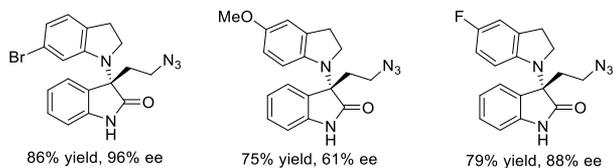
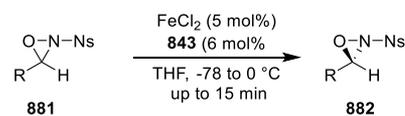
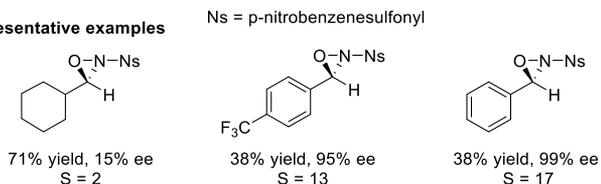


Figure 27. Psychotrimine.

99% *ee* and with selectivity factors up to 30 (Scheme 264). A variety of C-aryl oxaziridines **881** were screened in this

Scheme 264. Fe-Catalyzed Kinetic Resolution of *N*-Sulfonyl Oxaziridines

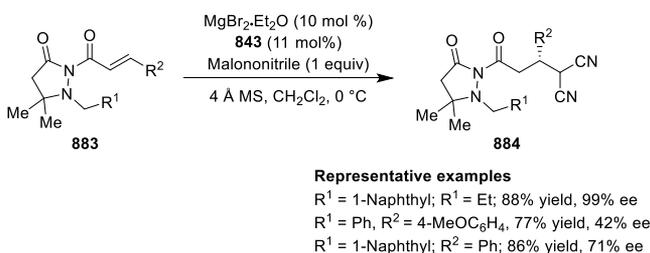
Representative examples



reaction with most substrates obtaining >90% *ee*. A major limitation of this method was that C-alkyl oxaziridines were not compatible with 15% *ee* being the highest enantioselectivity obtained.³¹⁰

Sibi developed a Mg-catalyzed asymmetric conjugate addition of malononitrile to pyrazolidone-derived enoates **883** (Scheme 265). Using MgBr₂·Et₂O and ligand **843** as the catalyst enantioselectivities up to 99% *ee* and good yields were obtained. It was also shown that when 4 Å MS were taken out of the optimized reaction conditions the enantioselectivity

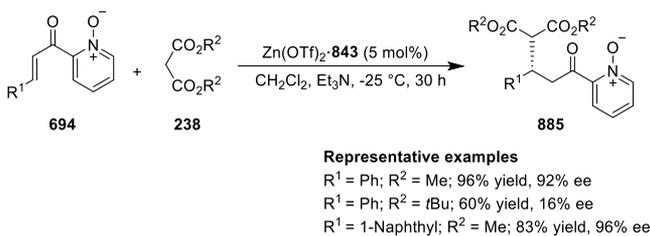
Scheme 265. Mg-Catalyzed Asymmetric Conjugate Addition to Pyrazolidone Derivatives



dropped as low as 44% *ee*. It was shown that the substituents on the enone component of the substrate greatly affected the enantioselectivity with electron donating *p*-methoxyphenyl groups resulting in enantioselectivities as low as 42% *ee*.³¹¹

Singh reported an asymmetric Zn-catalyzed Michael addition of malonates **238** to 2-enoylpyridine *N*-oxides **694** (Scheme 266). Using Zn(OTf)₂·**843** as the catalyst good yields

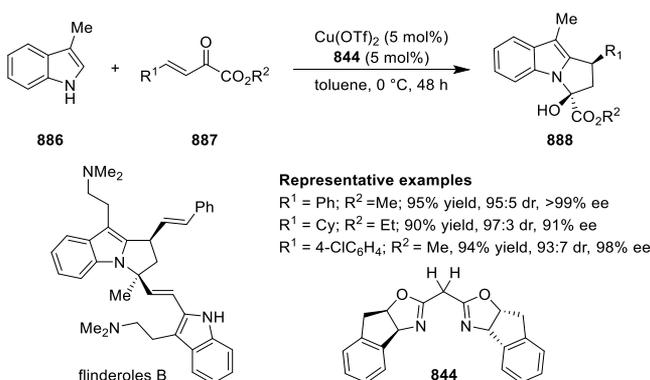
Scheme 266. Zn-Catalyzed Asymmetric Michael Addition of Malonates to 2-Enoylpyridine *N*-Oxides



and enantioselectivities of up to 96% *ee* were observed. It was shown that bulky malonates led to low enantioselectivities, such as di-*t*-butylmalonate which furnished the product in 60% yield and 16% *ee*. Interestingly, while many aromatic and heteroaromatic β -substituted 2-enoylpyridine *N*-oxides were suitable substrates in this reaction, the sterically hindered *t*-butyl β -substituted 2-enoylpyridine *N*-oxide did not give rise to any product.³¹²

Xiao developed a Cu-catalyzed Friedel–Crafts alkylation/*N*-hemiacetalization cascade reaction of indoles **886** with β,γ -unsaturated α -keto esters **887** (Scheme 267). Using Cu(OTf)₂ and the indanol-derived chiral ligand **844** as the catalyst enantioselectivities up to >99% *ee* and 97:3 dr were obtained.

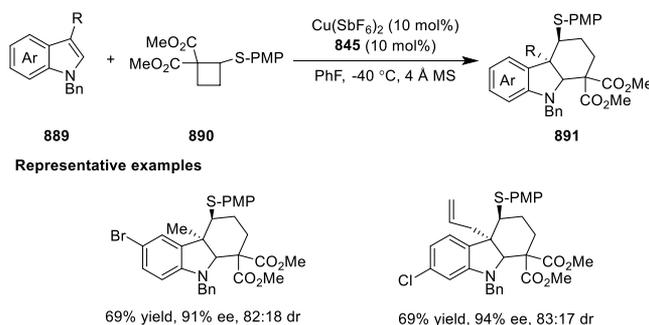
Scheme 267. Cu-Catalyzed Asymmetric Friedel–Crafts Alkylation/*N*-Hemiacetalization Cascade Reaction of Indoles



This methodology was then applied in the formal synthesis of flinderole B analogues. A series of β,γ -unsaturated α -keto ester substrates **887**, regardless of bulkiness or electronic nature, resulted in high levels of enantioselectivities of 91 to >99% *ee*.³¹³

3.1.3.1. Bis(oxazoline) Ligands with Benzyl Substituted Backbone Modifications. Tang developed a Cu-catalyzed [4 + 2] cycloaddition of indoles **889** and cyclobutanes **890** to yield cyclohexyl-fused indolines **891** (Scheme 268). This reaction

Scheme 268. Cu-Catalyzed Asymmetric Synthesis of Cyclohexyl-Fused Indolines



was initially developed using Cu(SbF₆)₂ in CH₂Cl₂ in a racemic manner and was then further developed using the chiral ligand **845** (Figure 28) affording up to 94% *ee* and 83:17

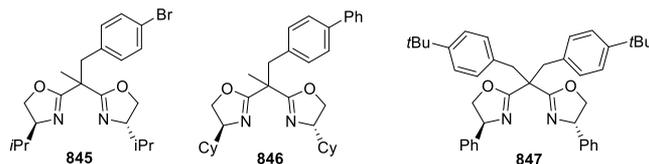


Figure 28. BOX ligands with substituted benzyl backbones.

dr improving upon the parent BOX ligand **600b**. This methodology was then applied to the formal total synthesis of (\pm)-strychnine and the total synthesis of (\pm)-akuammicine (Figure 29).³¹⁴

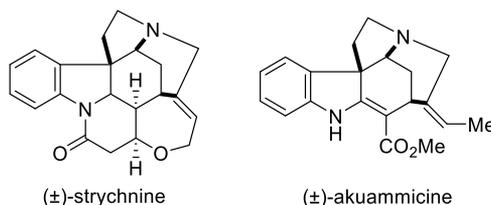
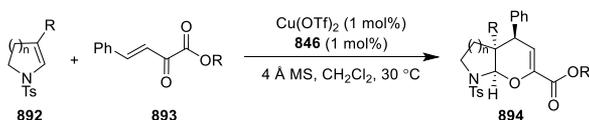


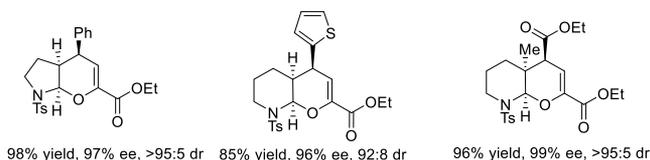
Figure 29. (\pm)-Strychnine and (\pm)-akuammicine.

Tang applied ligand **846** in the Cu-catalyzed enantioselective synthesis of bicyclic *N,O*-acetals **892** via a hetero-Diels–Alder reaction (Scheme 269). Catalyzed by a Cu(OTf)₂·**846** complex, β,γ -unsaturated α -keto esters **893** reacted with cyclic enamines **892** efficiently, affording the desired products **894** in excellent yields with excellent stereoselectivities (up to 99% yields up to >95:5 dr; and 95–99% *ee*). Aryl and heteroaryl moieties were tolerated in the β,γ -unsaturated α -keto ester **893** substrate scope without any deterioration in the enantioselectivity observed (95–99% *ee*).³¹⁵

Scheme 269. Cu-Catalyzed Asymmetric Synthesis of *N,O*-Acetals

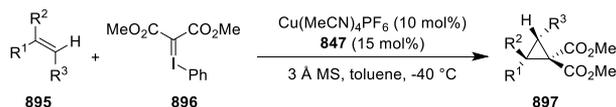


Representative examples

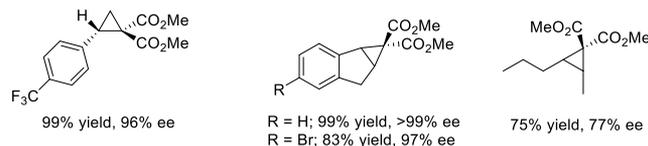


Tang applied ligand **847** in the asymmetric Cu-catalyzed cyclopropanation of alkenes **895** to yield the 1,1-cyclopropane diesters **897** (Scheme 270). Using phenyliodonium ylides **896**

Scheme 270. Cu-Catalyzed Enantioselective Cyclopropanation of Alkenes



Representative examples

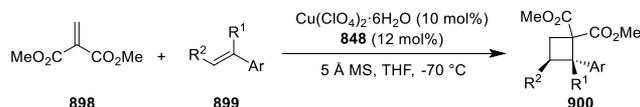


as the carbene transfer reagent, $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ as the catalyst and **847** as the chiral ligand, enantioselectivities of up to >99% ee were observed. A variety of terminal alkenes were very well tolerated in the reaction most of which gave enantioselectivities in the range of 87–96% ee. When nonterminal alkenes were subjected to the optimized reaction conditions, 5-, 6- and 7-membered cyclic alkenes yielded the product in up to >99% ee. One limitation of this reaction appeared to be aliphatic-substituted alkenes afforded the product in enantioselectivities as low as 77% ee. In 2018 Tang further developed the asymmetric cyclopropanation of trisubstituted olefins using modified bis(oxazoline) ligands.^{316,317}

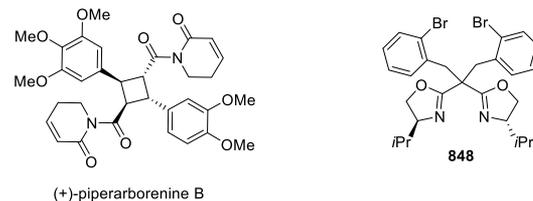
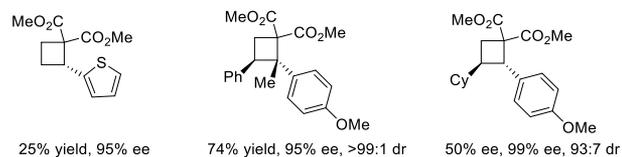
Tang also reported the Cu-catalyzed asymmetric construction of cyclobutanes **900** from methylenemalonate **898** and styrenes **899** (Scheme 271). Using ligand **848** and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ as the catalyst, enantioselectivities up to >99% ee and >99:1 dr were obtained. A range of styrenes **899** (aryl and heteroaryl) were well tolerated with all enantioselectivities observed ranging between 95 and 99% ee. This methodology was then applied to the synthesis of (+)-piperarborinine B a potential anticancer agent.³¹⁸

Building on this work, Tang developed a Cu-catalyzed enantioselective [3 + 2] annulation of cyclic enol silyl ethers **901** and cyclopropanes **902** (Scheme 272). Using a catalyst derived from $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and ligand **849**, enantioselectivities of up to 99% ee and >99:1 dr were observed. Bulky adamantyl groups on the cyclopropyl esters were deemed necessary as less bulky ester groups resulting in lower

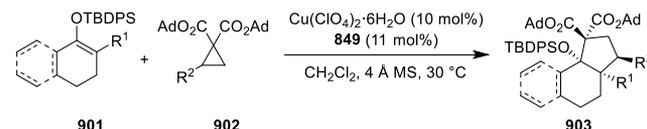
Scheme 271. Cu-Catalyzed Asymmetric Synthesis of Cyclobutanes



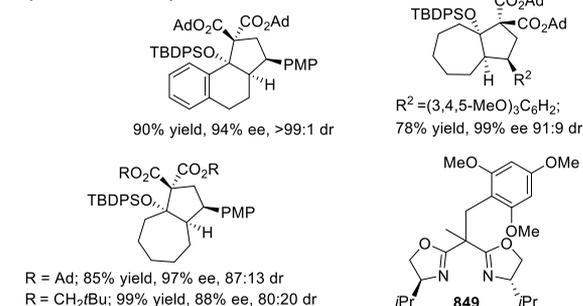
Representative examples



Scheme 272. Cu-Catalyzed [3 + 2] Annulation of Cyclic Enol Silyl Ethers and Cyclopropanes



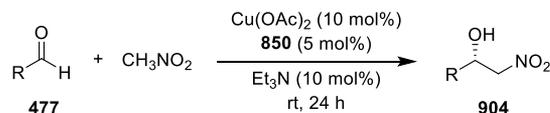
Representative examples



enantioselectivities (94% ee). A range of electronically variable cyclopropanes were tested with optimized conditions showing no significant drop in enantioselectivity (91–99% ee).³¹⁹

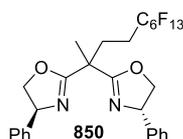
Cai utilized ligand **850**, a fluorinated derivative of ligand **600c**, in the Henry reaction between aldehydes **477** and nitromethane (Scheme 273). Using $\text{Cu}(\text{OAc})_2$ and ligand **850** enantioselectivities of up to 99% ee were achieved. While most aldehydes **477** performed well in the catalysis (90–99% ee), electron rich aldehydes such as *p*-methoxybenzaldehyde provided no product whatsoever. Cai further extended this

Scheme 273. Cu-Catalyzed Asymmetric Henry Reaction



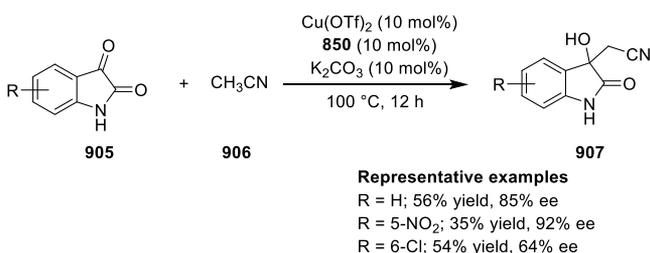
Representative examples

R = 4-O₂NC₆H₄; 75% yield, 99% ee
R = 4-BrC₆H₄; 69% yield, 94% ee
R = 4-FC₆H₄; 70% yield, 93% ee
R = 4-MeOC₆H₄; 0% yield



methodology to the Cu-catalyzed asymmetric addition of acetonitrile **906** to isatins **905** to produce a series of 3-hydroxy-2-oxindoles **907** (Scheme 274). Using Cu(OTf)₂ and ligand

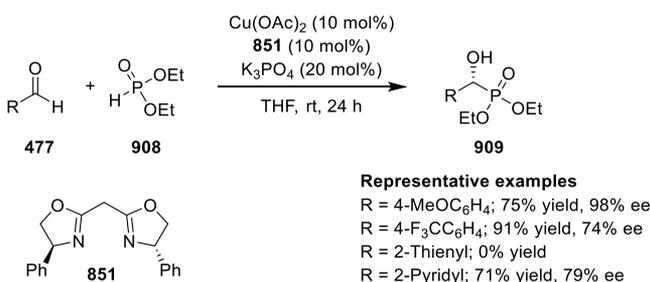
Scheme 274. Cu-Catalyzed Asymmetric Synthesis of 3-Hydroxy-2-oxindoles



850 enantioselectivities up to 92% ee were obtained. Regarding the substrate scope placing the electron-withdrawing chloro-group in the 6-position of the isatin led to lower enantioselectivities of 64% ee.^{320,321}

Cai reported the use of ligand **851** in the Cu-catalyzed hydrophosphonylation of aldehydes **477** to give the corresponding products **909** in good yields and with enantioselectivities of up to 98% ee (Scheme 275). Various electron-

Scheme 275. Cu-Catalyzed Asymmetric Hydrophosphonylation of Aldehydes



withdrawing and donating aldehydes **477** were screened in this reaction and these formed the products **909** in moderate to high levels of enantioselectivity (74–98% ee). The highly electron-withdrawing *p*-trifluoromethylbenzaldehyde gave the lowest enantioselectivity with 74% ee albeit in good yields (91% yield). Heteroaromatic systems largely were not compatible in this reaction with 2-thienyl- and 2-furyl-aldehydes not affording any product; the use of pyridine-2-carboxylaldehyde as substrate was more successful, with the product formed in 71% yield albeit with modest enantioselectivity (79% ee).³²²

Wang reported a Cu-catalyzed Friedel–Crafts reaction of indoles **792** with isatin-derived β,γ -unsaturated α -keto esters **910** (Scheme 276). Using the BINOL-derived ligand **853** (Figure 30), the products **911** were formed in good yields and enantioselectivities of up to 99% ee while using relatively low catalyst loadings of 0.5 mol %. Regarding the scope of this reaction a wide variety of isatin substrates **910** were well tolerated with most products being formed in 82–99% ee. Interestingly 6-bromoisatin gave rise to the corresponding product in 60% yield and a low enantioselectivity of 75% ee. The scope for indole substrates **792** was similarly impressive with a variety of functional groups being tolerated in good to excellent levels of enantioselectivity (82–99% ee). 7-Methyl-

Scheme 276. Cu-Catalyzed Asymmetric Friedel–Crafts Alkylation of Indoles and Isatin-Derived β,γ -Unsaturated α -Keto Esters

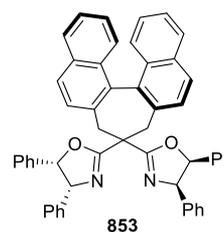
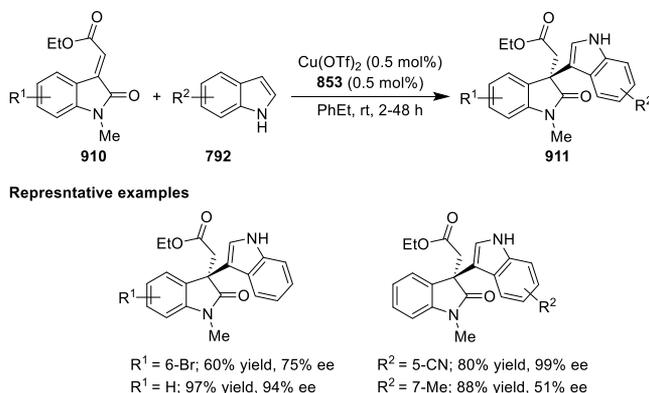
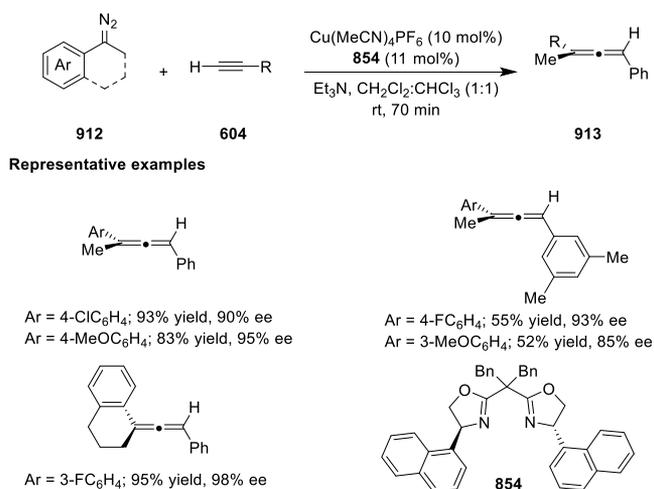


Figure 30. BINOL-derived BOX ligand **853**.

indole however formed the product in 88% yield and 51% ee.³²³

Wang developed an enantioselective synthesis of trisubstituted allenes **913** from a Cu-catalyzed cross-coupling of diazoalkanes **912** and terminal alkynes **604** (Scheme 277). The

Scheme 277. Cu-Catalyzed Asymmetric Synthesis of Trisubstituted Allenes

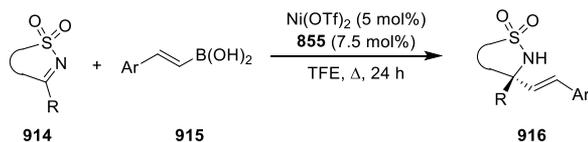


optimal catalyst complex was a combination of Cu-(MeCN)₄PF₆ and the naphthyl-containing ligand **854** which gave the product in good yields and up to 98% ee. A series of aryldiazoalkanes **912** bearing electron-deficient or -rich aromatic substituents were smoothly reacted with phenylacetylene to give the corresponding trisubstituted allenes **913** in high yields (78–95% yield) and very high levels of enantioselectivity (84–95% ee). The scope of the terminal

alkynes afforded the product in good enantioselectivities (92–98% *ee*) although the yields were lowered (46–60%)³²⁴

3.1.3.2. Bis-Phenyl BOX Ligands with Backbone Modifications. Zhang reported the asymmetric Ni-catalyzed alkenylation of ketimines **914** using alkenylboronic acids **915** (Scheme 278). The optimal catalyst combination of ligand **855**

Scheme 278. Ni-Catalyzed Asymmetric Alkenylation of Ketimines



Representative examples

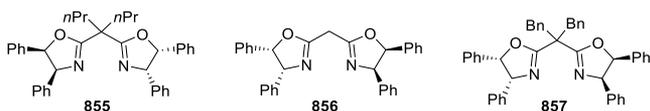
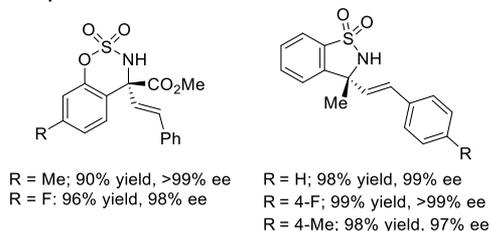
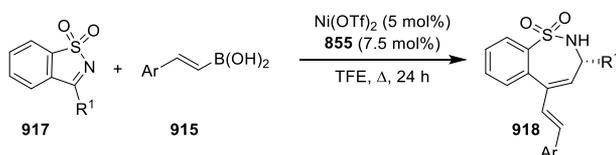


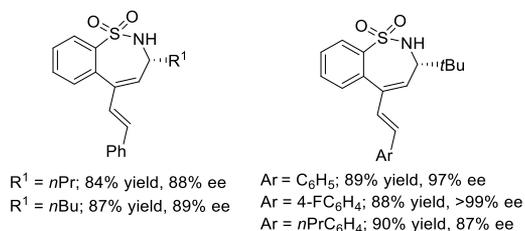
Figure 31. Bis-phenyl BOX ligands with backbone modifications.

(Figure 31) and Ni(OTf)₂ proved to be an extremely effective system providing the product in yields up to >99% and enantioselectivities of up to >99% *ee*. The initial ketimine **914** scope gave high to excellent enantioselectivities irrespective of the nature of the ketimine (88 to >99% *ee*). The alkenylboronic acid **915** scope showed tolerance of both alkyl and styrenylboronic acids with enantioselectivities remaining very high (93% to >99% *ee*). This methodology was then expanded to the π -conjugation-controlled site-selective asymmetric ketimine-alkenylation/ring-expansion (Scheme 279). Once again, this methodology proved robust with routinely high

Scheme 279. Ni-Catalyzed Asymmetric Ketimine Alkenylation/Ring-Expansion



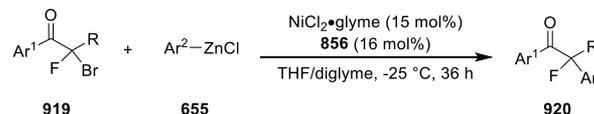
Representative examples



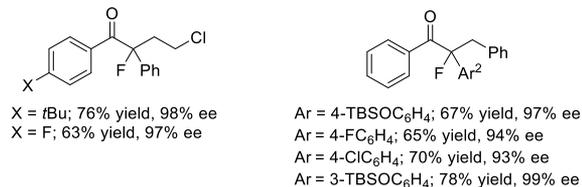
enantioselectivities being obtained (up to >99% *ee*).³²⁵ This methodology was further employed in the allylation of cyclic ketimines.³²⁶

Fu reported the development of an asymmetric Ni-catalyzed Negishi cross-coupling of α,α -dihaloketones **919** to give the corresponding products **920** containing quaternary-fluorinated stereocenters (Scheme 280). Using NiCl₂·glyme and ligand

Scheme 280. Ni-Catalyzed Asymmetric Negishi Cross-Coupling of α,α -Dihaloketones



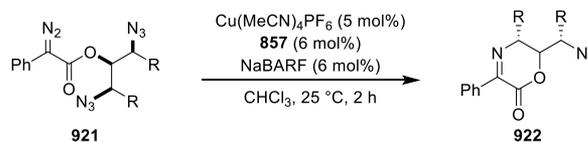
Representative examples



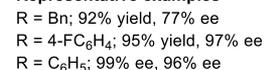
856 enantioselectivities of up to 99% *ee* were obtained. The structure of the ketone **919** had no major effect on the enantioselectivity with most substrates furnishing the product in high levels of enantioselectivities (92% to 98% *ee*). In a similar fashion the nature of the nucleophilic zinc reagent **655** had little impact on the enantioselectivity, all giving high enantioselectivities (91 to 99% *ee*). This methodology was further applied by Futo in the Negishi phenylation of racemic α -bromonitriles and the Kumada cross-coupling of racemic α -bromoketones^{327–329}

An asymmetric Cu-catalyzed desymmetrization of *meso*- α,α' -diazido alcohols **921** to produce cyclic α -imino esters **922** was reported by Gu (Scheme 281). The optimized conditions

Scheme 281. Cu-Catalyzed Desymmetrisation of *meso*- α,α' -Diazido Alcohols



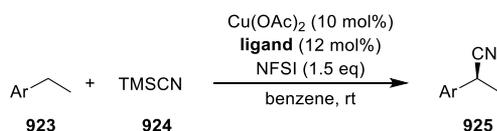
Representative examples



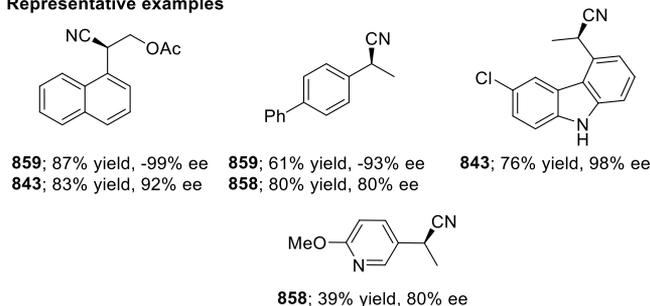
utilized CuPF₆(MeCN)₄ and ligand **857** as the catalyst complex and NaBARF as the noncoordinating counterion. This combination furnished the corresponding products **922** in up to 97% *ee*, which was carried out on gram scale. Aryl-substituted *meso*- α,α' -diazido alcohol substrates **921** afforded the products in very high levels of enantioselectivity (92 to 97% *ee*). When alkyl-containing substrates were used, the enantioselectivity dropped as low as 77% *ee*.³³⁰

3.1.3.3. Bis(oxazoline) Ligands with Cyclopentyl Backbone Modifications. Liu developed an asymmetric Cu-catalyzed cyanation by C–H activation of benzylic C–H bonds for the synthesis of benzylic nitriles **925** (Scheme 282). This reaction was catalyzed by a Cu(OAc)₂·BOX complex using NFSI (*N*-fluorobenzenesulfonylimide) as the oxidant.

Scheme 282. Cu-Catalyzed Asymmetric Synthesis of Benzylic Nitriles



Representative examples



Enantioselectivities up to 99% *ee* were obtained but each substrate had to be screened for the optimal ligand, with BOX ligand **843** and the modified BOX ligands **858** and **859** found to be the ligands of choice (Figure 32). Alkyl-naphthylenes, alkyl arenes and alkyl heteroarenes all performed well under the optimized conditions with the lowest enantioselectivities obtained being 80% *ee*.³³¹

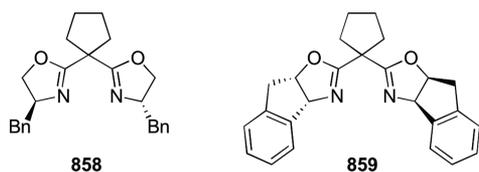
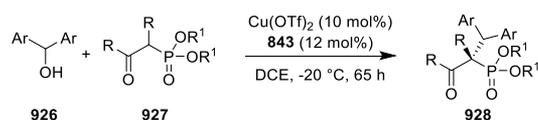


Figure 32. BOX ligands with cyclopentyl backbone modification.

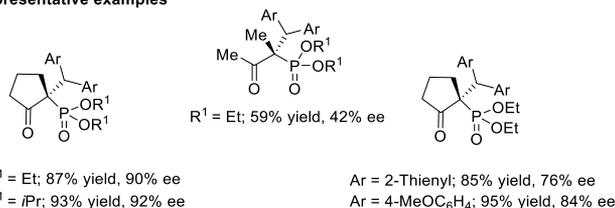
Nishibayashi developed the Cu-catalyzed enantioselective alkylation of β -keto phosphonates **927** using diaryl methanols **926** as the electrophiles (Scheme 283). $\text{Cu}(\text{OTf})_2$ and ligand

Scheme 283. Cu-Catalyzed Asymmetric Alkylation of β -Keto Phosphonates



Ar = 4-MeO-3-MeC₆H₃

Representative examples

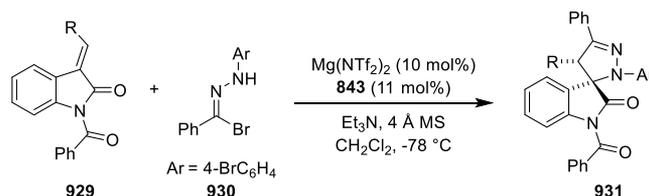


843 was shown to be the optimal catalyst giving the alkylated product **928** in up to 92% *ee*. Cyclic phosphonates were shown to be compatible with this catalysis affording the product in up to 92% *ee*, while acyclic phosphonates furnished the product in as low as 42% *ee*. Regarding the diarylmethanol the electronic nature of the aryl groups had little effect on the

enantioselectivity (84–90% *ee*), heteroaryl substrates however produced the largest drop in enantioselectivity to 76% *ee*.³³²

Stanley reported the Mg-catalyzed asymmetric cycloaddition of nitrile imines **930** with methyleneindolinones **929** to produce enantioenriched spirocyclic products **931** in up to 99% *ee* employing ligand **843** (Scheme 284). A range of

Scheme 284. Mg-Catalyzed Asymmetric Cycloaddition of Nitrile Imines with Methyleneindolinones



Representative examples

R = 4-BrC₆H₄; 63% yield, 94% ee
R = 4-MeOC₆H₄; 81% yield, 99% ee
R = 2-BrC₆H₄; 43% yield, racemic
R = (*E*)-*t*-butyl; 70% yield, 99% ee

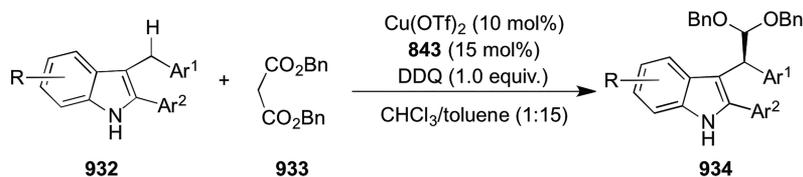
methyleneindolinones were screened in the reaction with electron withdrawing and donating substituents giving rise to the product in up to 99% *ee*. Interestingly, an *ortho*-bromo substituent on the methyleneindolinone substrate led to racemic product.³³³

Gong developed an asymmetric Cu-catalyzed cross-coupling of 3-indolmethyl C–H bonds **932** with diaryl malonates **933** (Scheme 285). With $\text{Cu}(\text{OTf})_2$ as the Lewis acid, **843** as the chiral ligand and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as the oxidant, the product was formed in up to 99% yield and 96% *ee*. The substrate scope included a range of 3-arylmethylindole derivatives **932** which proved successful for both electronically rich or poor 3-arylmethyl substituted substrates (up to 99% yield and 94% *ee*). The electronic properties of the aryl substituent had little effect on the enantioselectivity (86 to 94% *ee*). The introduction of substituents onto the indole moiety afforded the product in high enantioselectivity (78% yield and 96% *ee*).³³⁴

Liu reported the trifluoromethylalkynylation of alkenes **464** via Cu-catalyzed radical relay producing chiral CF₃-containing propargylic compounds **936** in up to 97% *ee* (Scheme 286). Using a complex formed from $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ and ligand **860** as the catalyst complex and Togni's reagent **750** as the CF₃ source, a wide range of products were accessed in good yields (up to 88% yield). The substrate scope for the alkene **464** coupling partner included a series of structurally diverse alkenes with electron-rich and poor styrenes affording the product in enantioselectivities up to 97% *ee*. Heteroaryl alkenes also yielded the product in high enantioselectivities (87 to 95% *ee*).³³⁵

Pan reported the photoredox cyanoalkylation of alkenes **464** using redox active *N*-hydroxy-phthalimide esters **937**. By merging Ir-catalyzed photocatalysis and Cu-catalysis the products were formed in up to 94% *ee* when using CuBr and ligand **859** (Scheme 287). A range of styrenes **464** were tested using the optimized reaction conditions, most of which gave the product in high enantioselectivities (84 to 94% *ee*). Large *p-t*-butylstyrene or 2-naphthylstyrene led to a drop in enantioselectivity (76% *ee* and 65% *ee*, respectively). *m*-Bromostyrene as substrate led to the most substantial drop

Scheme 285. Cu-Catalyzed Asymmetric C–H Activation of Indole Derivatives



Representative examples

R = 5-Cl; Ar¹ = 4-BrC₆H₄; Ar² = Ph; 78% yield, 96% ee

R = H; Ar¹ = 4-BrC₆H₄; Ar² = Ph; 97% yield, 93% ee

R = H; Ar¹ = 4-MeOC₆H₄; Ar² = Ph; 74% yield, 86% ee

Scheme 286. Cu-Catalyzed Asymmetric Trifluoromethylalkynylation of Alkenes



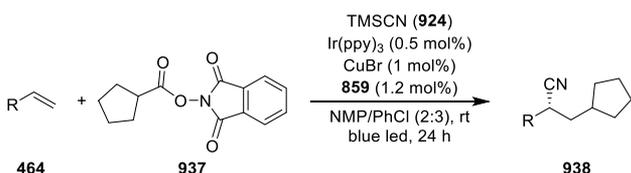
Representative examples

R = 2-Thienyl; 63% yield, 91% ee

R = 4-MeO₂CC₆H₄; 66% yield, 97% ee

R = 4-BrC₆H₄; 80% yield, 92% ee

Scheme 287. Photoredox Cyanoalkylation of Alkenes



Representative examples

R = 2-BrC₆H₄; 72% yield, 94% ee

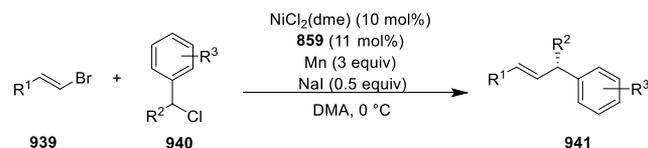
R = 3-BrC₆H₄; 73% yield, 54% ee

R = 2-Naphthyl; 76% yield, 65% ee

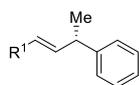
in enantioselectivity with the product being obtained in 54% ee.³³⁶

Reisman reported the Ni-catalyzed cross-electrophile reductive coupling between vinyl and benzyl electrophiles (Scheme 288). Using NiCl₂(dme) as the catalyst and the chiral ligand 859, enantioselectivities up to 97% ee were observed. Both the bromostyrene 939 and benzyl chloride 940 substrate scope had little effect on the enantioselectivity (as low as 85% ee)

Scheme 288. Ni-Catalyzed Asymmetric Cross-Electrophile Coupling of Vinyl and Benzyl Electrophiles



Representative examples



R¹ = 4-BpinC₆H₄; 59% yield, 94% ee

R¹ = 4-HOC₆H₄; 86% yield, 93% ee

R¹ = 3,4-(MeO)₂C₆H₃; 73% yield, 96% ee

R² = Et; R³ = H; 80% yield, 97% ee

R² = Me; R³ = 2-Me; 44% yield, 85% ee

R² = Me; R³ = 4-MeO; 64% yield, 93% ee

with pinacol boronate and free phenol functional groups being compatible with the reaction.³³⁷

3.1.3.4. Bis(oxazoline) Ligands with Unsaturated Backbone Modifications. Fu detailed the synthesis of the novel ligand 861 (Figure 33) and its application in the Cu-catalyzed

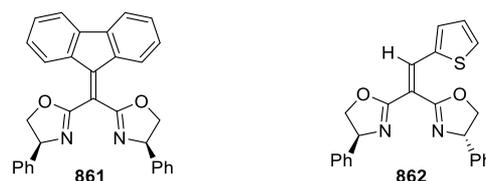
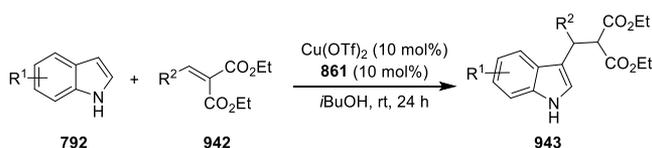


Figure 33. BOX ligands with unsaturated backbone modifications.

Friedel–Crafts alkylation of indoles 792 by alkylidene malonates 942 (Scheme 289). The optimal reaction conditions

Scheme 289. Cu-Catalyzed Friedel–Crafts Alkylation of Indoles and Alkylidene Malonates



Representative examples

R¹ = H; R² = 2-ClC₆H₄; 60% yield, 88% ee

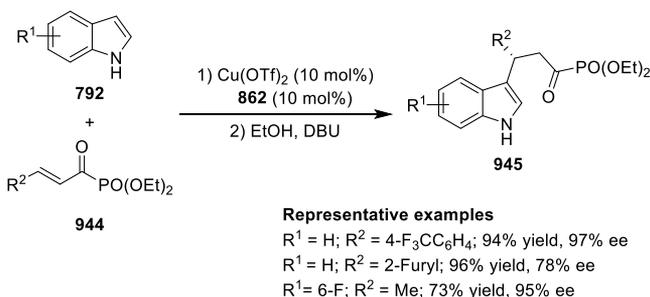
R¹ = H; R² = 4-MeC₆H₄; 99% yield, 37% ee

R¹ = 6-Cl; R² = C₆H₄; 80% yield, 10% ee

utilized a combination of Cu(OTf)₂ and ligand 861, which yielded the product in up to 88% ee. The substrate scope probed electronic properties of the alkylidene malonates with *p*-substituted substrates leading to a significant drop in enantioselectivities (37% ee). Substitution on the indole ring also played a large effect with 6-chloroindole forming the product in just 10% ee.³³⁸

Fu reported the Cu-catalyzed conjugate addition of indoles 792 to β -substituted unsaturated acyl phosphonates 744 to produce 3-indolyl adducts in good yields (Scheme 290). Heteroarylidene-tethered bis(oxazoline) ligand 862 and Cu(OTf)₂ were used as the optimized catalytic conditions forming products in modest to very high yields (73–96%) and achieving very high levels of enantioselectivities of up to 97% ee. Regarding the substrate scope it appears that esters, nitrile, halides and ethers are all well tolerated on the indole ring with enantioselectivities remaining high (90–96% ee). Regarding the scope of the acyl phosphonates 744 a range of aryl and heteroaryl substrates were tested with 2-furyl

Scheme 290. Cu-Catalyzed Conjugate Addition of Indoles to β -Substituted Unsaturated Acyl Phosphonates



providing the product in the lowest enantioselectivity (78% ee).³³⁹

Gu applied ligand **863** (Figure 34) in the Cu-catalyzed ring opening of diaryliodonium salts **946** in the synthesis of chiral

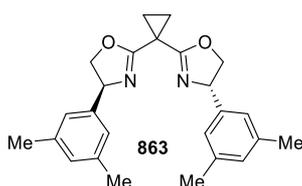
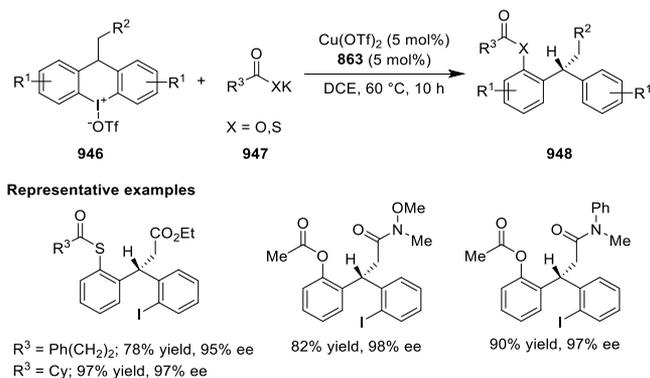


Figure 34. BOX ligand with xylene-derived substituents.

Scheme 291. Cu-Catalyzed Asymmetric Synthesis of Diarylmethanes



diarylmethanes **948** (Scheme 291). Using thiolates and carboxylates **947** as nucleophiles the asymmetric Cu(OTf)₂-catalyzed ring opening gave the products **948** in good yields (up to 99% yield) and enantioselectivities up to 98% ee. Substituted thioacetates appeared to have a small effect on the enantioselectivity with most substrates ranging between 91 to 97% ee. The substrate scope for the carboxylates gave high enantioselectivity once again (93 to 98% ee) but the reaction time was extended from 10 to 48 h.³⁴⁰

3.1.3.5. Application of Semicorrin Derived Ligands. Toste developed the Re-catalyzed asymmetric reduction of ketones **949** and imines **951** using Semicorrin ligands **864** and **865** developed by Pfaltz.^{341a,c} When carrying out the asymmetric hydrosilylation of ketones **949** both ligands **864** and **865** (Figure 35) were screened reaching up to 94% ee and 93% ee, respectively, for substituted tetralones (Scheme 292). This methodology appeared to work only with aryl ketone

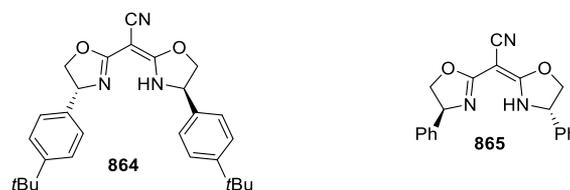
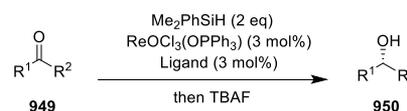
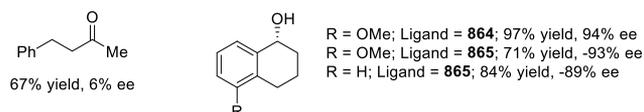


Figure 35. Semicorrin derived BOX ligands **864**–**865**.

Scheme 292. Re-Catalyzed Asymmetric Reduction of Ketones

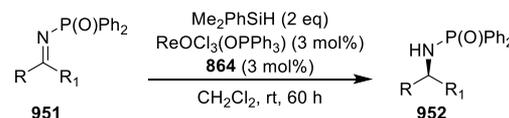


Representative examples

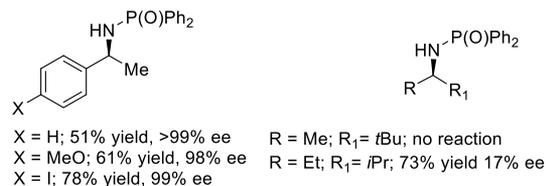


substrates with 4-phenyl-2-butanone furnishing the product in 67% yield and 6% ee. This methodology was then expanded to the reduction of aryl phosphinyl imines **951** which furnished the product in up to >99% ee for some aryl and heteroaryl imines (Scheme 293). Similarly, this reaction was limited as alkyl imines furnished the products **952** in lower enantioselectivities (0–32% ee).^{341d}

Scheme 293. Re-Catalyzed Asymmetric Reduction of α -Aryl Phosphinyl Imines



Representative examples



3.1.3.6. Application of Bi-Functional BOX Ligand with Photosensitizer Backbone Modifications. Xiao developed a bifunctional box derived ligand **866** (Figure 36), which has a built-in diarylketone photosensitizer which allows the ligand to function as a chiral catalyst and a photocatalyst. Using ligand

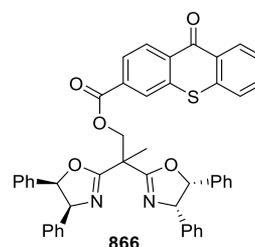
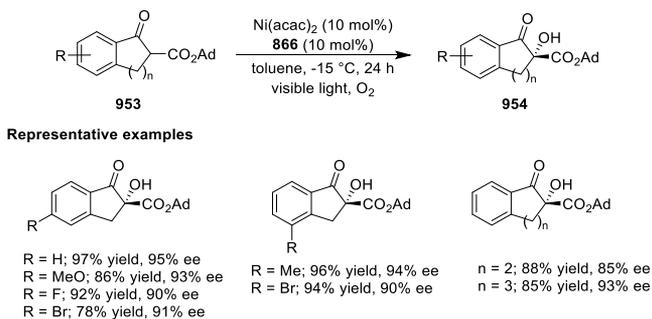


Figure 36. Bifunctional BOX ligand **866** with photosensitizer.

866 and $\text{Ni}(\text{acac})_2$ the oxidation of β -keto esters **953** afforded the desired products **954** in up to 95% *ee* (Scheme 294).

Scheme 294. Ni-Catalyzed Asymmetric Oxidation of β -Keto Esters



Regarding the substrate scope a range of cyclohexanone-derived β -keto esters **953** formed the products in high enantioselectivity (88–95% *ee*). Cycloheptanone-derived β -keto esters also formed the products in up to 93% *ee*.³⁴²

3.1.3.7. Bis(oxazoline) Ligands with Miscellaneous Backbone Modifications. You applied ligand **867** in the Cu-catalyzed dearomative amination of tryptamines **955**. Using ligand **867** (Figure 37), CuBr and *O*-(2,4-dinitrophenyl)-

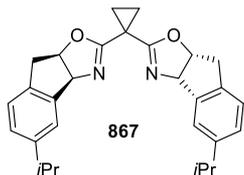


Figure 37. Functionalized indene-derived ligand **867**.

hydroxylamine **956**, an efficient electrophilic aminating reagent a range of 3-amino-pyrroloindolines **957** were synthesized in up to 95% *ee*. A range of indole protecting groups were attempted with allyl, methyl and benzyl all affording the product in high enantioselectivities (86–92% *ee*) (Scheme 295). An indole substrate scope was carried out with a variety of electron withdrawing and donating groups in the 4–7 positions providing the products in high enantioselectivities (82–95% *ee*). This methodology was then applied to the formal synthesis of tryptophan-derived alkaloids (–)-psychotriasine (Figure 38).³⁴³

Scheme 295. Cu-Catalyzed Enantioselective Synthesis of 3-Amino-pyrroloindolines

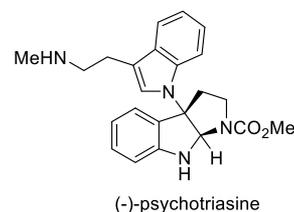
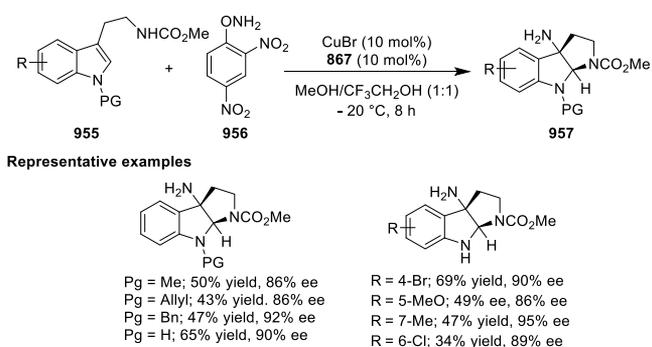
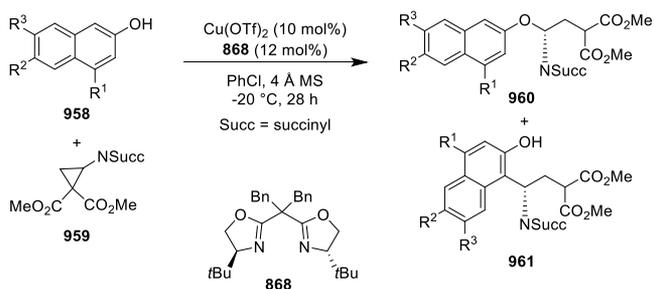


Figure 38. (–)-Psychotriasine.

Guo reported the Cu-catalyzed Friedel–Crafts alkylation of β -naphthols **958** and aminocyclopropanes **959** to make γ -aminobutyric acid-like structures **961**. Using the chiral ligand **868** and $\text{Cu}(\text{OTf})_2$ the desired Friedel–Crafts products were isolated in up to 98% *ee* (Scheme 296). The undesired *O*-

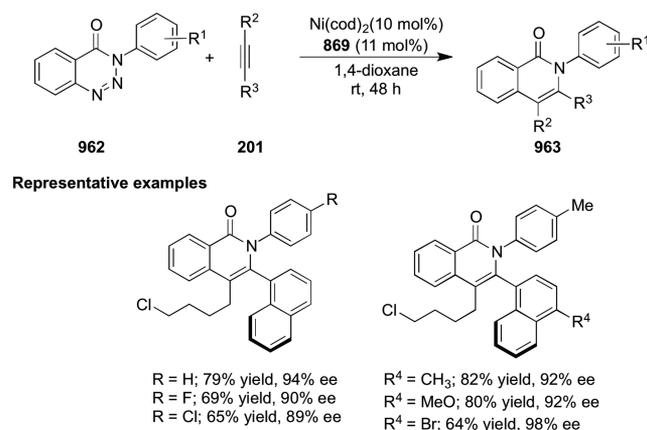
Scheme 296. Cu-Catalyzed Asymmetric Friedel–Crafts Alkylation of β -Naphthols and Aminocyclopropanes



alkylation product **960** was seen when less sterically demanding β -naphthols were used. Besides the chemoselectivity issue presented by the *O*-alkylation product a large number of electronically diverse β -naphthols were applied to this catalysis forming the products in high levels of enantioselectivity (90–98% *ee*).³⁴⁴

Liu reported the synthesis of axially chiral isoquinolones **963** via a Ni-catalyzed denitrogenative transannulation (Scheme 297). $\text{Ni}(\text{cod})_2$ and ligand **869** (Figure 39) proved to be the optimal conditions for the denitrogenative transannulation of 1,2,3-benzotriazin-4(3H)-ones **962** and bulky internal alkynes

Scheme 297. Ni-Catalyzed Enantioselective Denitrogenative Transannulation



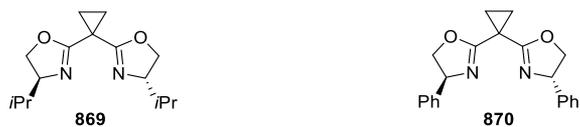
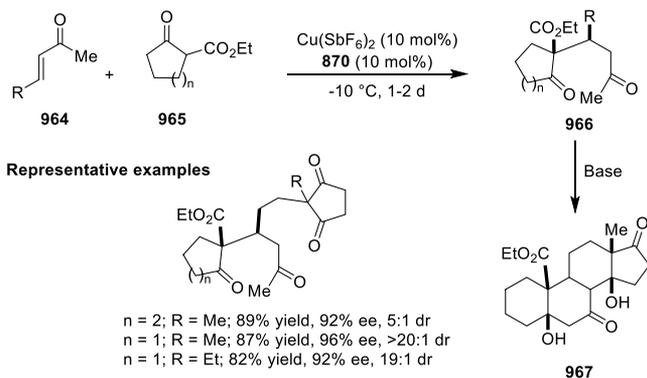


Figure 39. BOX ligand with cyclopropyl-modified backbone.

201, to give the product **963** in good yields and enantioselectivities of up to 98% *ee*. This reaction is amenable to both electron-withdrawing and electron donating groups at the 4-position of the naphthalene ring with 4-bromonaphthalene giving the highest *ee* of 88%. The stability of these axially chiral products **963** was tested by refluxing them in toluene for 1 day. No erosion of enantioselectivity was observed demonstrating the high barrier to rotation about the naphthyl–isoquinolone bond.³⁴⁵

Nagorny developed a concise Cu-catalyzed synthesis of oxygenated steroids *via* a sequential Michael-addition/intramolecular aldol cyclization protocol (Scheme 298). Using

Scheme 298. Cu-Catalyzed Asymmetric Synthesis of Oxygenated Steroid Derivatives



ligand **870** (Figure 39) and Cu(SbF₆)₂ to catalyze the Michael addition of β,β' -enones **964** and substituted β,β' -keto esters **965** resulted in Michael adducts which can undergo base-promoted aldol cascade reactions resulting in steroid skeletons **967**. Regarding the substrate scope of the Michael addition, five-membered β -keto esters **965** proceeded with high levels of diastereocontrol (up to >20:1 dr and up to 96% *ee*). Six-membered β -keto esters **965** proceeded in high enantioselectivities (up to 94% *ee*) but the diastereocontrol dropped to as low as 4:1 dr. Once treated with base the double aldol cyclization occurred to form the steroidal backbone.³⁴⁶

Kobayashi applied ligand **871** (Figure 40) in the Ca-catalyzed 1,4-addition to form product **969** and a [3 + 2] cycloaddition toward the synthesis of pyrrolidine derivatives **970** (Scheme 299). Using CaCl₂ and ligand **871** as the optimized catalyst the tandem reaction sequence between imines **968** and enones **157** proceeded in up to 99% *ee* and in

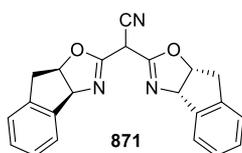
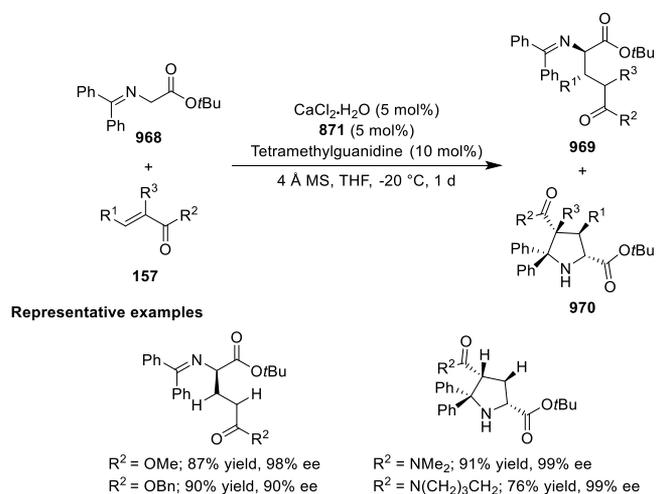


Figure 40. Indene BOX ligand **871** with nitrile backbone modification.

Scheme 299. Calcium-Catalyzed Asymmetric Synthesis of Pyrrolidine Derivatives



good yields (up to 98% yield). Imines **968** containing amides appeared to give complete conversion to the pyrrolidine products **970** while ester-containing imines underwent the 1,4-addition with complete selectivity to form **969**.³⁴⁷

Miñana reported the application of the recyclable ligand **872** (Figure 41) in the Cu-catalyzed Henry reaction of aldehydes

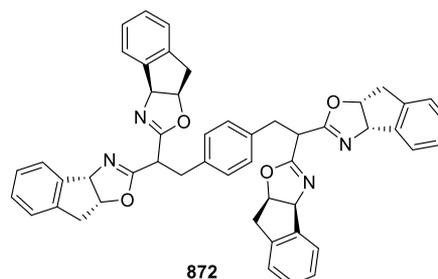
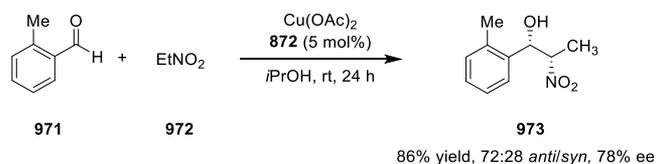


Figure 41. Recyclable BOX ligand **872**.

971. Using Cu(OAc)₂ and ligand **872** enantioselectivities up to 78% *ee* were observed with *anti/syn* ratios of up to 72:28 (Scheme 300). This ligand avails of a release-capture technique

Scheme 300. Cu-Catalyzed Enantioselective Henry Reaction with a Non-supported Recyclable Ligand



which can be recycled after a run of catalysis without the need for a heterogeneous support. After the reaction solvent is removed the ligand is precipitated by washing with hexane/ether removing it from the product solution. The precipitated ligand is dried and reused in another reaction. The viability of **872** as a recyclable ligand was tested by placing it through 14 subsequent runs of catalysis after recovery. This showed a slight decrease in enantioselectivity to 72% *ee* after 14 cycles in catalysis.³⁴⁸

Gong reported the Cu-catalyzed asymmetric alkylation of imines **974** driven by light. The light promotes radical formation of the trifluoroborates and acts as a reducing agent for the copper catalyst. Using ligand **873** (Figure 42), a

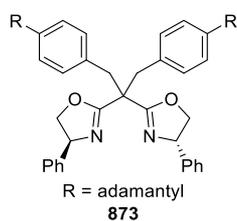
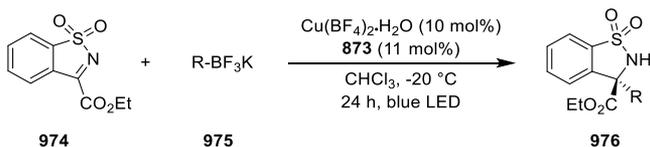


Figure 42. BOX ligand **873** with adamantyl backbone modification.

range of *N*-sulfonylimines **974** were alkylated using alkyl trifluoroborates **975** in high yields and enantioselectivities of up to 94% *ee* (Scheme 301). The scope of this reaction

Scheme 301. Cu-Catalyzed Asymmetric Alkylation of Imines

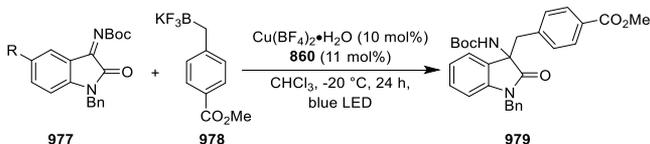


Representative examples

- R = CH₂-4-MeOC₆H₄; 99% yield, 60% *ee*
- R = CH₂-2-F₃CC₆H₄; 97% yield, 94% *ee*
- R = CH₂-4-BrC₆H₄; 99% yield, 89% *ee*
- R = CH₂-Thiophene; 98% yield, 75% *ee*
- R = *t*Bu; 88% yield, 24% *ee*

investigated various electron-withdrawing and donating alkyl trifluoroborates and all were found to maintain high enantioselectivities (81–94% *ee*). Lower enantioselectivities were observed when using *p*-methoxyphenyl, heteroaryl and bulky *t*-butyl trifluoroborates (as low as 24% *ee*). This methodology was then applied to the benzylation of isatin-derived ketimines with **860** as the ligand. A variety of isatin-derived ketimines were attempted furnishing the product in up to 98% *ee* (Scheme 302).³⁴⁹

Scheme 302. Cu-Catalyzed Enantioselective Alkylation of Isatin-Derived Ketimines

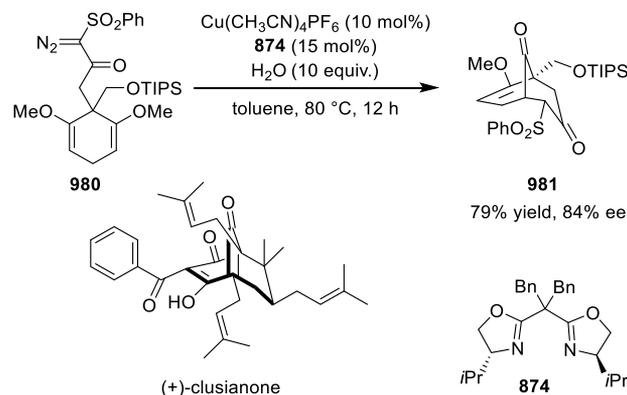


Representative examples

- R = H; 77% yield, 96% *ee*
- R = F; 84% yield, 98% *ee*
- R = Cl; 80% yield, 96% *ee*
- R = MeO; 73% yield, 96% *ee*
- R = Me; 76% yield, 96% *ee*

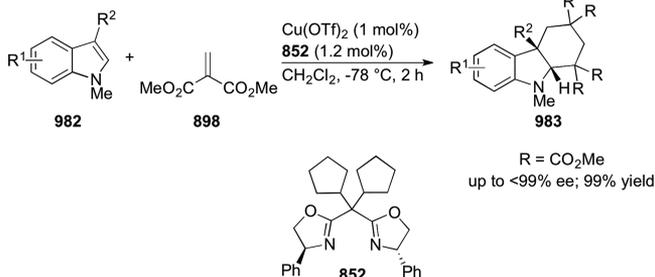
Nakada reported the Cu-catalyzed catalytic asymmetric intramolecular cyclopropanation of α -diazo ketones **980** in the synthesis of polycyclic polyprenylated acylphloroglucinols (Scheme 303). Using ligand **874** with Cu(CH₃CN)₄ the cyclopropylated product is formed and undergoes a subsequent rearrangement with water present to furnish the diketone **981** (79% yield, 84% *ee*), a valuable intermediate in the formal synthesis of (+)-clusianone.^{350a}

Scheme 303. Cu-Catalyzed Asymmetric Intramolecular Cyclopropanation of α -Diazo Ketones



In 2017, Tang reported the synthesis of Wing-BOX ligand **852** and its application in the synthesis of optically active hexahydrocarbazoles **983** in up to <99% *ee* and 99% yield (Scheme 304). Ligand **852** exploits the Thorpe–Ingold effect

Scheme 304. Tandem [2 + 2 + 2] Asymmetric Reaction of Indole with Methylene malonate



using the cyclopentyl groups on the backbone to enhance enantioselectivity (the parent bis(oxazoline) ligand **600c** furnished the product in 45% *ee* and 76% yield).^{350b}

It has been shown that BOX ligands with backbone modification are used largely within Lewis acid catalysis and cross-coupling to great effect. On multiple occasions they are employed in a scenario where parent BOX ligands achieve moderate enantioselectivity and are used to fine-tune the bite angles, electronics and achieve excellent enantioselectivity. From this section of the review, it is plain to see the far-reaching applications of BOX ligands and modified BOX ligands in asymmetric catalysis. A large proportion of this catalysis entails Lewis acid activation and inherently inexpensive metals such as Zn and Cu. While traditional enantioselective cross-couplings with Pd catalysts are still popular the increased use of inexpensive metals such as Ni or Co has been noted. One key reason for the Nickel's rise to prominence is its use in asymmetric cross-electrophile coupling with simple coupling partners such as pseudohalides and halides. It is envisaged that the increased research activity in photochemistry and electrochemistry will further enhance and complement the asymmetric methods developed and discussed above.

3.2. Bis(oxazoline) Ligands with Other Linkers

3.2.1. Bis(oxazoline) Ligands Directly Connected at C₁.

Bioxazoline (BiOX) ligands **984a–e** are bis(oxazoline) ligands with the oxazoline moieties directly attached to each

other (Figure 43). They have emerged as a useful class of chiral ligand, especially in asymmetric Ni-catalyzed cross-coupling reactions.

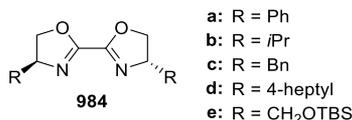
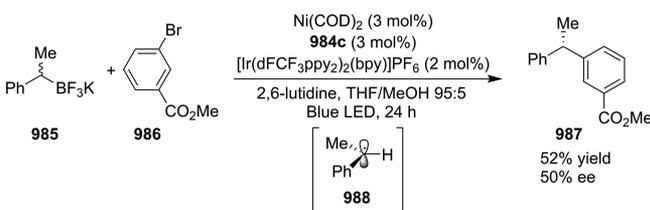


Figure 43. BiOX ligands.

Molander reported a dual photoredox/Ni-catalyzed cross coupling reaction of benzyltrifluoroborates with aryl bromides. They showed that the application of BiOX ligand **984c** in the cross coupling of secondary benzyltrifluoroborate **985** with aryl bromide **986** led to the isolation of the enantioenriched product **987** in 52% yield and with 50% *ee* (Scheme 305). The

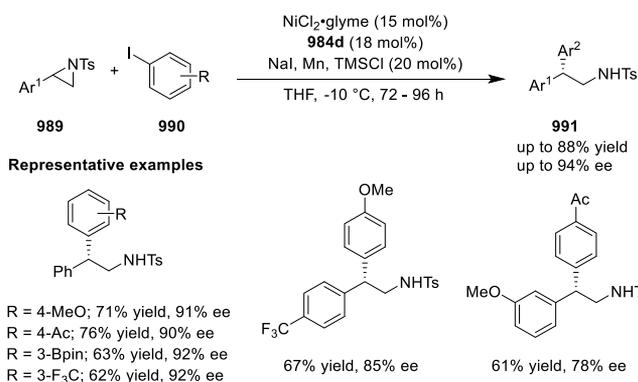
Scheme 305. Dual Photoredox/Ni-Catalyzed Cross-Coupling Reaction of Benzyltrifluoroborates with Aryl Bromides



stereoconvergent single-electron transmetalation event in this reaction (unlike traditional stereospecific transmetalation) allows for facial discrimination of the prochiral alkyl radical **988** by a chiral ligand.³⁵¹

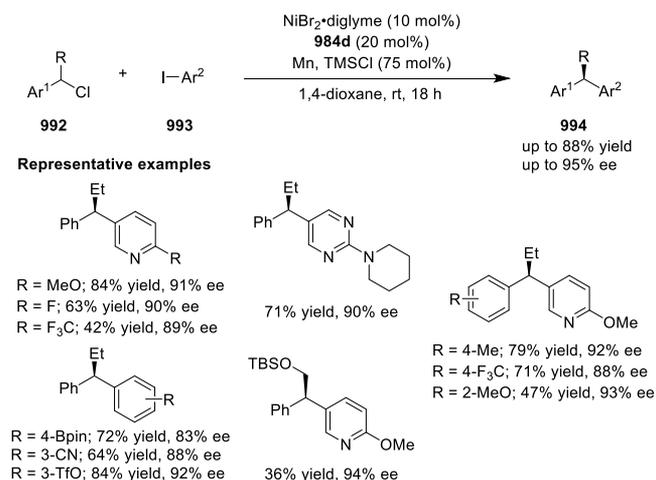
Doyle and Sigman have applied BiOX ligand **984d** in an enantioselective Ni-catalyzed reductive cross-coupling of styrenyl aziridines **989** with aryl iodides **990**. A range of racemic aryl aziridines **989** were subjected to the reaction with multiple aryl iodides **990** to give the enantioenriched amines **991** in good yields up to 88% and high enantioselectivities up to 94% *ee* (Scheme 306). Switching from the initial nonchiral ligand (bpp) for the racemic transformation led to a decrease in the yield of the cross-coupling reaction, however the addition of NaI and catalytic TMSCl was found to increase the yields.³⁵²

Scheme 306. Enantioselective Ni-Catalyzed Reductive Cross-Coupling of Styrenyl Aziridines with Aryl Iodides



Contemporaneously, Reisman reported an enantioselective Ni-catalyzed reductive cross-coupling reaction of aryl iodides **993** with secondary benzyl chlorides **992**, utilizing 4-heptyl BiOX ligand **984d**. A range of aryl and heteroaryl iodides **993** were well tolerated in the reaction, as were a range of secondary benzyl chlorides **992**, giving the diaryl alkanes **994** in moderate to good yields up to 88% and with high enantioselectivities up to 95% *ee* (Scheme 307). Mn⁰ was

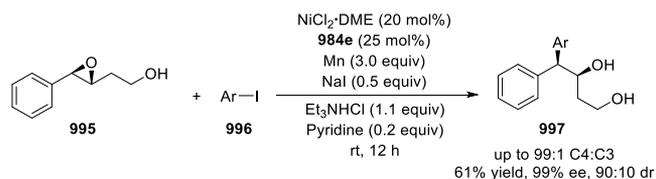
Scheme 307. Enantioselective Ni-Catalyzed Reductive Cross-Coupling Reaction of Aryl Iodides with Secondary Benzyl Chlorides



found to be an essential reductant and TMSCl an essential activator for the outcome of the reaction which, unlike the previous example, could be run at ambient temperature.³⁵³

Yamamoto has reported a regio- and diastereoselective Ni-catalyzed reductive cross-coupling of enantioenriched-3,4-epoxyalcohols **995** with aryl iodides **996**, utilizing BiOX ligand **984e** (Scheme 308). This general protocol furnishes a new

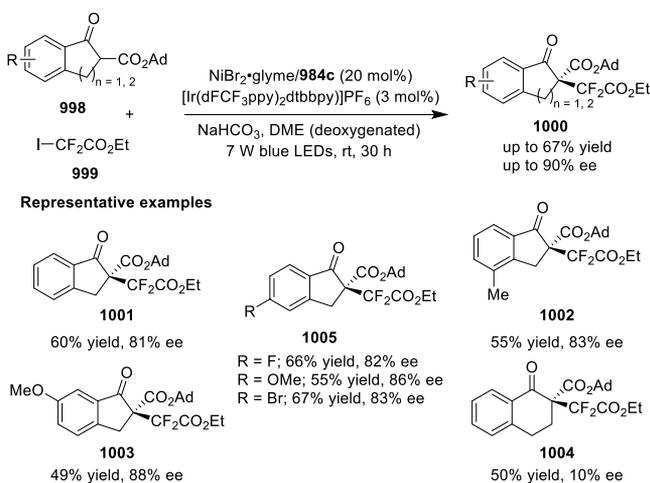
Scheme 308. Regio- and Diastereoselective Ni-Catalyzed Reductive Cross-Coupling between Epoxide and Aryl Iodides



type of enantioenriched 4,4-diaryl alkane **997**, which also incorporates an additional 1,3-diol, in up to 61% yield and with up to 99% *ee*. The diol can be easily transformed to a variety of functional groups.³⁵⁴

Lu and Xiao have described an enantioselective difluoroalkylation of β -keto esters by dual photoredox/Ni-catalysis. Employing Bn-BiOX ligand **984c**, a range of indanone- and tetralone- β -keto esters **998** were successfully difluoroalkylated with iodofluoroacetates **999** to give the corresponding indanones and one tetralone **1000** bearing α -quaternary stereocenters in moderate yields up to 67% and with high enantioselectivities up to 90% *ee* (Scheme 309). The reaction was found to work with bromofluoroacetates in a slightly lower yield and preliminary studies showed it could also be applied

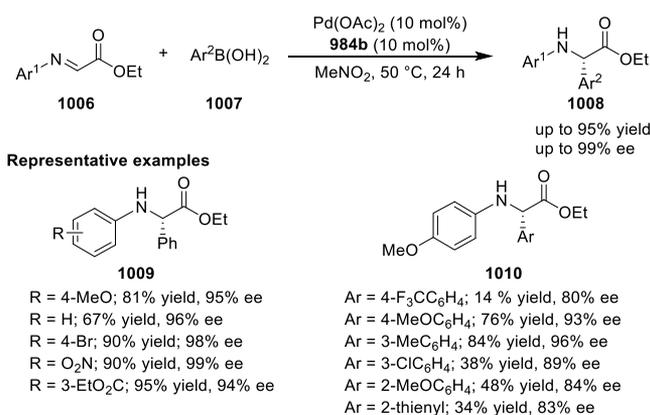
Scheme 309. Enantioselective Difluoroalkylation of β -Keto Esters by Dual Photoredox/Ni-Catalysis



to perfluoroalkylation with iodofluoro compounds under altered reaction conditions.³⁵⁵

BiOX ligands of the type **984** have also found application in asymmetric Pd-catalyzed transformations. For example, Zeng has reported an asymmetric Pd-catalyzed arylation of α -imino esters **1006** with aryl boronic acids **1007**. A range of enantioenriched α -diaryl amino esters **1008** were accessed in low to high yields up to 95% and with excellent enantioselectivities up to 99% ee, utilizing *i*Pr-BiOX ligand **984b** as the chiral ligand (Scheme 310). Electron-withdrawing

Scheme 310. Asymmetric Pd-Catalyzed Arylation of α -Imino Esters with Aryl Boronic Acids

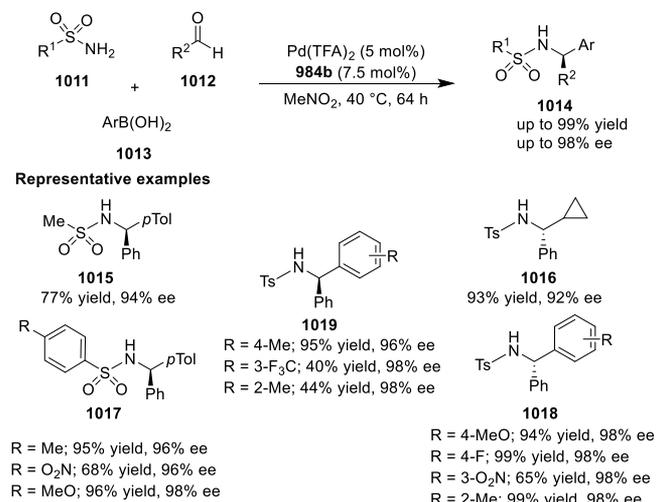


groups on the α -imino ester **1006** were well tolerated while electron-donating groups led to a decrease in reaction yield. Variation of the aryl boronic acid **1007** had a more dramatic effect on the outcome of the reaction, with electron-withdrawing and -donating groups decreasing the reaction yield.³⁵⁶ Yang later reported a related C–H oxidative cross-coupling, in which the same α -imino esters are formed by *in situ* oxidation with 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, which enters the same catalytic cycle as in Zeng's report.³⁵⁷

Manolikakes reported a related enantioselective Pd-catalyzed three-component synthesis of α -substituted amines. An array of aryl or alkyl sulfonamides **1011** and aldehydes **1012** were reacted together with aryl boronic acid **1013** in the presence of

Pd(TFA)₂ and *i*Pr-BiOX ligand **984b** to give enantioenriched α -substituted amines **1014** in up to 99% yield and with excellent enantioselectivities up to 98% ee (almost all >95% ee) (Scheme 311). The reaction was found to be insensitive to air

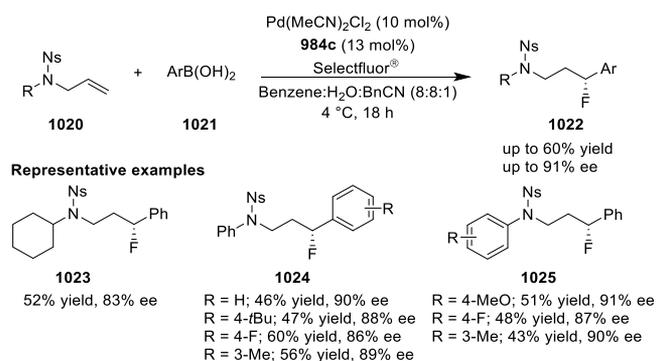
Scheme 311. Enantioselective Pd-Catalyzed Three-Component Synthesis of α -Substituted Amines



and moisture.³⁵⁸ Later, Manolikakes reported the same reaction with glyoxylic acid derivatives in place of regular aldehydes giving enantioenriched arylglycines with similar results.³⁵⁹

Toste has reported an enantioselective Pd-catalyzed 1,1-fluoroalkylation of amino alkenes **1020** with aryl boronic acids **1021** and Selectfluor. Utilizing Bn-BiOX ligand **984c**, a range of fluorinated amines **1022** were synthesized in moderate yields up to 60% and with high enantioselectivities up to 91% ee (Scheme 312). It was found that the exclusion of water from

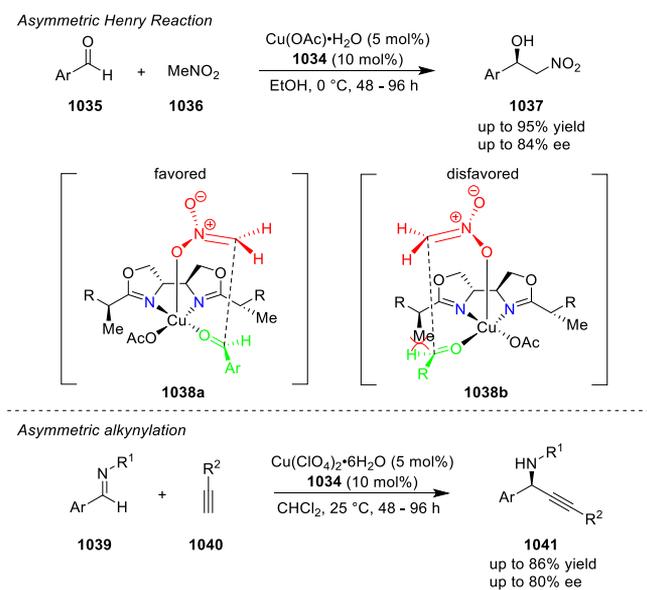
Scheme 312. Enantioselective Pd-Catalyzed 1,1-Fluoroalkylation of Amino Alkenes with Aryl Boronic Acids and Selectfluor



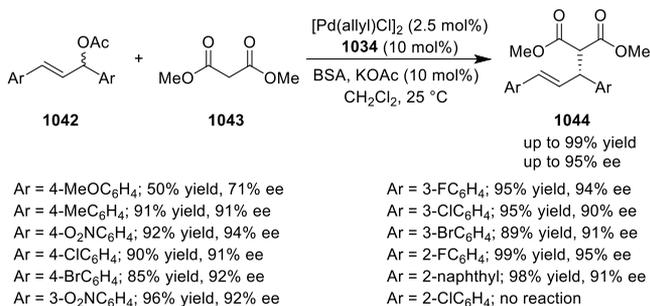
the racemic reaction mixture led to no observable product formation, while the addition of acetonitrile dramatically increased the yield of the product. Interestingly, in the asymmetric reaction, the removal of the nitrile led to trace amounts of product formation, while the use of benzonitrile, in place of acetonitrile, led to the highest levels of enantioselectivity.³⁶⁰

Correia has developed an enantioselective Heck–Matsuda arylation of (*Z*)-allyl alcohols with aryl diazonium tetrafluor-

Scheme 315. Asymmetric Transformations Mediated by Chiral Bis(oxazoline) Ligand 1034



Scheme 316. Asymmetric Pd-Catalyzed Alkylation of Allyl Acetates



mixture of products, with mostly high enantioselectivities.³⁶⁵ The scope of this reaction was later extended to include 3-OBoc-oxindoles as the nucleophile with slightly lower levels of enantioselectivity.³⁶⁶

The development of bis(oxazoline) ligands connected at the C₄-chiral center remains a significantly underdeveloped area. It is clear from the reports described in this Review that these ligands have the potential to induce high levels of stereo-selectivity when a second element of chirality is introduced into the scaffold, and as such, these ligands should be considered by researchers in the future.

3.2.3. Bis(oxazoline) Ligands with Pyrimidine and Pyrazine Linkers. Building on their previous work into the Heck–Matsuda arylation (Scheme 313), Correia and Pfaltz have reported the development of two new classes of bis(oxazoline) ligands, based on pyrimidine- (1045) and pyrazino-oxazoline (1046) motifs, for use in this transformation (Figure 45). With the aim of using the Heck–Matsuda arylation for the enantioselective synthesis of (*R*)-verapamil, they screened a number of ligands to improve the regioselectivity of the initial arylation reaction. In Correia's previous report, arylation occurs on a symmetrical allyl diol, giving the lactol intermediate as a single regioisomer, which is then converted to the corresponding lactone by a Jones oxidation. In this report, the diol 1047 is asymmetrical, so an

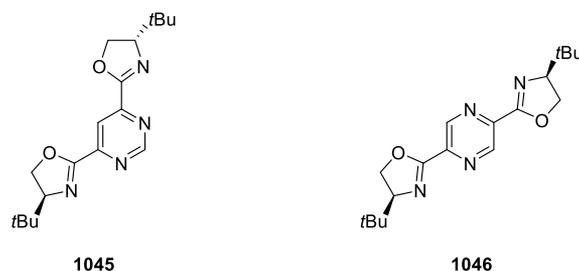
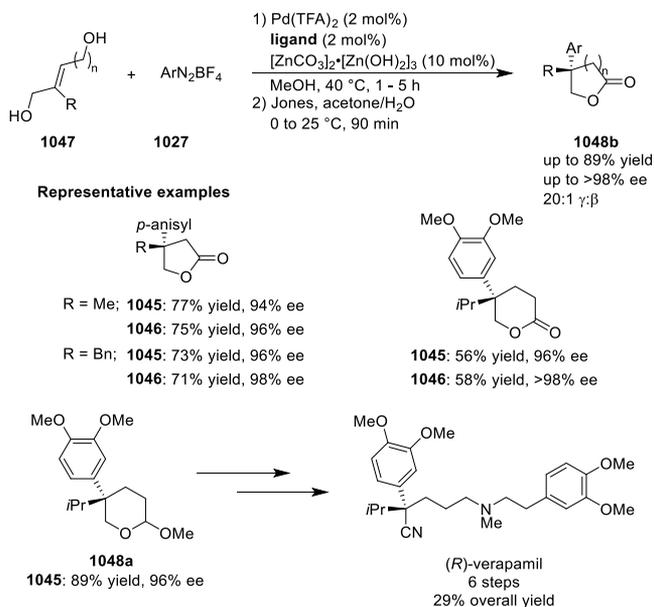


Figure 45. Bis(oxazoline) ligands 1045 and 1046.

alternative chiral ligand was sought to control the regioselectivity of the process.

Following a screen of ligands, 1045 and 1046 were found to induce high levels of stereo- and regioselectivity, giving the corresponding lactones 1048b in good yields of up to 89% yield, with high enantioselectivities up to >98% ee and with regioselectivities >20:1 γ/β in all cases (Scheme 317). O-

Scheme 317. Heck–Matsuda Arylation for Enantioselective Synthesis of (*R*)-Verapamil

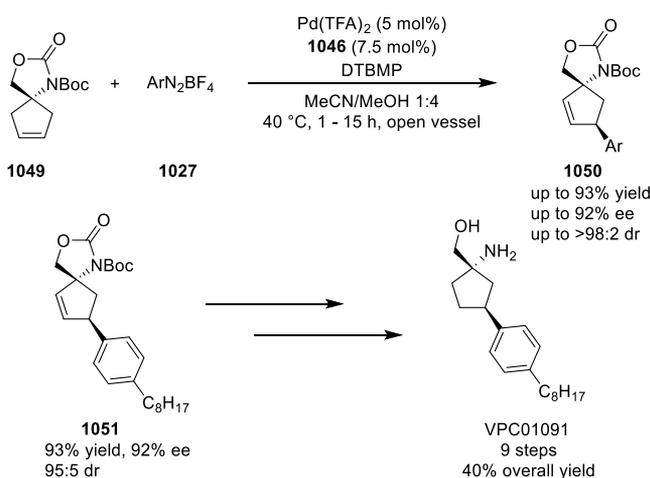


Methyl lactol 1048a (the product of the reaction before the Jones oxidation) was synthesized in 89% yield and with 96% ee, utilizing pyrimidine ligand 1045. This was taken forward to synthesize (*R*)-verapamil in 29% overall yield (six steps). Experimental results obtained for the Heck–Matsuda arylation with the mononuclear Pd(TFA)₂(1045) complex and the dinuclear Pd₂(TFA)₄(1045) complex suggested that the active species in this process is mononuclear.³⁶⁷

Correia later developed a Heck–Matsuda arylation of spirocyclic pyrrolidinones 1049 with aryl diazonium tetrafluoroborates 1027 generating the corresponding enantioenriched pyrrolidinones 1050 in good yields up to 93%, with high enantioselectivities up to 92% ee and with high diastereoselectivities up to >98:2 dr, when PyraBOX ligand 1046 was used (Scheme 318). Pyrrolidinone 1050 was then taken forward to the synthesize S1P1 agonist VPC01091 in 40% overall yield (9 steps) and with 94% ee.³⁶⁸

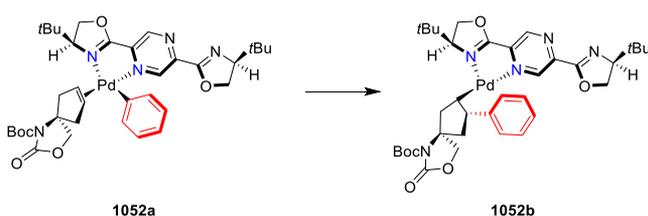
The stereochemical outcome of the transformation is explained by the stereoselective migratory insertion of one

Scheme 318. Heck–Matsuda Arylation of Spirocyclic Pyrrolidinones with Aryl Diazonium Tetrafluoroborates



face of the alkene in **1052a** into the Pd–Ar bond to give **1052b** (Scheme 319). It is proposed that the alkene

Scheme 319. Stereochemical Model for Heck–Matsuda Arylation with Ligand 1046



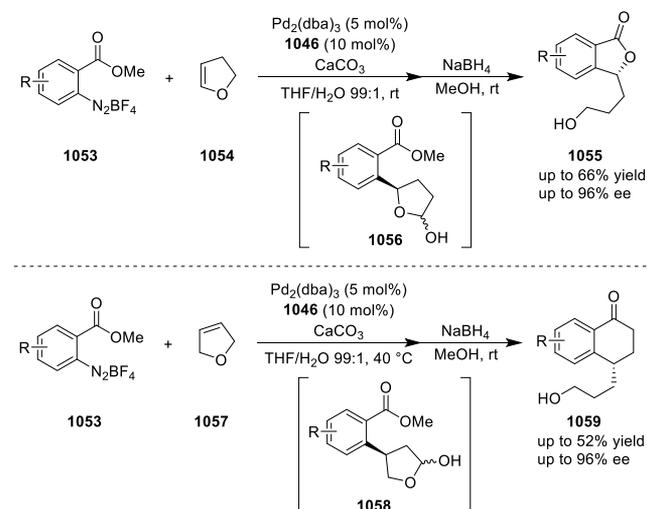
coordinates to Pd on the opposite face to the carbamate due to the steric bulk of the –NBoc group, giving the intermediate **1052a** with the aryl group on the opposite side to the carbamate. PyraBOX **1046** has also been applied to the Heck–Matsuda reaction of five-membered cyclopentene rings containing *S*- and *P*-stereogenic centers with similarly high levels of enantioselectivity.³⁶⁹

Correia has also developed an enantioselective phthalide and isochromanone synthesis via a Heck–Matsuda arylation of dihydrofurans. When 2,3-dihydrofuran **1054** is subjected to the arylation with a range of aryl diazonium tetrafluoroborates **1053**, the corresponding lactols **1056** can then be subjected to NaBH₄ reduction/cyclization to form enantioenriched phthalides **1055** in moderate yields up to 66% and with high enantioselectivities up to 96% *ee* (Scheme 320). When 3,4-dihydrofurans **1057** are subjected to the same reaction sequence, the corresponding isochromanones **1059** are isolated in up to 52% yield and with up to 96% *ee*.

In recent years, the use of chiral pyrimidine- and pyrazine-linked bis(oxazoline) ligands has been spearheaded by Correia. It is clear that these ligands can be used to induce high levels of enantioselectivity in Pd-catalyzed processes. In future, these unique ligands could be further developed for other transition-metal-catalyzed asymmetric transformations. In particular, the binding mode of these ligands could be suitable for developing chiral nickel catalysts.

3.2.4. Bis(oxazoline) Ligands with Spirocyclic Linkers. The SpiroBOX ligands **1060** have been developed and applied

Scheme 320. Heck–Matsuda Arylation of Dihydrofurans



in the asymmetric insertion of carbenoids into O–H bonds by Zhou (Figure 46).

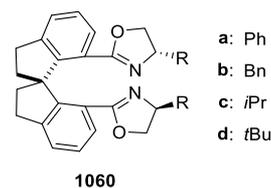
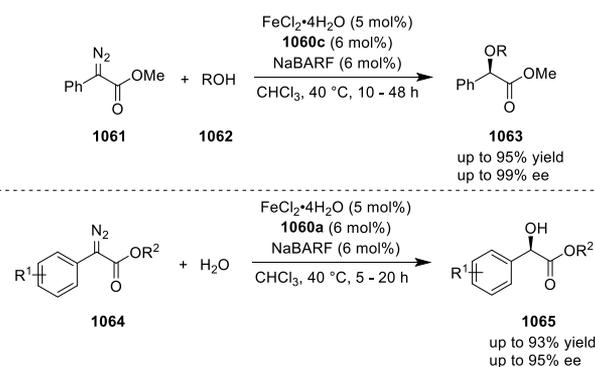


Figure 46. SpiroBOX ligands **1060**.

By utilizing a chiral bis(oxazoline) ligand with a highly rigid backbone, Zhou thought that tighter chelation would give access to successful Fe-catalyzed processes. Subjecting diazo compound **1061** to optimized conditions for Fe-catalyzed O–H insertion, with a range of alcohols **1062**, led to the isolation of enantioenriched benzyl ethers **1063** in up to 95% yield and with up to 99% *ee*, with *i*Pr-SpiroBOX **1060c** as the chiral ligand (Scheme 321). Subjecting a range of diazo

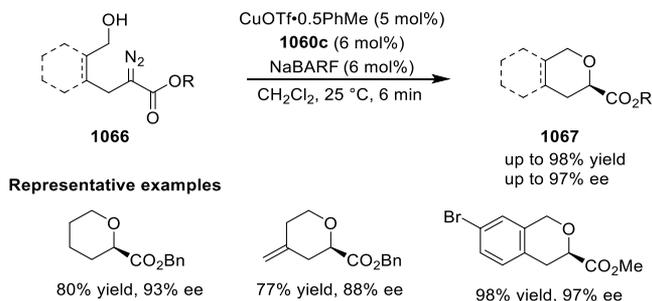
Scheme 321. Asymmetric Fe-Catalyzed O–H Insertion



1064 to the reaction with water led to the isolation of enantioenriched benzyl alcohols **1065** in up to 93% yield and with up to 95% *ee*, when Ph-SpiroBOX **1060a** was used as chiral ligand. Almost all examples are >90% *ee*, with *ortho*-substituted diazo compounds giving lower levels of enantioselectivity.³⁷⁰

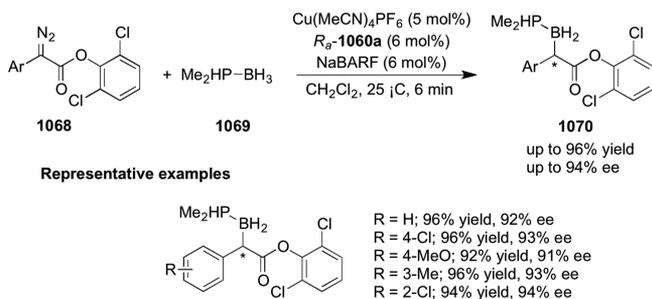
Zhou has applied their Cu-catalyzed O–H insertion chemistry to the enantioselective synthesis of 2-carboxy cyclic ethers **1067**. Employing *i*Pr-SpiroBOX ligand **1060c**, enantioenriched 2-carboxy cyclic ethers **1067** can be accessed by an intramolecular carbenoid O–H insertion of diazo compounds **1066** in up to 98% yield and with up to 97% *ee* (Scheme 322).³⁷¹ Zhou has applied the SpiroBOX ligands **1060** to asymmetric Cu-catalyzed α -diazo phosphonate carbenoid O–H insertions³⁷² and Pd-catalyzed carbenoid insertions into phenol O–H bonds.³⁷³

Scheme 322. Asymmetric Cu-Catalyzed Carbenoid O–H Insertion



Zhou has also extended the application of the SpiroBOX ligands **1060** to include other X–H bonds. Subjecting the dimethylphosphorus-borane adduct **1069** to a Cu-catalyzed carbenoid β -H insertion, utilizing ligand (*R_a*)-**1060a**, a range of enantioenriched phosphorus-borane adducts were accessed in high yields up to 96% and with high enantioselectivities up to 94% *ee* (Scheme 323). The stereochemical outcome of the reaction required very specific 2,6-dichlorophenyl α -diazo esters **1068**.³⁷⁴

Scheme 323. Cu-Catalyzed Carbenoid β -H Insertion

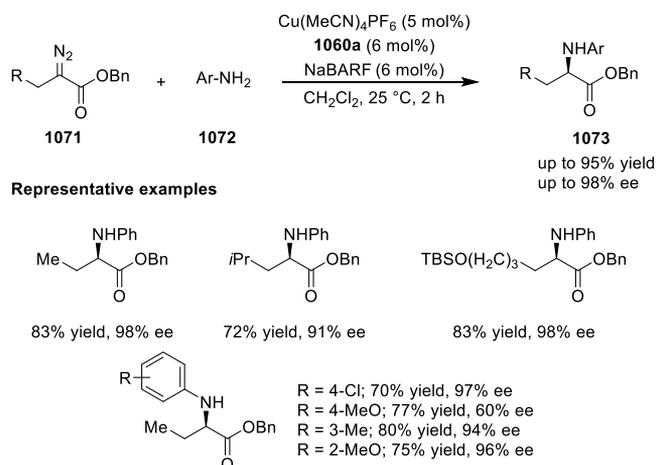


Zhou extended the enantioselective Cu-catalyzed carbenoid insertion reaction to include N–H bonds. A range of α -alkyl- α -diazo esters **1071** were reacted with aniline derivatives **1072** to access a range of enantioenriched secondary amines **1073** in up to 95% yield and with up to 98% *ee* (Scheme 324). Most of the aniline derivatives performed well in the reaction except *p*-anisidine which gave the product with only 60% *ee*. The active catalytic species was found to be a binuclear $[\text{Cu}_2(\text{1060a})_2]$ species.³⁷⁵

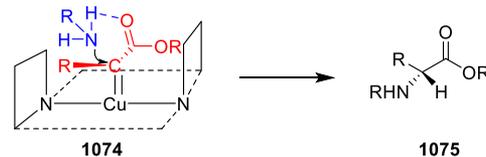
They proposed a stereochemical model based on this dinuclear Cu-species with a perfect C_2 -symmetric pocket (Scheme 325).

Zhou has also applied an intramolecular Cu/**1060a**-catalyzed carbenoid N–H insertion reaction to the enantioselective synthesis of 2-carboxytetrahydroquinolines.³⁷⁶

Scheme 324. Asymmetric Cu-Catalyzed Carbenoid N–H Insertion

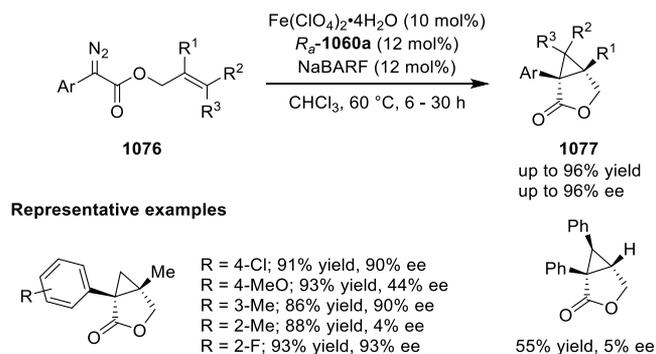


Scheme 325. Stereochemical Model for Asymmetric Cu-Catalyzed N–H Insertion with Ligand 1060a



Zhou has described an intramolecular Fe-catalyzed asymmetric cyclopropanation of alkenes with carbenoids. Applying **1060a** in this reaction, a range of enantioenriched cyclopropanes **1077** were accessed in high yields up to 96% and with low to high enantioselectivities up to 96% *ee* (Scheme 326).³⁷⁷

Scheme 326. Intramolecular Fe-Catalyzed Asymmetric Cyclopropanation of Alkenes



They have also reported an Fe/**1060a**-catalyzed carbenoid indole C–H insertion, but with only low to moderate enantioselectivities.³⁷⁸ Other bis(oxazoline) ligands with spirocyclic backbones, like HMSI-BOX **1078** and SpanBOX **1079** have been reported (Figure 47).

Xie and Lin have reported the use of spirocyclic HMSI-BOX ligand **1078** in the Fe-catalyzed carbenoid Si–H insertion. A range of silanes **1081** were reacted with α -aryl- α -diazo esters **1080** to give the corresponding enantioenriched silanes in up to 99% yield and with up to 96% *ee* (Scheme 327). During optimization, **1078** gave the product of the model reaction with 91% *ee*, compared to SpiroBOX ligand (*R_a*)-**1060a**, which

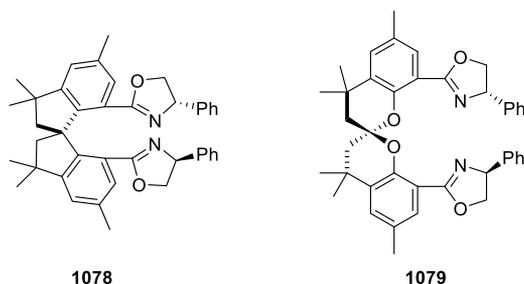
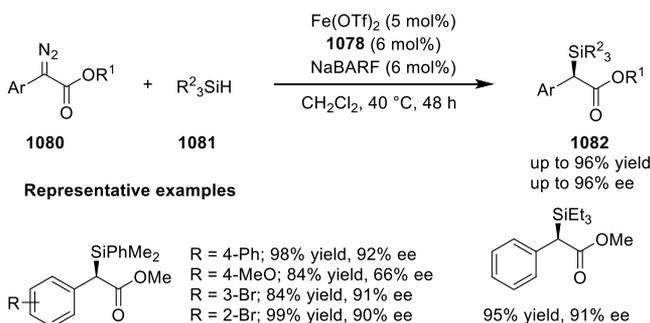


Figure 47. HMSI-BOX **1078** and SpanBOX **1079**.

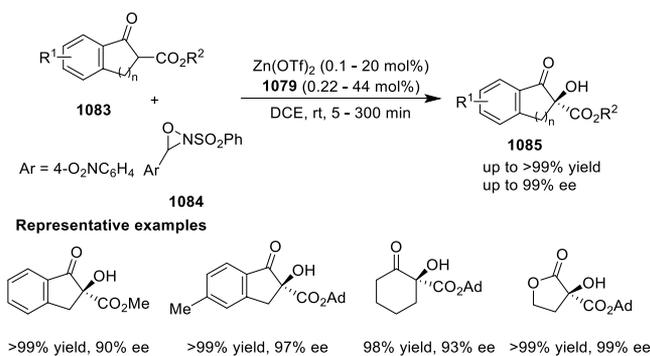
Scheme 327. Asymmetric Fe-Catalyzed Carbenoid Si–H Insertion



gave the product in 84% *ee*. As in the other carbenoid insertion reactions, 4-methoxy-substitution on the α -aryl- α -diazo esters **1080** leads to a dramatic decrease in enantioselectivity, in this case to 66% *ee*.³⁷⁹

Ding has applied SpanBOX **1079** in the Zn-catalyzed α -hydroxylation of β -keto esters **1083** with racemic oxaziridines **1084** to give the enantioenriched α -hydroxy- β -keto esters **1085** in up to >99% yield and with up to 99% *ee* (Scheme 328). A range of substituted β -keto esters were well tolerated

Scheme 328. Asymmetric Zn-Catalyzed α -Hydroxylation of β -Keto Esters



with all reported transformations proceeding with >98% yields and >90% *ee*. The majority of substrates were successfully hydroxylated using 1 mol % $\text{Zn}(\text{OTf})_2$ and 2.2 mol% of ligand **1079**.³⁸⁰ Ding also reported the Zn- and Cu-catalyzed α -chlorination of the same β -keto esters, utilizing **1079** with similar results.³⁸¹

Overall, bis(oxazoline) ligands with spirocyclic backbones are clearly an optimal choice for asymmetric transformations of carbenoids with both iron and copper catalysts. Researchers developing these types of transformations in the future should consider spirocyclic bis(oxazoline) ligands. More importantly,

these ligands could be used to develop new asymmetric Fe-catalyzed processes.

3.2.5. Bis(oxazoline) Ligands with One Boron Separating the Oxazoline Rings. Pfaltz pioneered the use of bis(oxazoline) ligands linked by a boron atom, like the BoraBOX ligands **1086a–d**, in asymmetric catalysis (Figure 48).^{382,383}

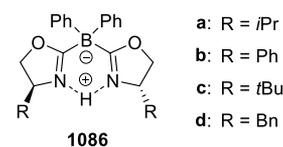


Figure 48. BoraBOX ligands **1086**.

More recently, Sadow has developed boron-bridged bis(oxazoline) ligands **1087** and **1088** for use in enantioselective transition metal-catalyzed hydroaminations of alkenes (Figure 49). The former ligand exploits the gem-dimethyl effect which

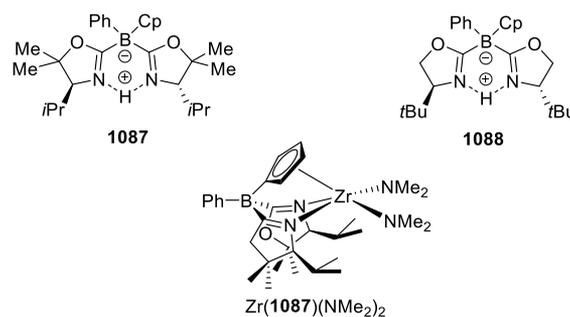
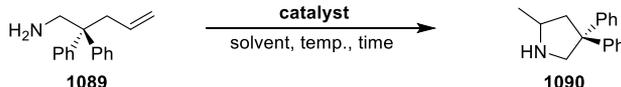


Figure 49. Boron-bridged bis(oxazoline) ligands and $\text{Zr}(\text{1087})-(\text{NMe}_2)_2$.

forces the *i*Pr-containing ligand to behave like a *t*Bu-substituted ligand. The ligands form complexes like $\text{Zr}(\text{1087})-(\text{NMe}_2)_2$, in the case of Zr, in which the Cp ring participates in bonding to the metal center.

Sadow has reported detailed studies on the effects of different catalysts, based on Zr, Y, Ti and Hf, which incorporate these BoraBOX ligands.^{384–386} As an example, a comparison of different BoraBOX precatalysts on the outcome of the hydroamination/cyclization of aminoalkene **1089** to give enantioenriched pyrrolidine **1090** is presented in Table 5. Both the $\text{Zr}(\text{1087})(\text{NMe}_2)_2$ and $\text{Hf}(\text{1087})(\text{NMe}_2)_2$ complexes were found to be efficient catalysts in this transformation, giving the product **1090** in 95% and 98% yield, and with 93% and 97% *ee*, respectively, with the Hf-catalyst reaction performed at 0 °C (entries 1 and 4). Interestingly, $\text{Ti}(\text{1087})(\text{NMe}_2)_2$ was found to operate at a much lower rate of reaction, and gave the product **1090** in much lower enantioselectivity of 76% *ee* (entry 5). Therefore, the metal center affects the rate of the reaction, such that $\text{Zr} > \text{Hf} \gg \text{Ti}$. It is also apparent that the ancillary ligand **1087** or **1088** has a positive effect on the rate of the reaction, such that $\text{Zr}(\text{1087})(\text{NMe}_2)_2$ (1.25 h) > $\text{Zr}(\text{1088})(\text{NMe}_2)_2$ (18 h), but not the enantioselectivity of the transformation (entry 6). Interestingly, $\text{Y}(\text{1088})(\text{CH}_2\text{SiMe}_3)$ proved to be an effective catalyst, giving the opposite enantiomer (*S*) in 100% yield and 94% *ee* in only 10 min (entry 7).

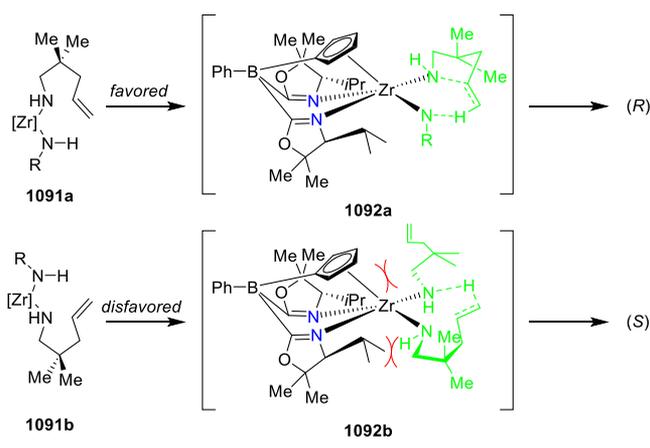
Sadow proposed a model to explain the stereochemical outcome of the cyclization catalyzed by the $\text{Zr}(\text{1087})(\text{NMe}_2)_2$

Table 5. Asymmetric Hydroamination/Cyclization of Aminoalkene 1089 with Ligands 1087 and 1088


entry	precatalyst ^a	solvent	temp (°C)	time	yield (%) ^b	ee (%)
1	Zr(<i>S</i> - 1087)(NMe ₂) ₂	C ₆ H ₆	25	1.25 h	95	93 (<i>R</i>)
2	Zr(1087)(NMe ₂) ₂	C ₇ H ₈	-30	5 d	98	98 (<i>R</i>)
3	Zr(<i>R</i> - 1087)(NMe ₂) ₂	C ₆ H ₆	25	1.25 h	95	93 (<i>S</i>)
4	Hf(1087)(NMe ₂) ₂	C ₇ H ₈	0	15 h	98	97 (<i>R</i>)
5	Ti(1087)(NMe ₂) ₂	C ₆ D ₆	25	5 d	93	76 (<i>R</i>)
6	Zr(1088)(NMe ₂) ₂	C ₆ H ₆	25	18 h	95	93 (<i>R</i>)

^aFor Zr, Hf and Ti: 10 mol % precatalyst, for Y: 5 mol % precatalyst.
^bDetermined by ¹H NMR spectroscopic analysis of the crude reaction mixture.

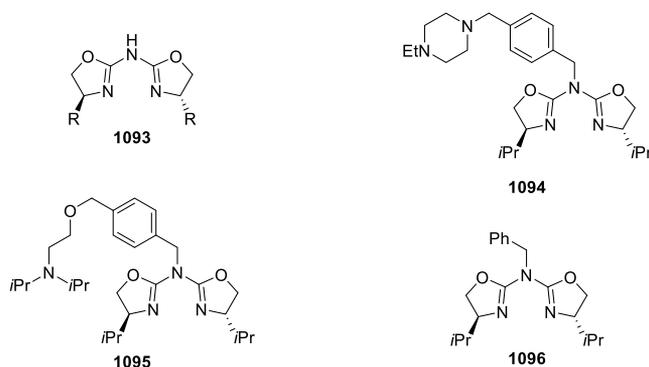
precatalyst (Scheme 329). From their experimental results, they proposed that optimal levels of enantioselectivity could be

Scheme 329. Stereochemical Model to Explain the Outcome of Cyclization Catalyzed by Zr(1087)(NMe₂)₂ Precatalyst

obtained by using a 2:1 substrate/catalyst ratio. The coordination of the substrates to the Zr-catalyst occurs, and the cyclization of one Zr-amide is facilitated by the other. Because of the steric interactions in the transition states depicted below, only one of the amides cyclizes to selectively give the (*R*)-product.

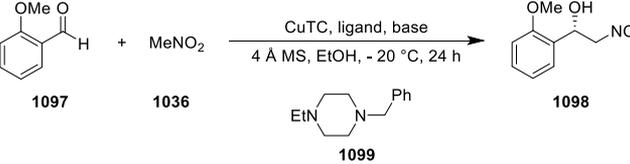
The application of oxazoline-containing ligands in asymmetric Zr-catalyzed transformations is limited. Clearly, the boron-linked bis(oxazoline) ligands described in this Review represent a foundation for the development of more Zr-catalyzed asymmetric transformations. The unique structure of these ligands could also be useful for developing novel chemistry with other metals.

3.2.6. Bis(oxazoline) Ligands with One Nitrogen Separating the Oxazoline Rings. Reiser has developed a related class of bis(oxazoline) ligand, azaBOX, in which there is a central bridging amine (Figure 50).³⁸⁷ The standard azaBOX ligand **1093** has a simple secondary amine bridge, but this amine is an excellent functional handle for further

**Figure 50. AzaBOX ligands.**

derivatization, and it has been used to create polymer-supported azaBOX ligands, but this is outside the scope of this Review.

The central amine has been used by Hong to develop a base-functionalized azaBOX ligand **1094** for use in bifunctional catalysis. Hong compared the activity of benzyl-substituted azaBOX **1096** and bifunctional piperazine-substituted azaBOX **1094** in the Cu-catalyzed Henry reaction of 2-anisaldehyde **1097** with nitromethane **1036** for the asymmetric synthesis of alcohol **1098**. In the reaction with **1096** as the chiral ligand, 1-benzyl-4-ethyl-piperazine **1099** was added as a base. When 2 mol% of **1099** was used with 2 mol% **1096** and 2 mol% CuTC, the alcohol **1098** was furnished in 56% yield and with 95% *ee* (Table 6, entry 1). Increasing the amount of base was found to

Table 6. Asymmetric Cu-Catalyzed Henry Reaction of 2-Anisaldehyde 1097 with Nitromethane 1036


entry	CuTC mol %	ligand (mol %)	base (mol %)	yield (%) 1098	% <i>ee</i>
1	2 mol %	1096 (2 mol %)	1099 (2 mol %)	56	95
2	2 mol %	1096 (2 mol %)	1099 (30 mol %)	85	90
3	2 mol %	1094 (2 mol %)		90	92

increase the yield of the reaction but slightly decrease the enantioselectivity (30 mol % **1099**: 85% yield, 90% *ee*) (entry 2). When 2 mol% of **1094** was used with 2 mol% CuTC, a significant rate acceleration was observed, furnishing the alcohol **1098** 90% yield and with 92% *ee* (entry 3).

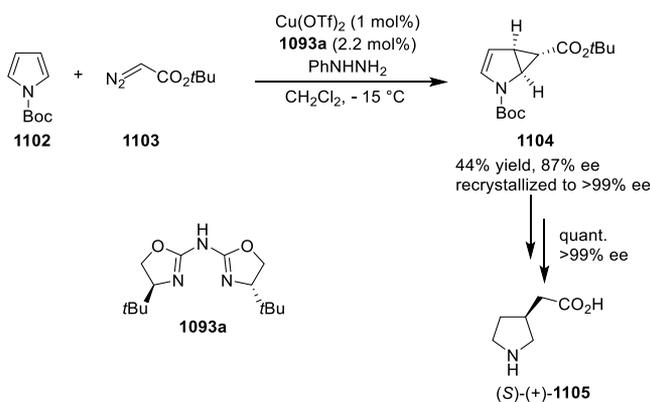
Applying the **1096/1099** system in the Cu-catalyzed Henry reaction of 2-anisaldehyde **1097** with nitroethane **1100** led to the isolation of alcohol **1101** in 54% yield, 1.3:1 *syn/anti*, and with 72% *ee* (*syn*)/96% *ee* (*anti*) (Table 7, entry 1). The same reaction with piperazine-azaBOX **1094** gave alcohol **1101** in 81% yield, 1.3:1 *syn/anti*, and with 92% *ee* (*syn*)/97% *ee* (*anti*), an overall significant improvement in the yield and enantioselectivity (entry 3). A di-*iso*-propylamine-functionalized azaBOX ligand **1095** was also applied in this reaction, giving alcohol **1101** in 99% yield, 1.5:1 *syn/anti*, and with 92% *ee* (*syn*)/96% *ee* (*anti*), these results indicated that ligand **1095** is an overall more efficient ligand than **1094** for this transformation. However, neither bifunctional ligand **1094**

Table 7. Asymmetric Cu-Catalyzed Henry Reaction of 2-Anisaldehyde 1097 with Nitromethane 1036

entry	ligand	base	yield (%)	1101	syn/anti	% ee (syn/anti)
1	1096	1099	54		1.3:1	72/96
2	1096	DIPEA	96		1.6:1	94/95
3	1094		81		1.3:1	92/97
4	1095		99		1.5:1	92/96

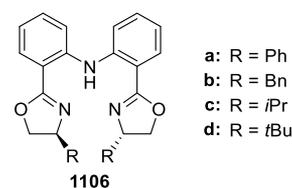
nor **1095** have a significant advantage over the combination of unfunctionalized azaBOX **1096** with DIPEA in this reaction, which gave alcohol **1101** in 96% yield, 1.6:1 *syn/anti*, and with 94% *ee* (*syn*)/95% *ee* (*anti*) (entry 2). While the bifunctional ligand systems do not give largely improved outcomes for the Henry reaction over the unfunctionalized ligand/base systems, they are excellent additions to the library of bis(oxazoline) ligands for the application in new enantioselective catalytic transformations.³⁸⁸

Reiser has achieved an enantioselective synthesis of the GABA uptake inhibitor (+)-homo- β -proline **1105** via a key Cu-catalyzed pyrrole cyclopropanation. Utilizing *t*Bu-azaBOX **1093a**, cyclopropane **1104** was accessed in 44% yield and with 87% *ee*, which can be recrystallized up to >99% *ee* (Scheme 330). (+)-Homo- β -proline **1105** was then synthesized in three further synthetic steps, all quantitative with regards to the reaction yield, and with >99% *ee*.³⁸⁹

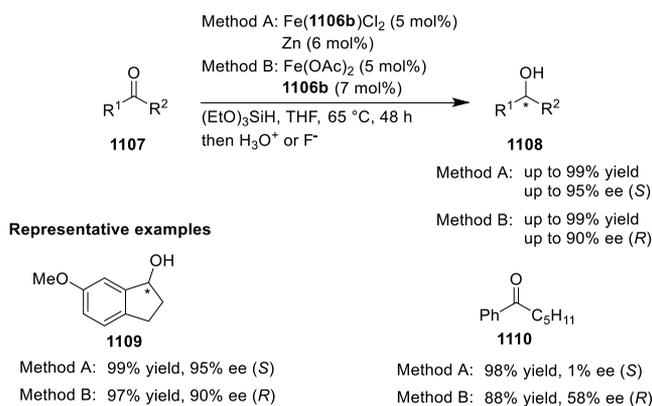
Scheme 330. Enantioselective Synthesis of GABA Uptake Inhibitor (+)-Homo- β -proline 1105

Overall, azaBOX ligands have not received significant attention in the past decade. Clearly, they can be used for inducing high levels of enantioinduction, and the free-amine has been shown to be a useful functional handle for accessing not only novel ligand structures but bifunctionality as well.

3.2.7. C₂-Symmetric Bis(oxazoline) Ligands with Diphenylamine Linkers. Since they were first developed by Guiry, diphenylamine-linked bis(oxazoline) ligands of the type **1106a–d** have been applied in a diverse range of asymmetric transformations (Figure 51).³⁹⁰ Ligands **1106** can be both bidentate (through the oxazoline moieties) and tridentate (through the oxazoline moieties and the bridging amine), depending on what metal ion the ligand is coordinated to.

**Figure 51. Diphenylamine-linked bis(oxazoline) ligands 1106.**

Nishiyama has applied Bn-ligand **1106b** in the Fe-catalyzed hydrosilylation of ketones **1107** for the asymmetric synthesis of secondary alcohols **1108**. Under two sets of optimized conditions, a range of enantioenriched alcohols **1108** were accessed in up to 99% yield and with up to 95% *ee* (*S*) or up to 99% yield and 90% *ee* (*R*) (Scheme 331). The stereoselectivity

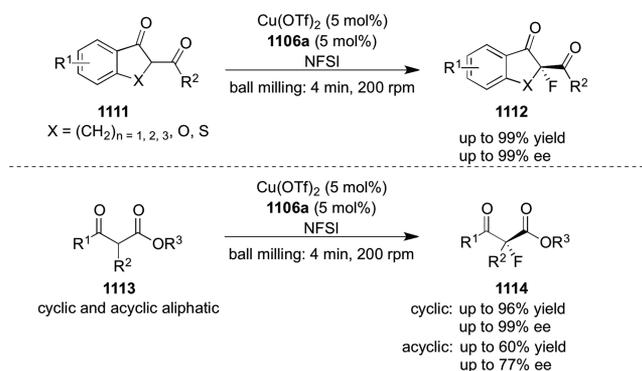
Scheme 331. Asymmetric Fe-Catalyzed Hydrosilylation of Ketones

varied depending on whether the preprepared Fe(**1106b**)Cl₂ catalyst and Zn were used in the reaction (method A), or the free ligand **1106b** was precomplexed with Fe(OAc)₂ directly in the reaction mixture without any Zn (method B). The major difference is the presence of Zn in method A. Both methods gave better levels of enantioselectivity depending on the substrate. For example, in the formation of alcohol **1109**, method A gave **1109** in 95% *ee* (*S*) as compared to method B, which gave **1109** in 90% *ee* (*R*). However, in the case of **1110**, method A gave essentially racemic alcohol **1110** (1% *ee* (*S*)) while method B gave **1110** in 58% *ee* (*R*). Analytical results for the complexes with and without the Zn additive suggested that the Zn was acting to reduce Fe(III) to Fe(II), however no active species has been characterized as of yet.³⁹¹ Nishiyama has also applied Bn-ligand **1106b** and *i*Pr-ligand **1106c** in the Fe-catalyzed and Co-catalyzed hydrosilylation of ketones and Co-catalyzed hydrosilylation of enones.³⁹²

A Cu/**1106a**-catalyzed solvent-free α -fluorination of β -keto esters/amides **1111** with NSFI, mediated by ball-milling, has been reported by Xu. A range of indanone-, tetralone-, benzosuberone-, benzofuran-3-(2*H*)-one-, and benzothiophen-3-(2*H*)-one-based β -keto esters/amides were successfully fluorinated to give the enantioenriched products **1112** in up to 99% yield and with up to 99% *ee* (Scheme 332). Cyclic aliphatic β -keto esters **1113** were also subjected to the α -fluorination to give the products **1114** in up to 96% yield and 99% *ee*, while acyclic aliphatic β -keto esters gave the products with lower levels of enantioselectivity up to 75% *ee*.³⁹³

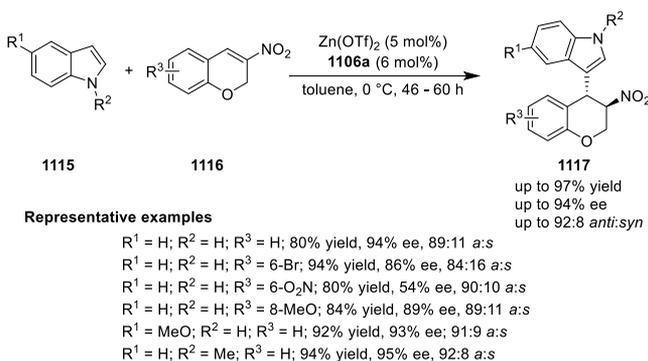
Du has described the asymmetric Zn-catalyzed Friedel–Crafts alkylation of indoles **1115** with 3-nitro-2*H*-chromenes

Scheme 332. Asymmetric Cu-Catalyzed Solvent-Free α -Fluorination of β -Keto Esters/Amides



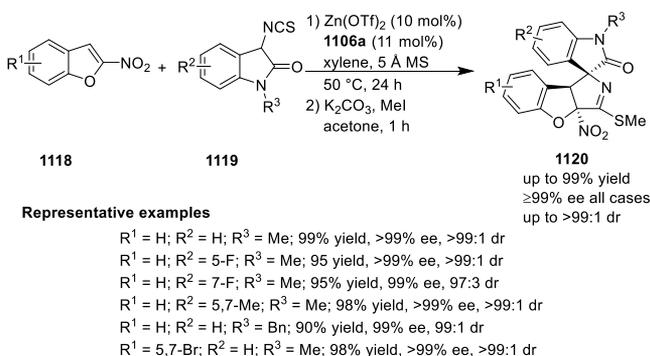
1116, utilizing the Ph-ligand **1106a**. The products **1117** were isolated in up to 97% yield, with up to 94% ee and with up to a 92:8 *anti/syn* ratio (Scheme 333).³⁹⁴

Scheme 333. Asymmetric Zn-Catalyzed Friedel–Crafts Alkylation of Indoles with 3-Nitro-2H-chromenes



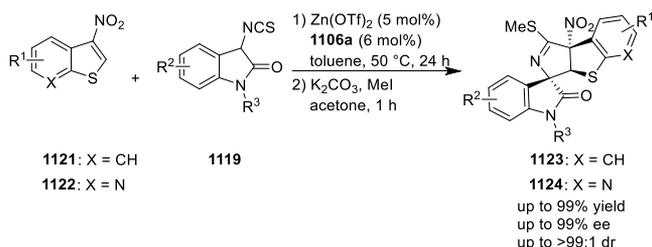
Yuan has reported an asymmetric Zn-catalyzed dearomative [3 + 2] cycloaddition of 2-nitrobenzofurans **1118** and 3-isocyanato oxindoles **1119**. Employing Ph-ligand **1106a** in the process, followed by treatment with MeI in acetone, a range of spirocyclic products **1120**, containing three contiguous stereocenters, were accessed in up to 99% yield, with $\geq 99\%$ ee in all cases and with up to >99:1 dr. (Scheme 334).³⁹⁵ Yuan later extended the scope of this reaction to include 2-nitroindoles.³⁹⁶

Scheme 334. Asymmetric Zn-Catalyzed Dearomative [3 + 2] Cycloaddition of 2-Nitrobenzofurans and 3-Isocyanato Oxindoles



Yuan has also described an enantioselective Zn-catalyzed dearomative [3 + 2] cycloaddition of 3-nitrobenzothiophenes **1121** and 3-nitrothiopheno[2,3-*b*]pyridines **1122** with 3-isocyanato oxindoles **1119**. Again, utilizing Ph-ligand **1106a** under similar optimized conditions to the previous reactions, a range of spirocyclic products **1123/1124** containing three contiguous stereocenters were accessed in up to 99% yield, with up to >99% ee and with up to >99:1 dr (Scheme 335).³⁹⁷

Scheme 335. Enantioselective Zn-Catalyzed Dearomative [3 + 2] Cycloaddition of 3-Nitrobenzothiophenes/3-Nitrothiopheno[2,3-*b*]pyridines with 3-Isocyanato Oxindoles



Xu and Yuan have reported the application of diPh-ligand (*R,R*)-**1125** in the asymmetric Zn-catalyzed dearomative [3 + 2] cycloaddition of 3-nitroindoles **1127** with 3-isocyanato oxindoles **1119** (Figure 52).

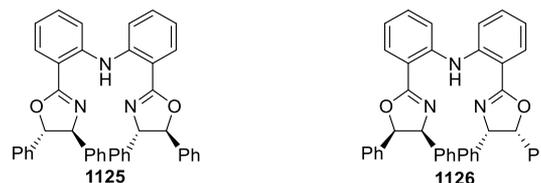
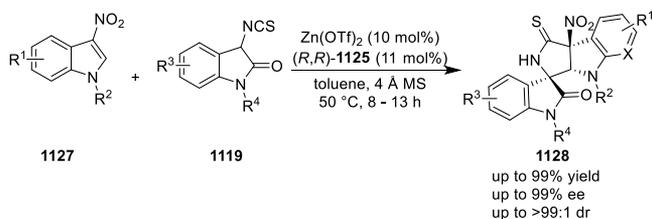


Figure 52. DiPh-Diphenylamine-Linked Bis(oxazoline) Ligands.

The spirocyclic products **1128** were isolated in up to 99% yield, with up to 99% ee and with up to 99:1 dr (Scheme 336).³⁹⁸

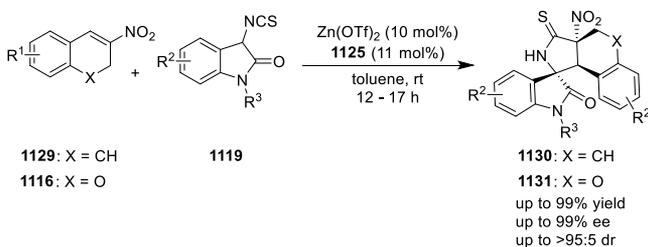
Scheme 336. Asymmetric Zn-Catalyzed Dearomative [3 + 2] Cycloaddition of 3-Nitroindoles with 3-Isocyanato Oxindoles



Chen and Xiao have also applied ligand **1125** in the enantioselective [3 + 2] cycloaddition of 3-nitro-2H-chromenes **1129/1116** with 3-isocyanato oxindoles **1119** to give the spirocyclic products **1130/1131** in up to 99% yield, with up to 99% ee and >99:5 dr (Scheme 337).³⁹⁹

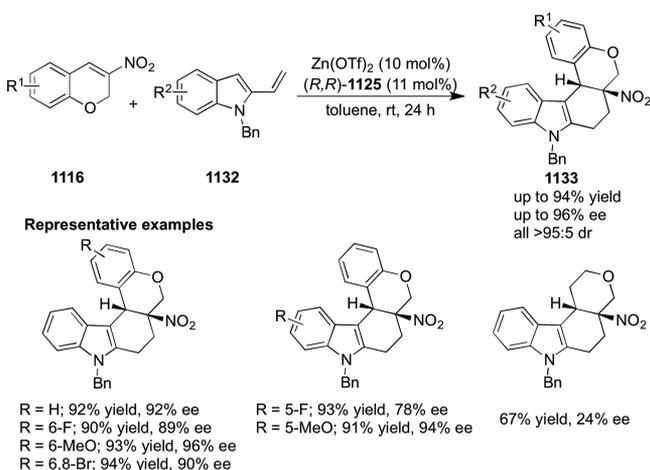
Ding and Xiao have described an asymmetric Zn-catalyzed [4 + 2] cycloaddition of 2-vinyl indoles **1132** with 3-nitro-2H-chromenes, utilizing **1125** as the chiral ligand. The tetracyclic products **1133**, containing two contiguous stereocenters were

Scheme 337. Enantioselective [3 + 2] Cycloaddition of 3-Nitro-2H-chromenes with 3-Isocyanato Oxindoles



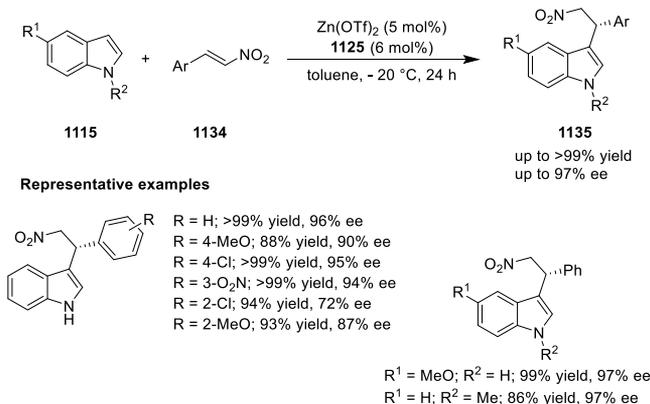
isolated in up to 94% yield, with up to 96% ee and >99:5 dr (Scheme 338).⁴⁰⁰

Scheme 338. Asymmetric Zn-Catalyzed [4 + 2] Cycloaddition of 2-Vinyl Indoles with 3-Nitro-2H-chromenes



Ligand **1125** has been applied in the Zn(OTf)₂-catalyzed asymmetric Friedel–Crafts alkylation of indoles **1115** with *trans*- β -nitrostyrene derivatives **1134**, for the synthesis of enantioenriched nitroalkanes **1135** in high yields up to >99% and with excellent enantioselectivities up to 97% ee (Scheme 339). Substituents on the *trans*- β -nitrostyrene derivatives **1134** were well tolerated in terms of steric and electronic changes, except *ortho*-substitution, for example, in the reaction of indole with 2-chloro-*trans*- β -nitrostyrene, the product was

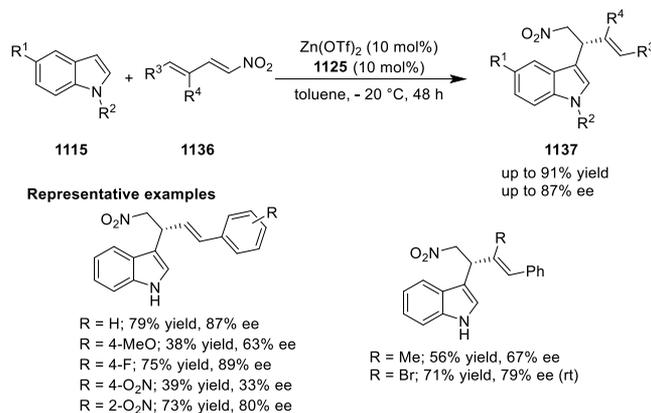
Scheme 339. Zn-Catalyzed Asymmetric Friedel–Crafts Alkylation of Indoles with *trans*- β -Nitrostyrenes



isolated with only 72% ee, compared to 95% ee for the reaction with 4-chloro-*trans*- β -nitrostyrene. In the same report, ligand **1106a** was applied to the asymmetric Friedel–Crafts alkylation of pyrrole with *trans*- β -nitrostyrene derivatives, but the products were isolated with low levels of enantioselectivity of 11–91% ee.⁴⁰¹

Du showed that the scope of the reaction of indoles with *trans*- β -nitrostyrene derivatives, utilizing ligand **1125**, could be extended to include 2-propargyloxy- β -nitrostyrenes, giving the products with more inconsistent levels of enantioselectivity of 36–93% ee. In the same report, Du explored the Zn(**1125**)-catalyzed asymmetric Friedel–Crafts alkylation of indoles **1115** with nitrodienes **1136**, giving the enantioenriched products **1137** in up to 91% yield and with lower levels of enantioselectivity compared to *trans*- β -nitrostyrenes **1134**, of up to 87% ee (Scheme 340).⁴⁰²

Scheme 340. Zn-Catalyzed Asymmetric Friedel–Crafts Alkylation of Indoles with Nitrodienes



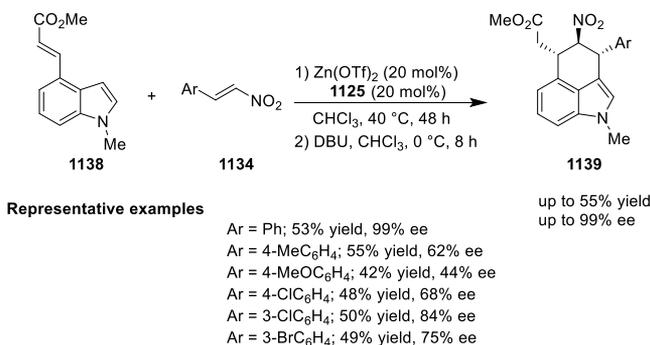
Guiry has described a one-pot/two-step Zn/**1125**-catalyzed Friedel–Crafts alkylation/Michael addition sequence of 4-(methylacrylato)indole **1138** with *trans*- β -nitrostyrene derivatives **1134** for the enantioselective synthesis of tricyclic indoles **1139**, representing the C₄-substituted core structure of the ergoline derivatives. Subjecting the indole **1138** to the Zn(OTf)₂/**1125**-catalyzed reaction with a range of *trans*- β -nitrostyrene derivatives **1134**, followed by the addition of DBU, the tricyclic products **1139** were isolated as the *anti*–*anti* diastereomers in up to 55% yield and with up to 99% ee (Scheme 341). The reaction was very sensitive to changes on the aryl group of the *trans*- β -nitrostyrene derivative **1134**.⁴⁰³

Wang and Xu have applied ligand **1125** in the Cu-catalyzed conjugate addition of 2-substituted benzofuran-3-2H-ones **1140** to α,β -unsaturated ketones **1141** to give the corresponding enantioenriched β -substituted- β -keto esters **1142** in up to 95% yield and with high enantioselectivities up to >99% ee (Scheme 342).⁴⁰⁴

In the same report, the substrate scope was extended to include linear β -substituted and cyclic enones, giving the linear products **1143** and **1144** with excellent enantio- and diastereoselectivities, while the cyclic products **1145** and **1146** were isolated in excellent enantioselectivities but low diastereoselectivities (Figure S3).

Diphenylamine-linked bis(oxazoline) ligands have been successfully applied in a range of Zn-, Cu- and Fe-catalyzed processes. The future for these ligands probably lies in new asymmetric transformations catalyzed by these metals. In

Scheme 341. One-Pot/Two-Step Asymmetric Zn-Catalyzed Friedel–Crafts Alkylation/Michael Addition of 4-(Methylacrylato)indole with *trans*- β -Nitrostyrenes



Scheme 342. Asymmetric Cu-Catalyzed Conjugate Addition of 2-Substituted Benzofuran-3-2*H*-onesto α,β -Unsaturated Ketones

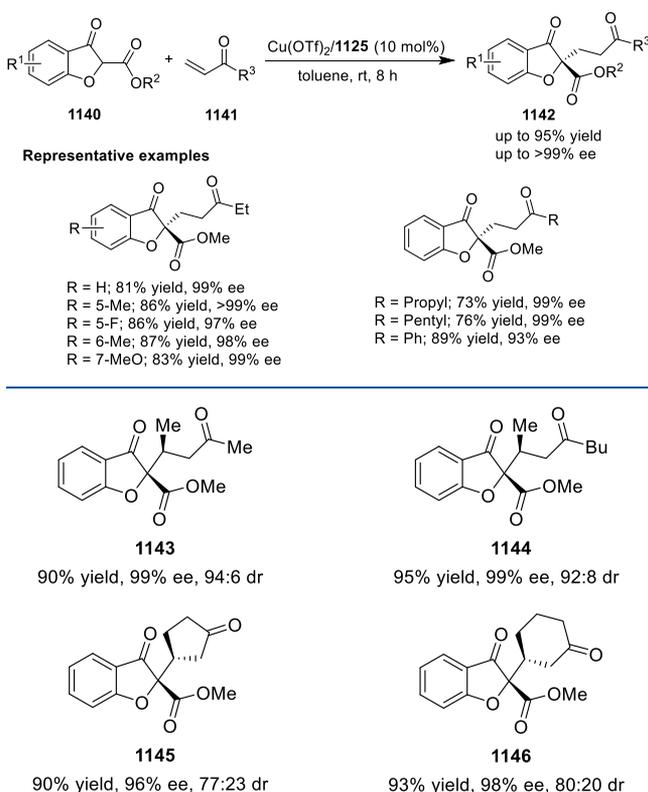


Figure 53. Products of the asymmetric Cu-catalyzed conjugate addition of 2-substituted benzofuran-3-2*H*-onesto β -substituted enones and cyclic enones.

particular, new applications of these ligands in Fe-catalysis should be explored.

3.2.8. C₁-Symmetric Bis(oxazoline) Ligands with Diphenylamine Linkers. Most commonly, bis(oxazoline) ligands are designed to incorporate C₂-symmetry. This leads to simpler synthetic routes (utilizing a single amino alcohol in one cyclization step) and decreases the amount of transition states possible in the asymmetric transformation, thus increasing the enantioselectivity of the process. However, C₁-symmetric bis(oxazoline) ligands have been applied to asymmetric catalytic transformations with excellent results.⁴⁰⁵

Guiry introduced diphenylamine-linked bis(oxazoline) ligands of the type **1106** by developing a modular synthesis, in which the two oxazoline moieties are linked by a Pd-catalyzed aryl amination. This allowed for the synthesis of both C₁-(**1147**) and C₂-symmetric ligands which have been applied in asymmetric catalysis (Figure 54).

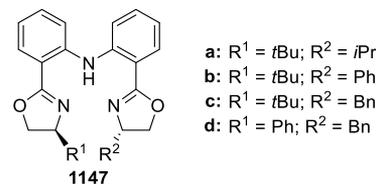


Figure 54. C₁-symmetric diphenylamine-linked bis(oxazoline) ligands **1147**.

Guiry has reported that C₁-symmetric ligands of the type **1147a–d**, where R¹ \neq R², are excellent at controlling the regio- and enantioselectivity in the enantioselective Cr-catalyzed homoallylation of aldehydes, NHK reaction. In the reaction of allene **1149** with benzaldehyde **1148**, in the presence of CrCl₃, Mn, TMSCl and the appropriate chiral ligand, C₁-symmetric ligand **1147a** was found to give the allenyl alcohol **1150**, following acid hydrolysis, with perfect regioselectivity (over the diene **1151**) and excellent enantioselectivity of 96% ee (Table 8, entry 3). The C₂-symmetric ligand **1106c** gave the

Table 8. Enantioselective Cr-Catalyzed Homoallylation of Benzaldehyde

entry	ligand	conv (%)	yield (%)	1150/1151	% ee
1	1106c	35	16	100:0	84 (R)
2	1106d	80	39	71:29	8 (S)
3	1147a	87	71	100:0	96 (R)
4	1147b	85	40	84:16	49 (R)
5	1147c	45	23	100:0	91 (R)
6	1147d	93	33	74:26	11 (R)

allenyl alcohol **1150** with much lower regioselectivity of 71:29 and almost no enantioselectivity at all (entry 1). The C₂-symmetric ligand **1106d** gave the allenyl alcohol **1150** with perfect regioselectivity, high enantioselectivity of 84% ee, but with low conversion (entry 2). The methodology was applied to a range of aryl, alkenyl and aliphatic aldehydes, generating allenyl alcohols in moderate to good yields up to 71%, with perfect regioselectivity in all but one case (naphthaldehyde) and with high enantioselectivities of up to 98% ee. This was the first example of a regio- and enantioselective homoallylation of aldehydes.⁴⁰⁶

A possible transition state, to explain the stereochemical outcome for this transformation with ligand **1147a**, is depicted in **1152** (Figure 55). The diene sits in the equatorial position, while the aldehyde coordinates in the apical position in an *anti*-geometry to avoid a steric interaction between the oxazoline *i*Pr-group (R²). This leads to *Re*-face attack to yield the (*R*)-enantiomer. The oxazoline *t*Bu-group (R¹) might prevent the aldehyde to coordinate from the opposite apical position.

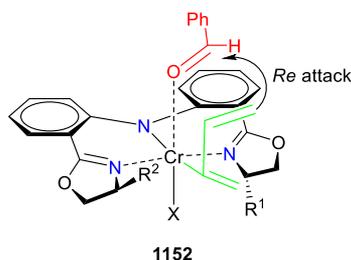


Figure 55. Stereochemical model for the enantioselective Cr-catalyzed homoallyenylation of benzaldehyde utilizing ligand **1147a**.

Guiry later explored the *gem*-disubstitution effect in the application of C_1 -symmetric ligands of the type **1153** (Figure 56) in the asymmetric Friedel–Crafts alkylation of indole **1154**

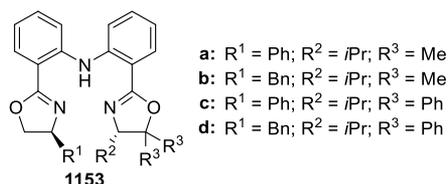
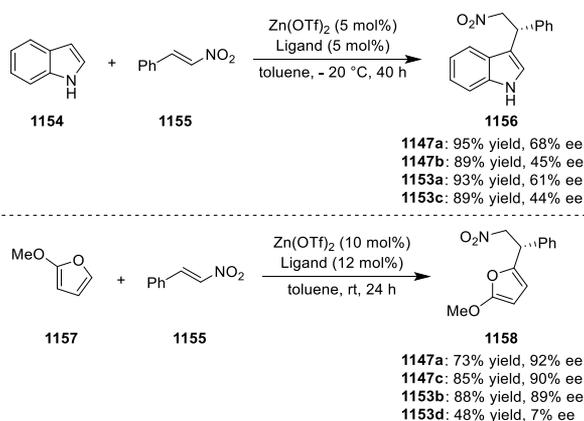


Figure 56. C_1 -symmetric *gem*-dimethyl diphenylamine-linked bis(oxazoline) ligands **1153**.

and 2-methoxyfuran **1157** with *trans*- β -nitrostyrene **1155**. In a number of transformations, one of the oxazoline moieties must be *t*Bu-substituted to achieve high levels of enantioselectivity. However, *L*-*tert*-leucine, the parent amino alcohol of these oxazolines, is very expensive, with *D*-*tert*-leucine being prohibitively expensive. They exploited the *gem*-disubstitution effect with C_3 -*i*Pr-substituted oxazoline-containing ligands to give the products of the Friedel–Crafts alkylations with enantioselectivities better than the normal *i*Pr-substituted ligands and approaching that of the normal *t*Bu-substituted ligands.

In the Friedel–Crafts reaction of indole **1154**, the enantioenriched nitroalkane **1156** was isolated in 95% yield and 68% *ee*, when the reaction was conducted with C_2 -symmetric-*t*Bu-ligand **1106d** (Scheme 343). *gem*-Dimethyl-*i*Pr/Ph-ligand **1153a** gave the product **1156** in 93% yield and 61% *ee*, which is a slightly lower enantiomeric excess than **1106d**, but actually higher than C_1 -symmetric-*t*Bu/Ph-ligand

Scheme 343. Asymmetric Friedel–Crafts Alkylation of Indole and 2-Methoxyfuran with *trans*- β -Nitrostyrene



1147b, which gave the product in 89% yield and 45% *ee*. In the Friedel–Crafts reaction of 2-methoxyfuran **1157**, the reaction with C_2 -symmetric-*t*Bu-ligand **1106d** gave the product **1158** in 73% yield and 92% *ee*, while C_1 -symmetric-*t*Bu/Bn-ligand **1147c** gave the product **1158** in 85% yield and 90% *ee*. The reaction with *gem*-dimethyl-*i*Pr/Bn-ligand **1153b** gave comparable results, giving product **1158** in 88% yield and 89% *ee*. In the reactions of both substrates, the *gem*-diphenyl ligands gave poor levels of enantioselectivity compared to the *gem*-dimethyl ligands.⁴⁰⁷

A transition state **1159**, to explain the stereochemical outcome of the two Friedel–Crafts alkylation reactions, was proposed (Figure 57). The bis(oxazoline) ligand coordinates

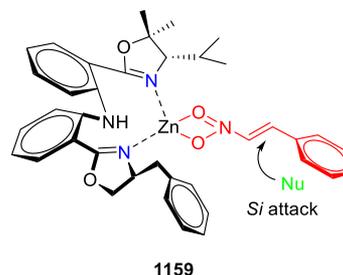


Figure 57. Stereochemical model for the two Friedel–Crafts alkylation reactions utilizing ligand **1153b**.

to the Zn-center in a bidentate fashion (based on X-ray crystallographic structures for Zn(**1153**)Cl₂ complexes), with the nitro-group coordinated to Zn in a bidentate manner through the oxygen atoms. Because of the influence of the oxazoline substituents, the appropriate nucleophile (Nu) preferentially attacks the *Si*-face of the nitrostyrene, to yield the (*R*)-enantiomer of the product **1156** in the case of the indole nucleophile and the (*S*)-enantiomer of the product **1158** in the case of the 2-methoxyfuran nucleophile.

Guiry has also developed C_1 -symmetric thiazoline-oxazoline hybrid ligands of the type **1160** (Figure 58). While these

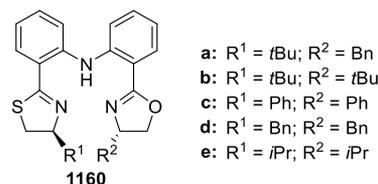


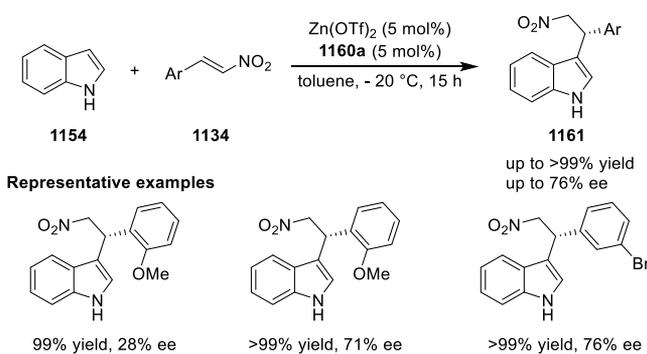
Figure 58. C_1 -symmetric thiazoline-oxazoline hybrid ligands **1160**.

ligands are not bis(oxazoline) ligands, they are more comparable to bis(oxazoline) ligands than mono(oxazoline) ligands; therefore, they have been included in this section of the Review.

The thiazoline-oxazoline ligands **1160** were successfully applied in the Zn-catalyzed asymmetric Friedel–Crafts reaction of indole with *trans*- β -nitrostyrene derivatives, with the reaction using *t*Bu/Bn-ligand **1160a** as the chiral ligand, yielding the corresponding enantioenriched nitroalkanes **1161** in up to >99% and with moderate levels of enantioselectivity up to 76% *ee* (Scheme 344).⁴⁰⁸

Thiazoline-oxazoline ligands **1160** were also applied by Guiry in the Cr-catalyzed asymmetric Nozaki-Hiyama-Kishi (NHK) reaction of allyl bromide **1162** with benzaldehyde **1148**. A range of these ligands were tested in this reaction, a selection

Scheme 344. Zn-Catalyzed Asymmetric Friedel–Crafts Reaction of Indole with *trans*- β -Nitrostyrene Derivatives



of which are shown in Table 9, which affords, following acidic hydrolysis, the corresponding alcohol **1163**. The nature of the

Table 9. Asymmetric NHK Reaction of Allyl Bromide with Benzaldehyde

entry	ligand	conv (%)	yield (%) 1163	% ee
1	1160a	100	84	85 (<i>R</i>)
2	1160b	100	87	10 (<i>R</i>)
3	1160c	100	81	31 (<i>S</i>)
4	1160d	85	67	6 (<i>S</i>)
5	1160e	94	78	39 (<i>S</i>)

substituents on the thiazoline (R^1) and oxazoline (R^2) moieties of ligands **1160** has a dramatic effect over the enantioselectivity of the reaction, with some ligands giving the (*R*)-product **1162** (entries 1–2) and some giving the (*S*)-product **1163** (entries 3–5). As in the Friedel–Crafts reaction, the reaction with *t*Bu/Bn-ligand **1160a** gave the best result, yielding alcohol **1163** in 84% yield and with 85% ee (*R*) (entry 1).⁴⁰⁹

A possible transition state **1164**, to explain the stereochemical outcome for this transformation with ligand **1160a**, is based on the X-ray crystallographic structure obtained for a tridentate Fe(**1160**)Cl₂ complex (Figure S9). This transition state **1164** is like the transition state **1152**, used to explain the stereochemical outcome in the Cr-catalyzed homoallylation with ligand **1147a**. In this case, the allyl moiety binds to chromium in the equatorial position, while the aldehyde binds in the apical position in the *anti*-geometry to avoid a steric

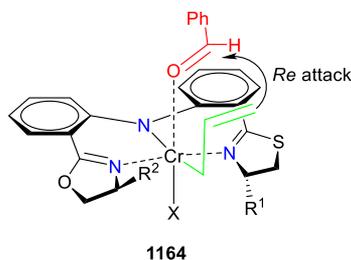


Figure 59. Stereochemical model for the asymmetric NHK reaction utilizing ligand **1160a**.

interaction between the aldehyde Ph-group and the oxazoline-benzyl (R^2) Ph-group. The allyl moiety then attacks the aldehyde from the *Re*-face to give the (*R*)-enantiomer. As in the homoallylation transition state **1152**, the thiazoline *t*Bu group (R^1) might block the aldehyde from coordinating from the opposite apical position.

While conventional wisdom suggests that C_2 -symmetry is important for applying chiral bis(oxazoline) ligands in highly enantioselective transformations, the reports described in this Review show that there is a place for C_1 -symmetric diphenylamine-linked bis(oxazoline) ligands. Significant progress has been made in the Cr-catalyzed asymmetric NHK reaction and in particular, the asymmetric and regioselective homoallylation of aldehydes. This chemistry requires the use of chemical reductants, and a potential future direction could be the application of electrochemistry to develop more environmentally sustainable processes.

3.2.9. C_1 -Symmetric Bis(oxazoline) Ligands with Modified Diphenylamine Linkers. Guiry has also developed related C_1 -symmetric bis(oxazoline) ligands **1165** based on a phenyl-thiophene-amine backbone (Figure 60).

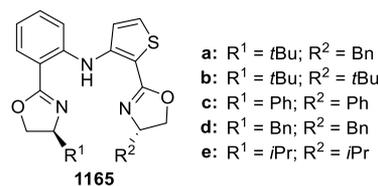


Figure 60. C_1 -Symmetric phenyl-thiophene-amine-linked bis(oxazoline) ligands **1165**.

These ligands **1165** were applied in the same Cr-catalyzed NHK reaction of allyl bromide **1162** with benzaldehyde **1148** to yield the enantioenriched alcohol **1163**. As with the previous report with C_1 -symmetric ligands **1160** (Table 9), the reaction with the *t*Bu/Bn-substituted ligand (**1165a**) gave the best result, yielding the alcohol **1163** in 83% and with 73% ee (*R*) (Table 10, entry 1). As before, the same trend in the formation of the (*R*)- or (*S*)-enantiomer of the product **1163** was observed for the different substituents on the oxazoline moieties.⁴¹⁰

3.2.10. Bis(oxazoline) Ligands with Carbazole Linkers. Developed by Nakada, carbazole-linked bis(oxazoline) ligands **1166** and **1167** are tridentate ligands with a more rigid backbone than their diphenylamine-linked counterparts

Table 10. Asymmetric NHK Reaction of Allyl Bromide with Benzaldehyde

entry	ligand	conv (%)	yield (%) 1163	% ee
1	1165a	88	83	73 (<i>R</i>)
2	1165b	83	79	22 (<i>R</i>)
3	1165c	80	72	38 (<i>S</i>)
4	1165d	80	78	8 (<i>S</i>)
5	1165e	82	78	63 (<i>S</i>)

(Figure 61).⁴¹¹ They have mostly been applied to Cr-catalyzed NHK-type transformations, with some exceptions.

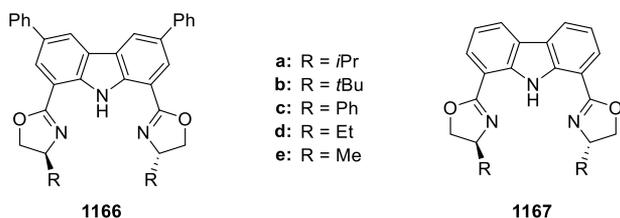
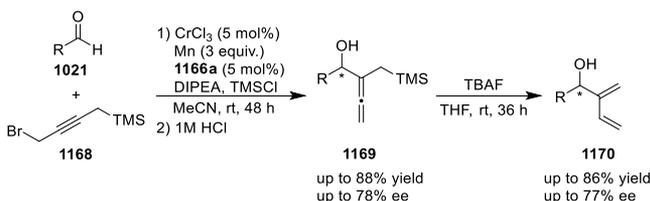


Figure 61. Carbazole-linked bis(oxazoline) ligands.

Connell has reported the enantioselective Cr-catalyzed addition of (4-bromobut-2-ynyl)-trimethylsilane **1168** to aldehydes **1021** for the asymmetric synthesis of (1,3-butadien-2-yl)methanols **1170** via [1-(silylmethyl)allenyl]-methanols **1169**. Using *i*Pr-ligand **1166a** as the chiral ligand, a small range of [1-(silylmethyl)allenyl]methanols **1169** were accessed in up to 88% yield and with up to 78% *ee* (Scheme 345). These were converted to (1,3-butadien-2-yl)methanols

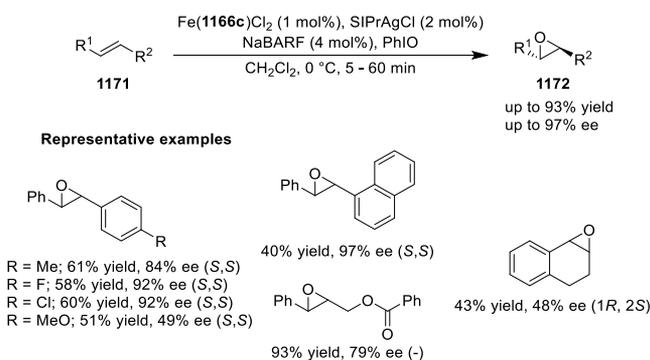
Scheme 345. Enantioselective Cr-Catalyzed Addition of (4-Bromobut-2-ynyl)-trimethylsilane to Aldehydes



1170 by treating with TBAF in up to 86% yield and with up to 77% *ee*, with a slight decrease in the enantiomeric excess (for R = Ph, 78% *ee* to 70% *ee*).⁴¹²

Nakada has reported that the Fe(III) complex of Ph-ligand **1166c** Fe(**1166c**)Cl₂ catalyzes the asymmetric epoxidation of *trans*-alkenes **1171** in up to 93% yield and with up to 97% *ee* (Scheme 346). *Trans*-stilbene derivatives and cinnamyl alcohol

Scheme 346. Asymmetric Fe-Catalyzed Epoxidation of *trans*-Alkenes

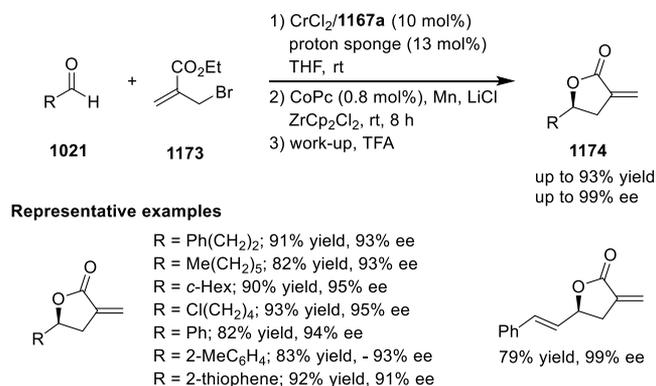


derivatives performed well in the reaction, although substrates bearing an electron-rich arene gave the epoxides with only moderate levels of enantioselectivity. The only cyclic alkene tested (1,2-dihydronaphthalene) gave the epoxide product with only 48% *ee*. The diphenylamine-linked ligand **1106a** did not catalyze the epoxidation, indicating that the π - π conjugation system of the carbazole ligand **1166c** is essential

to the catalytic activity of the Fe(III) complex in this transformation.⁴¹³

Zhang has reported the use of ligands **1167** in a variety of Cr-catalyzed processes, like the enantioselective synthesis of α -*exo*- γ -butyrolactones **1174** via a sequential 2-(alkoxycarbonyl)-allylation/lactonization process. Ethyl 2-(bromomethyl) acrylate **1173** was reacted with a variety of aldehydes **1021** in the presence of 10 mol % CrCl₂ and *i*Pr-ligand **1167a**, followed by acidic workup or treatment with K₂CO₃ overnight to give the enantioenriched lactones **1174** in up to 93% yield and with up to 99% *ee* (Scheme 347). The diphenylamine-linked bis(oxazoline) ligand **1106c** also catalyzed the model reaction but with a lower enantiomeric excess (79% *ee* compared to 93% *ee*).⁴¹⁴

Scheme 347. Cr-Catalyzed Enantioselective Synthesis of α -*exo*- γ -Butyrolactones



A possible transition state **1175**, similar to the other Cr-catalyzed processes utilizing these ligands and diphenyl-amine-linked bis(oxazoline) ligands, but invoking tridentate chelation, was proposed to explain the formation of the (*S*)-enantiomer of the product with the *i*Pr-ligand **1167a** (Figure 62).

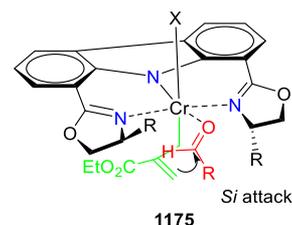
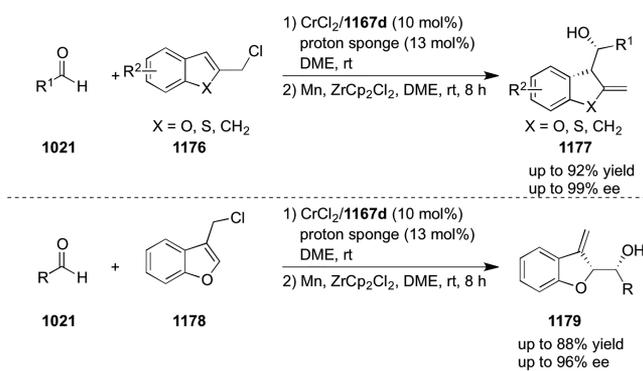


Figure 62. Stereochemical model for the sequential 2-(alkoxycarbonyl)allylation/lactonization process utilizing ligand **1167a**.

The asymmetric Cr-catalyzed dearomative addition of halomethylarenes **1176** to aldehydes **1021** for the asymmetric synthesis of secondary benzylic alcohols **1177** was also reported by Zhang, employing Et-ligand **1167d**. 2-(Chloromethyl)benzofurans, -benzothiophenes, and -indenes **1176** were successfully subjected to the reaction conditions with a range of aryl, alkenyl and aliphatic aldehydes **1021** to give the corresponding benzylic alcohols in up to 92% yield and with enantiomeric excesses up to 99% *ee* (Scheme 348). 3-(Chloromethyl)benzofuran **1178** was also subjected to the reaction to yield the corresponding secondary benzylic alcohols **1179** in up to 88% yield and with up to 96% *ee*.⁴¹⁵ The scope of this process was extended to include

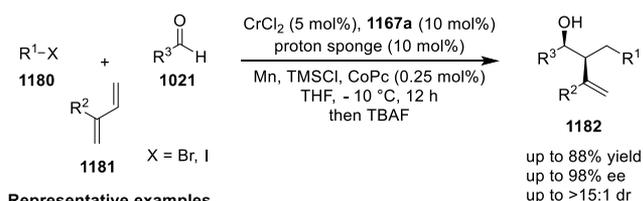
Scheme 348. Asymmetric Cr-Catalyzed Dearomative Addition of Chloro(methyl) Heteroarenes to Aldehydes



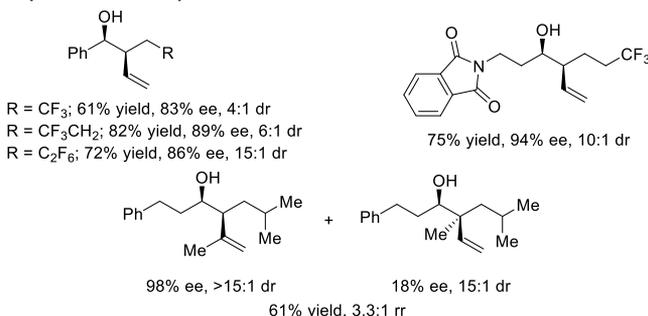
bromomethylnaphthalenes,⁴¹⁶ bromomethyl- and chloromethyloxazoles, and bromomethyl- and chloromethylindoles⁴¹⁷ with similar results.

An enantioselective 1,2-difunctionalization of 1,3-butadienes **1181** via an asymmetric Cr/Co-bimetallic alkylation/carbonyl allylation sequence was achieved by Zhang, with the *i*Pr-ligand **1167a**. A range of 1,3-butadienes **1181** were difunctionalized with various alkyl bromides and iodides **1180**, and aliphatic and aryl aldehydes **1021**. The enantioenriched alcohols **1182** were isolated in good yields up to 88%, with high levels of enantioselectivity up to 98% *ee* and with high diastereoselectivities up to >15:1 *dr* (Scheme 349). A range of fluorinated and nonfluorinated alkyl iodides/bromides were successfully applied in this transformation.⁴¹⁸

Scheme 349. Asymmetric Cr/Co-Bimetallic Alkylation/Carbonyl Allylation



Representative examples

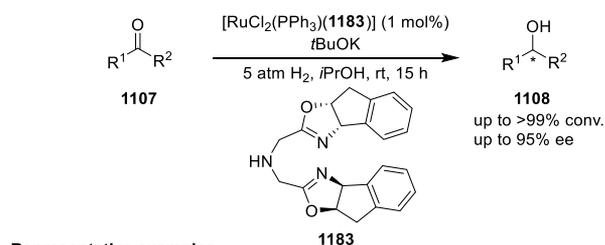


Like the diphenylamine-linked bis(oxazoline) ligands, carbazole-linked bis(oxazoline) ligands have been successfully applied in enantioselective Cr-catalyzed processes. The carbazole backbone is rigid compared to the flexible diphenylamine backbone; as a result, both ligand families have their own unique properties.

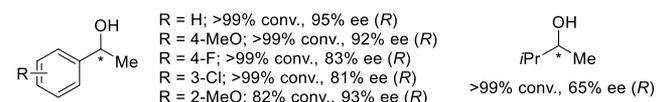
3.2.11. Miscellaneous Bis(oxazoline) Ligands with Free-Amine-Based Linkers. Zhang has reported the asymmetric Ru-catalyzed hydrogenation of ketones **1107** with a tridentate, bifunctional indaBOX ligand **1183** for the

synthesis of enantioenriched alcohols **1108** with up to >99% conversion and up to 95% *ee* (Scheme 350). Monoaryl and

Scheme 350. Asymmetric Ru-Catalyzed Hydrogenation of Ketones



Representative examples



cyclohexyl ketones performed well in the reaction, yielding the secondary alcohols with enantiomeric excesses >80%, but linear aliphatic ketones gave the corresponding alcohols in moderate enantioselectivities 42–65% *ee*.⁴¹⁹

A possible transition state **1184** was proposed to explain the stereochemical outcome of the transformation, highlighting the suggested ligand-assisted mechanistic pathway (Figure 63).

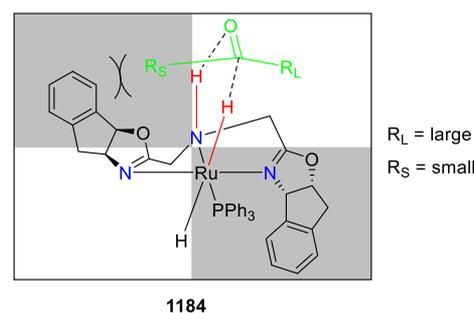


Figure 63. Stereochemical model for the asymmetric Ru-catalyzed hydrogenation utilizing ligand **1183**.

Gade has developed a new class of chiral, planar, rigid pincer-type ligand, bis(oxazolynylmethylidene)isoindolines **1185–1187** (boxmi), which contain a phthalimide-based linker in the backbone (Figure 64).

Gade first applied these ligands in the Ni-catalyzed asymmetric α -fluorination of oxindoles **1188** with NFSI. A range of α -aryl- α -fluorooxindoles **1189** (and one α -methyl example) were accessed in up to 95% yield and with up to >99% *ee*, using optimized reaction conditions with Ph-boxmi **1185c** as the chiral ligand (Scheme 351). They also extended the scope to include indanone-based β -keto esters with enantioselectivities up to 97% *ee*.⁴²⁰

In same report, Gade applied the ligands in the NHK-reaction of allyl bromide **1062** with benzaldehyde **1021** and Table 11 summarizes the results of this study. The reaction with *i*Pr-ligand **1186a** gave the best outcome, giving alcohol **1063** in 92% yield and with 86% *ee* (*S*) (entry 4). Unlike the diphenylamine- and carbazole-linked bis(oxazoline) ligands, all ligands tested in the boxmi series led to the formation of the (*S*)-alcohol.

Gade has developed an asymmetric Cu/**1186c**-catalyzed α -alkylation of β -keto esters **1190** with benzyl alcohols **1191**, for

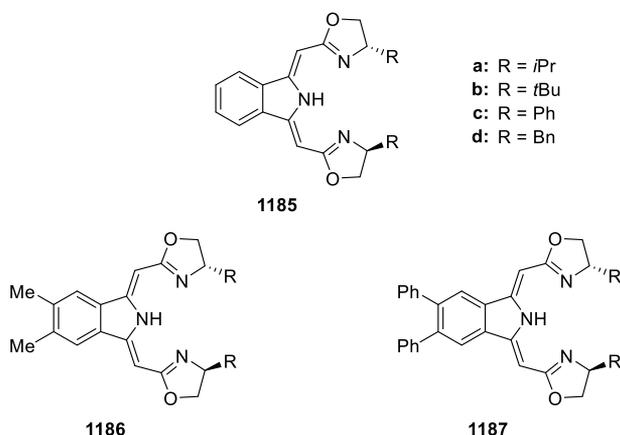


Figure 64. Boxmi ligands.

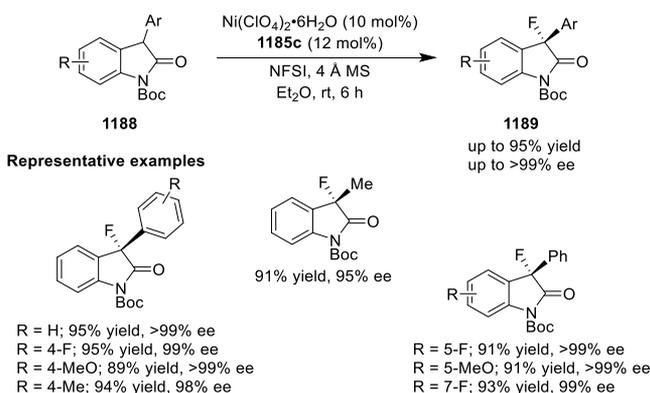
Scheme 351. Ni-Catalyzed Asymmetric α -Fluorination of Oxindoles

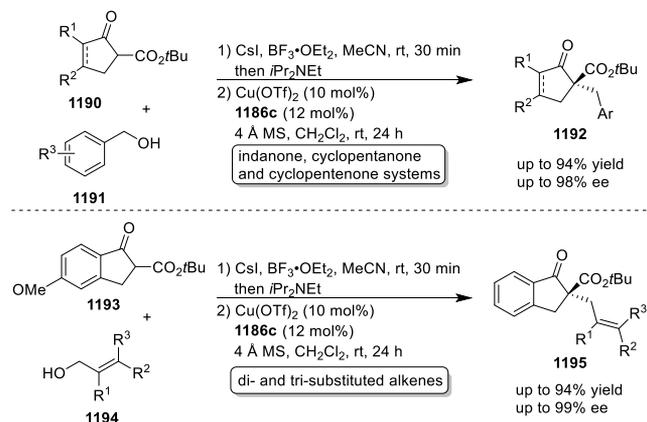
Table 11. Asymmetric NHK Reaction of Allyl Bromide with Benzaldehyde

1021 + **1062** $\xrightarrow[\text{THF, rt, 10-12 h}]{\text{1) CrCl}_3 \text{ (10 mol\%)}, \text{Mn (2 equiv.)}, \text{ligand (12 mol\%)}, \text{DIPEA, TMSCI}}$ **1063**

2) TBAF

entry	ligand	time (h)	yield (%) 1063	% ee
1	1185a	12	92	83 (S)
2	1185b	10	91	73 (S)
3	1185c	12	91	84 (S)
4	1186a	10	92	86 (S)
5	1186b	10	93	68 (S)
6	1186c	10	89	54 (S)
7	1186d	12	92	73 (S)
8	1187a	12	91	83 (S)
9	1187b	12	92	63 (S)
10	1187c	12	93	79 (S)

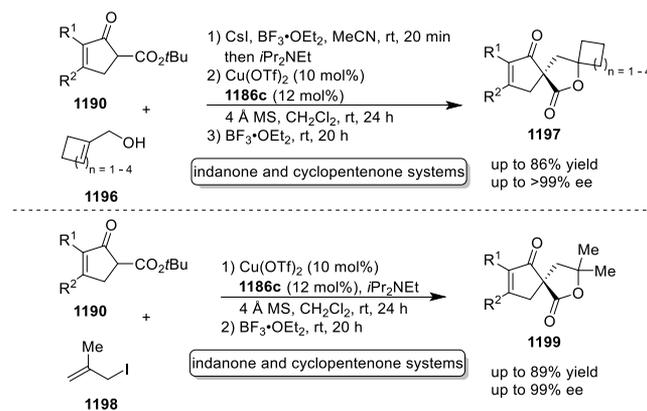
the enantioselective synthesis of enantioenriched β -keto esters **1192** in up to 94% yield and with 98% ee (Scheme 352). A variety of indanone-, cyclopentanone- and cyclopentenone-based β -keto esters **1192** were tolerated in the reaction. The initial step in the reaction converts the alcohols **1191** to the corresponding iodides with CsI, and the iodides then participate in the alkylation reaction in the second step. Benzyl alcohols **1191** bearing different substitutions were well tolerated; however, no heteroaromatic substrates were

Scheme 352. Asymmetric Cu-Catalyzed α -Alkylation/Alkylation of β -Keto Esters

reported. The reaction was then extended to include allyl alcohols **1194** as the alkylating agent. Both di- and trisubstituted alkenes were tolerated in the reaction, giving the enantioenriched β -keto esters **1195** in up to 94% yield and with up to 99% ee.⁴²¹

In the same report, Gade reported that treating the allylated- β -keto ester products from the reaction with cycloalkenes **1196** with $\text{BF}_3 \cdot \text{OEt}_2$, the allylation could be further extended to the synthesis of bispirolactones **1197** in up to 86% yield and with >99% ee (Scheme 353). When 3-iodo-2-methylpropene **1198**

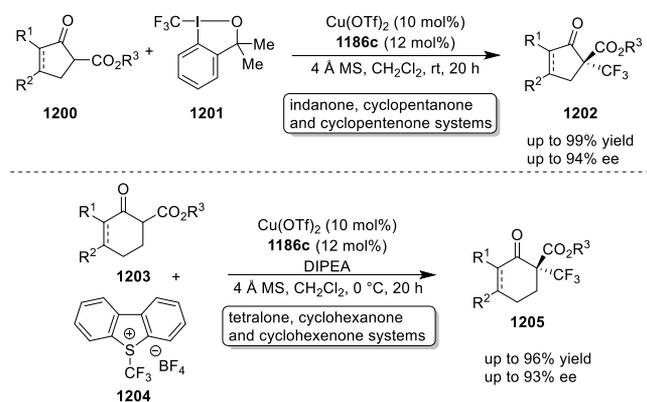
Scheme 353. Asymmetric Synthesis of Spirolactones



(which cannot be prepared from the corresponding alcohol by the CsI method) was used directly in the allylation/spirolactonization sequence, spirolactones **1199** were isolated in up to 89% yield and with 99% ee.

Gade later reported an asymmetric Cu/**1186c**-catalyzed trifluoromethylation of β -keto esters **1200** and **1203**. The 5-membered-ring-based β -keto esters **1200** were trifluoromethylated under optimized conditions with Togni's reagent **1201** to give the α -trifluoromethyl- β -keto esters **1202** in up to 99% yield and with up to 94% ee (Scheme 354). The 6-membered-ring-based β -keto esters **1203**, with a more enolizable ketone were found to undergo the trifluoromethylation with higher levels of enantioselectivity with Umemoto's reagent **1204** and DIPEA in place of Togni's reagent **1201**. The 6-membered-ring-based products **1205** were isolated in up to 96% yield and with up to 93% ee.⁴²² Gade subsequently developed a very similar methodology for a

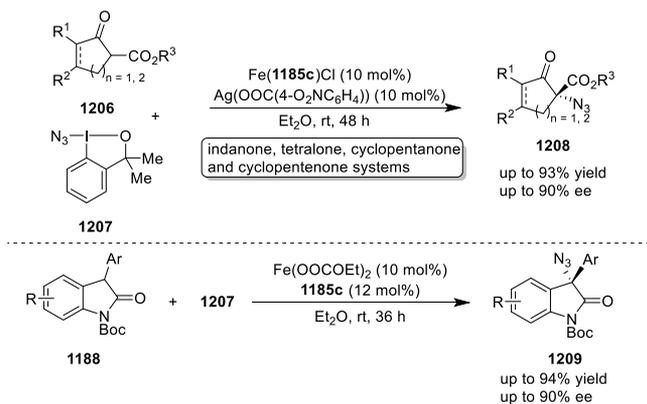
Scheme 354. Asymmetric Cu-Catalyzed Trifluoromethylation of β -Keto Esters



highly enantioselective Cu/1185c-catalyzed trifluoromethylthiolation of β -keto esters with the $-SCF_3$ analogue of Togni's reagent.⁴²³

Further expanding on their use of boxmi-ligands in the α -functionalization of oxindoles and β -keto esters, Gade described an asymmetric Fe-catalyzed azidation of β -keto esters **1206** and oxindoles **1188** with an azide-analogue of Togni's reagent **1207** (Scheme 355). During optimization they

Scheme 355. Asymmetric Fe-Catalyzed Azidation of β -Keto Esters and Oxindoles

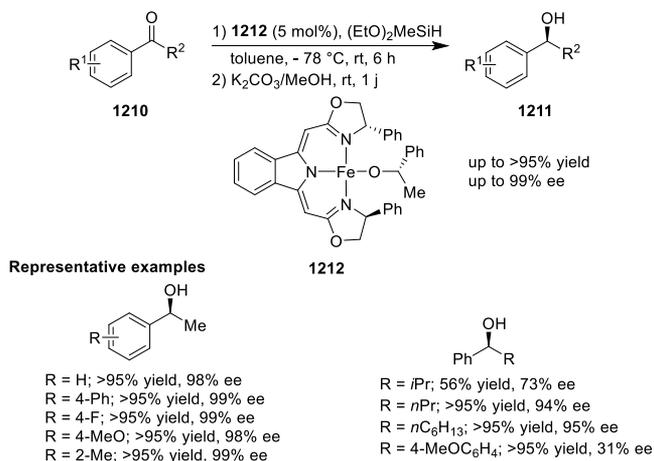


found that iron carboxylates gave the highest levels of enantioselectivity in the reaction. A screen of silver carboxylates in combination with the [Fe(1185c)Cl] complex led to the best result being obtained with silver *p*-nitrobenzoate. Using the optimized conditions, a range of 5- and 6-membered-ring-based β -keto esters **1206** were azidated to give the enantioenriched products **1208** in up to 93% yield and with up to 90% *ee*. A range of α -aryl-oxindoles **1188** were azidated to give the products in up to 94% yield and with up to 90% *ee*, utilizing Fe(OOCOEt)₂/1185c and no silver salts.⁴²⁴

Gade has furthered the application of boxmi ligands in Fe-catalysis by developing a highly reactive Fe/1185c system for the hydrosilylation of ketones **1210**. Under optimized conditions, Fe-catalyst **1212** successfully catalyzed the hydrosilylation of a range of ketones **1210**, the first Fe-catalyst to achieve >95% *ee* in this reaction and the first Fe-catalyst to operate at such relatively low temperatures. Monoarylated alcohols **1211** were isolated in up to >95% yield and with up to 99% *ee*, whereas diaryl ketones gave lower levels of

enantioselectivity due to less discrimination between the two groups (Scheme 356).⁴²⁵

Scheme 356. Asymmetric Fe-Catalyzed Hydrosilylation of Ketones



Tridentate bis(oxazoline) ligands bearing free-amine linkers have been shown to be useful in a range of transformations. In particular, Gade has pioneered the use of Boxmi ligands in Fe-catalysis. These ligands can be used to form very active Fe-catalysts, and future developments in this area are expected.

3.2.12. Bis(oxazoline) Ligands with Pyridine Linkers and Monosubstituted Oxazoline Rings. PyBOX ligands **1213a–h** are an extensively used class of pyridine-based tridentate bis(oxazoline) ligand (Figure 65).

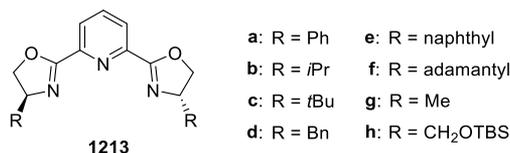
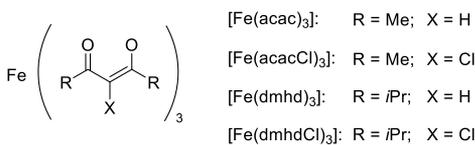
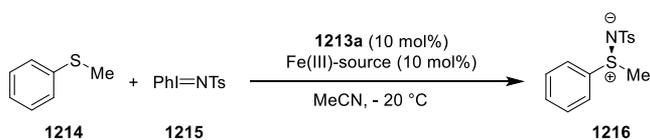


Figure 65. PyBOX ligands.

Bolm has applied ligand **1213a** in the Fe-catalyzed enantioselective transfer of nitrenes to sulfides to afford chiral sulfimides (nitrogen analogues of sulfoxides) in excellent yields and good enantiomeric excesses of up to 90% *ee*. Only Ph-PyBOX **1213a** was found to induce good levels of stereoinduction, while the other PyBOX ligands tested **1213b–c** gave almost racemic products. The Fe(III) source was found to have a dramatic effect on the stereoselectivity of the reaction, with only Fe(III) acetylacetonate derivatives yielding the product in good enantioselectivity (Table 12). Ultimately, the catalyst derived from [Fe(dmhdCl)₃] was found to be optimal giving sulfimide **1216** in 98% yield and 86% *ee* (entry 6). Only sulfides **1214** bearing at least one nonaliphatic group facilitated nitrene transfer with good stereoselectivity. For example, when the benzyl analogue of sulfide **1214** was subjected to the reaction, the product was isolated in 55% yield and 10% *ee*, the only example with an enantiomeric excess of less than 60% *ee*.⁴²⁶

Bolm applied the same ligand **1213a** in the Fe(III)-catalyzed imidative kinetic resolution of racemic sulfoxides, accessing the sulfamidates in moderate to good yields and enantioselectivities. When racemic sulfoxides **1217** are subjected to the

Table 12. Fe(III) Source Effect on Stereoselectivity of the Reaction

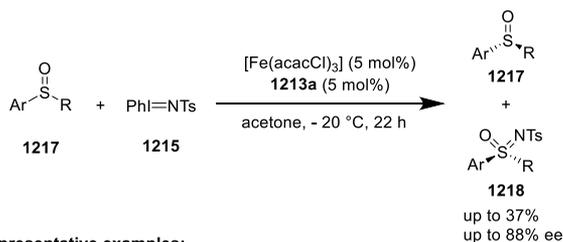


entry	Fe source	ligand	time	yield	% ee
1	$[\text{Fe}(\text{acac})_3]$	(<i>S,S</i>)- 1213a	14 h	75%	50%
2	$[\text{Fe}(\text{acacCl})_3]$	(<i>S,S</i>)- 1213a	1 h	97%	64%
3	$[\text{Fe}(\text{dmhd})_3]$	(<i>S,S</i>)- 1213a	6 h	99%	68%
5 ^a	$[\text{Fe}(\text{dmhdCl})_3]$	(<i>S,S</i>)- 1213a	2 h	99%	82%
6 ^a	$[\text{Fe}(\text{dmhdCl})_3]$	(<i>R,R</i>)- 1213a	16 h	98%	-86%

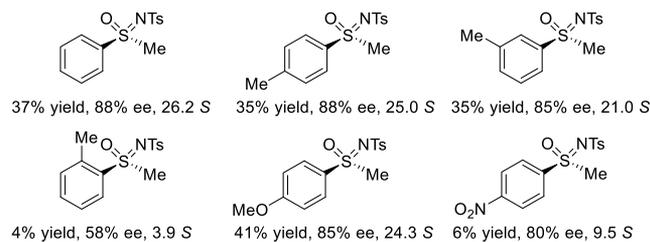
^aAcetone instead of MeCN.

reaction conditions, sulfamidates **1218** were obtained in up to 37% yield and 88% ee, with an *S* factor of up to 26.2 (Scheme 357). The reaction outcome, especially with regard to the yield

Scheme 357. Fe(III)-Catalyzed Imidative Kinetic Resolution of Racemic Sulfoxides



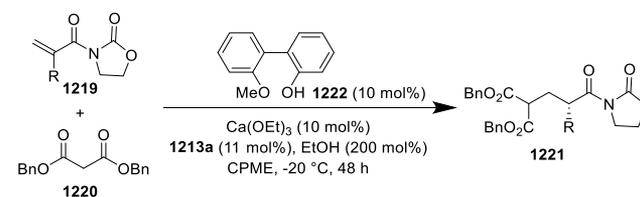
Representative examples:



of the reaction, was sensitive to steric and electronic modifications on the aryl ring of the sulfoxide **1217**. For example, the 2-methyl and 4-nitro-substituted examples gave the corresponding products in 4% and 6% yield with enantiomeric excesses of 58% and 80% ee, respectively.⁴²⁷

Ligand **1213a** was applied by Kobayashi in the asymmetric protonation of chiral calcium enolates formed from the 1,4-addition of malonates to oxazolindione-based Michael acceptors. Following addition of the malonate **1220** to the Michael acceptor **1219**, the chiral Ca(II)-PyBOX complex coordinates to and rigidifies the enolate, controlling its geometry, yielding enantiomerically enriched **1221** after protonation (Scheme 358). Only Ph-PyBOX **1213a** was found to induce good stereoselectivity and interestingly, best results were obtained when 10 mol% phenol **1222** and 200 mol% EtOH were used as additives in cyclopentyl methyl ether (CPME) at $-20\text{ }^\circ\text{C}$. The products **1221** were formed in excellent yields and

Scheme 358. Asymmetric Protonation of Chiral Calcium Enolates

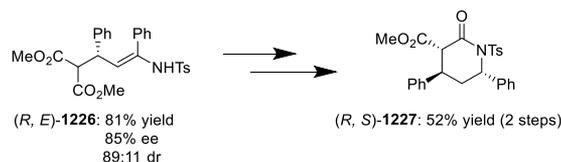
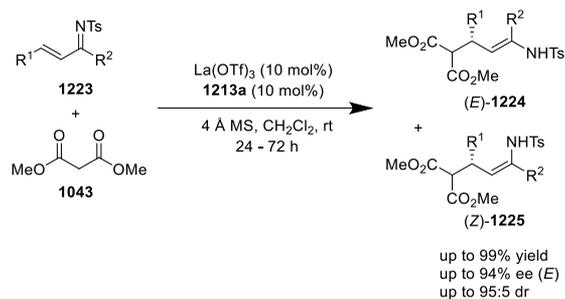


Representative examples

R = Me; 90% yield, 95% ee R = $\text{CH}_2\text{C}\equiv\text{CPh}$; 88% yield, 94% ee
 R = Allyl; 86% yield, 96% ee R = $\text{CH}_2=\text{CCH}_2\text{OBn}$; 77% yield, 93% ee
 R = Prenyl; 85% yield 93% ee R = $\text{CH}_2=\text{C}\text{Bu}$; 91% yield, 94% ee
 R = *cis*- $\text{CH}_2\text{CH}=\text{CHCl}$; 96% yield, 95% ee R = Ph; 72% yield, 48% ee
 R = cinnamyl; 85% yield, 94% ee

enantioselectivities of up to 91% and 96% ee, respectively, with a variety of alkyl groups. In the case of an aryl group (R = Ph) a diminished enantiomeric excess of 42% was achieved.⁴²⁸

Ligand **1213a** was employed by Blay and Pedro in the La(III)-catalyzed asymmetric conjugate addition of malonate esters to α,β -unsaturated *N*-sulfonyl imines **1223**. Of the ligands tested, only the Ph-PyBOX **1213a** gave appreciable levels of enantiomeric excess, with a range of (*E*)-enamine products **1224** isolated in moderate to excellent yields, moderate to high *E/Z* selectivities (up to 95:5 *E/Z*) and good enantioselectivities up to 94% ee (Scheme 359). The

Scheme 359. La(III)-Catalyzed Asymmetric Conjugate Addition of Malonate Esters to α,β -Unsaturated *N*-Sulfonyl Imines

enamine products can be used to synthesize chiral δ -aminoesters and lactams with good efficiency, for example, optically pure lactam (*R,S*)-**1227** was accessed in 2 steps and 52% yield from (*R,E*)-enamine **1226**.⁴²⁹

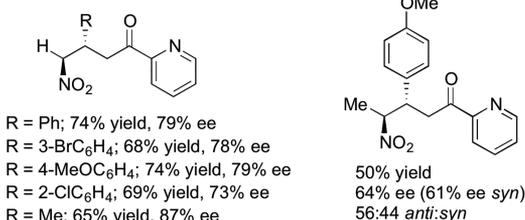
Pedro and Blay described a new naphthyl-PyBOX ligand **1213e** in the related La(III)-catalyzed conjugate addition of nitroalkanes to (*E*)-2-azachalcones **1228**, providing the nitro-Michael product **1230** in up to 74% yield and moderate to good enantioselectivities of up to 87% ee for a range of substrates (Scheme 360). The reaction proceeded well when R^1 was either aryl or alkyl, and R^2 was methyl. Where R^2 = ethyl or propyl, the dr of the corresponding products was often low.⁴³⁰

Maarseveen prepared a range of chiral propargylic amines via a Cu-**1213g**-catalyzed propargylation of both aromatic and

Scheme 360. La(III)-Catalyzed Asymmetric Conjugate Addition of Nitroalkanes to (*E*)-2-Azachalcones

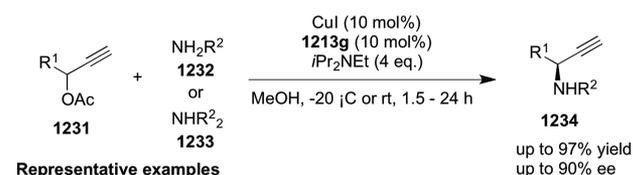


Representative examples

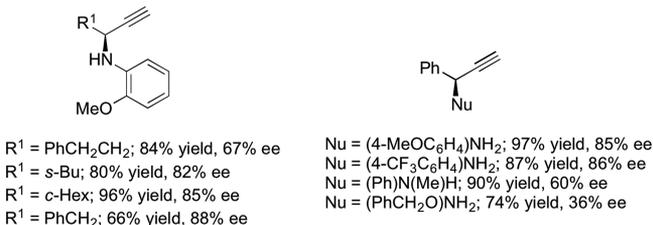


nonaromatic amines with propargylic esters **1231**. Using a range of primary (**1232**) and secondary amines (**1233**), several propargylic amines **1234** were synthesized in up to 97% yield and 90% ee (Scheme 361). Aniline derivatives performed best

Scheme 361. Asymmetric Cu-Catalyzed Propargylation of Amines



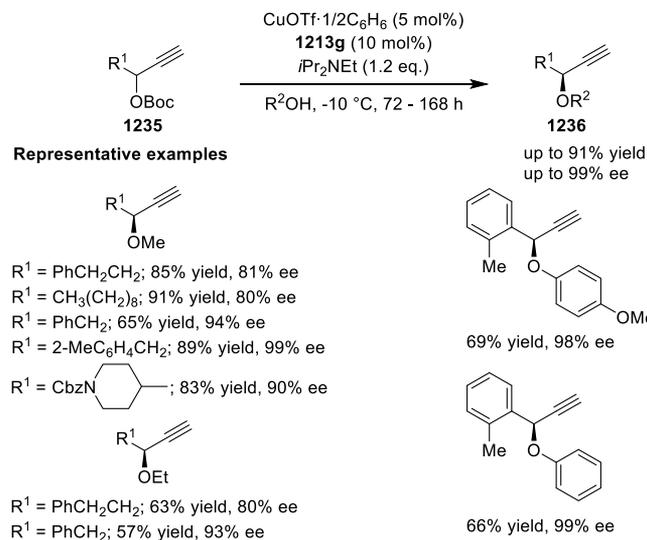
Representative examples



as nucleophiles, giving the corresponding products in high yields and enantioselectivities, while other amines generally performed poorly. A number of C-nucleophiles were also tested, with indole derivatives providing the products in up to 91% yield and 98% ee. Some of the propargylic amines synthesized by this protocol were converted into α -amino acid derivatives and further elaborated to provide formal total syntheses of the biologically active compounds (+)-anisomycin and (–)-cytoxazone.⁴³¹

Nishibayashi employed a Cu-**1213g** complex in the enantioselective propargylic etherification of propargylic esters **1235** with alcohols (Scheme 362). Initially, a range of PyBOX ligands were tested in the reaction, giving low enantioselectivities when the reaction was performed at rt. Performing the reaction at a lower temperature of -10°C for a longer reaction time (72 h) gave the propargyl ether products in generally high yields (57–91%) and enantioselectivities (79–99% ee) when using Me-PyBOX **1213g** as the chiral ligand. For reactions with MeOH and EtOH, the alcohol can be used as the reaction solvent. For reactions with phenol derivatives, 2 equiv of the corresponding phenol can be used in MeOH as the reaction

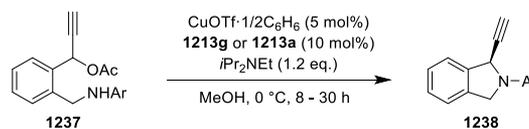
Scheme 362. Asymmetric Cu-Catalyzed Propargylation of Alcohols



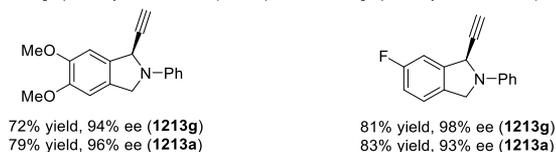
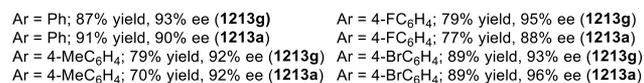
solvent. A dimeric $[\text{Cu}_2(\text{PyBOX})_2][\text{OTf}]$ species was proposed as the active catalytic agent in the reaction based on experimental evidence.⁴³²

Nishibayashi employed Ph- and Me-PyBOX ligands **1213a** and **1213g** in a related Cu-catalyzed intramolecular amination of propargylic acetates **1237** to yield nitrogen-containing heterocycles **1238** bearing ethynyl groups in the α -position. A range of PyBOX ligands bearing both mono- and disubstitution on the oxazoline ring were tested, with both **1213a** and **1213g** performing well. A range of nitrogen heterocycles were successfully synthesized in good yields and high enantioselectivities of up to 98% ee (Scheme 363).⁴³³

Scheme 363. Asymmetric Cu-Catalyzed Intramolecular Amination of Propargylic Acetates



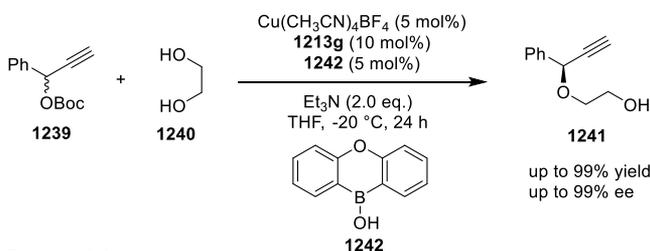
Representative examples



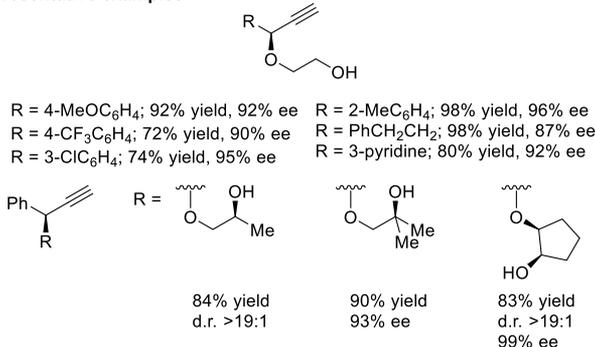
A Cu/boronic acid dual catalyzed enantioselective propargylation of polyols was reported by Niu and applied to the desymmetrization of *meso* 1,2-diols **1240** to furnish products with up to three stereocenters in one operation. Generally, aliphatic alcohols are not nucleophilic enough to engage in Cu-catalyzed propargylation reactions unless they are used as the reaction solvent, thus limiting the scope of the reaction to simple alcohols like MeOH and EtOH. Niu addressed this issue by taking advantage of the increased nucleophilicity of boronate complexes formed between diols and boronic acids. Subjecting propargylic esters **1239** to the reaction with various

diols **1240** in the presence of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ and chiral Me-PyBOX ligand **1213g** the desymmetrized propargylic ethers **1241** were obtained in yields up to 99% and enantioselectivities up to 99% *ee* (Scheme 364). The authors suggested the presence of a dinuclear Cu species as the active catalyst in the reaction, based on Nishibayashi's reports.⁴³⁴

Scheme 364. Asymmetric Cu-Catalyzed Desymmetrization of Diols with Propargylic Acetates

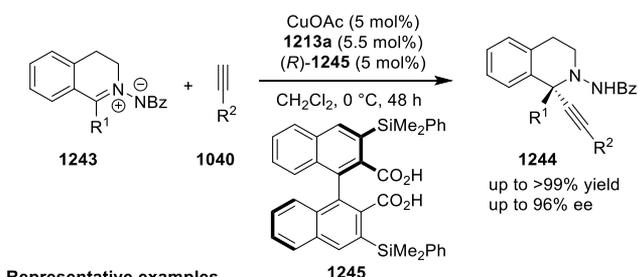


Representative examples

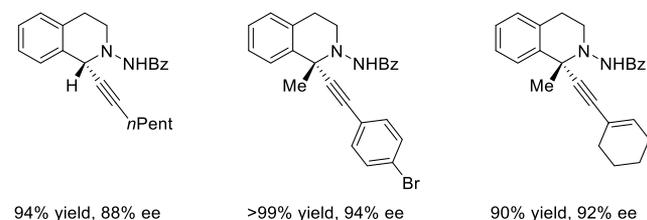


Maruoka has applied **1213a** in the catalytic asymmetric alkylation of C_1 -substituted C,N -cyclic azomethine imines **1243** with a Cu(I)/chiral Bronsted acid cocatalyst system (Scheme 365). This is the first example of an asymmetric direct alkyne addition to a CN double bond to give tetrasubstituted carbon centers in high stereoselectivity. A range of nitrogen heterocyclic products **1244** with tertiary and quaternary alkyl-substituted stereocenters were generated in excellent yields up to >99% and excellent enantioselectivities

Scheme 365. Cu/chiral Bronsted Acid-Catalyzed Asymmetric Alkylation of C_1 -Substituted C,N -Cyclic Azomethine Imines



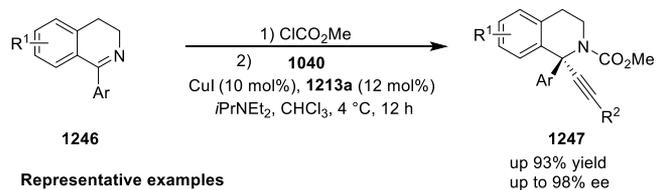
Representative examples



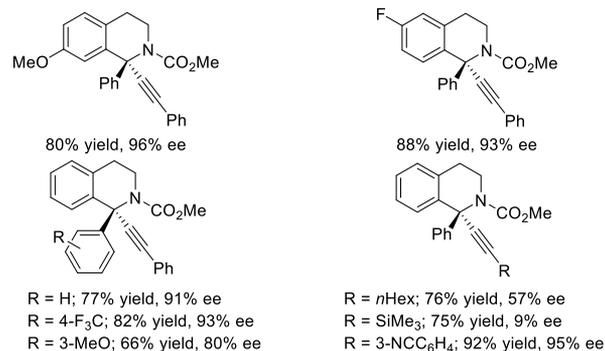
up to 96% *ee*. The tertiary stereocenters were formed in excellent yields and enantioselectivities without the need for a chiral Bronsted acid additive **1245**, however in the case of products containing a quaternary stereocenter, the additive dramatically improved the stereoselectivity of the process.⁴³⁵

Watson later reported a similar Cu-catalyzed asymmetric alkylation of diaryl ketimines **1246** (Scheme 366). Utilizing

Scheme 366. Cu-Catalyzed Asymmetric Alkylation of Diaryl Ketimines



Representative examples

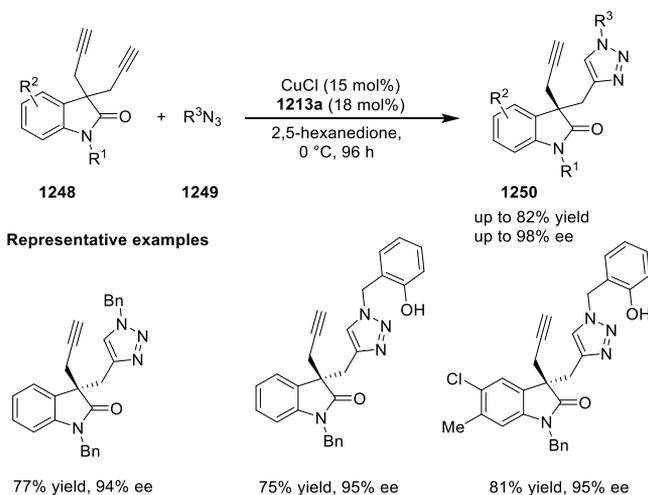


Ph-PyBOX ligand **1213a**, diaryl ketimines **1246** were first reacted with ClCO_2Me to form an iminium ion, followed by the $\text{CuI}/\text{1213a}$ -catalyzed addition of an alkyne to form a range of C_1 -tetrasubstituted nitrogen heterocyclic products **1247** in generally excellent yields up to 93% and enantioselectivities up to 98% *ee*. The reactions were run under basic conditions without the need for a chiral Bronsted acid additive. A wide range of aryl groups were tolerated on the ketimine **1246**; however, no heteroaryl groups were reported. The alkyne was found to tolerate a range of substituted aryl groups, however alkyl and silyl groups were detrimental to the stereoselectivity of the process.⁴³⁶

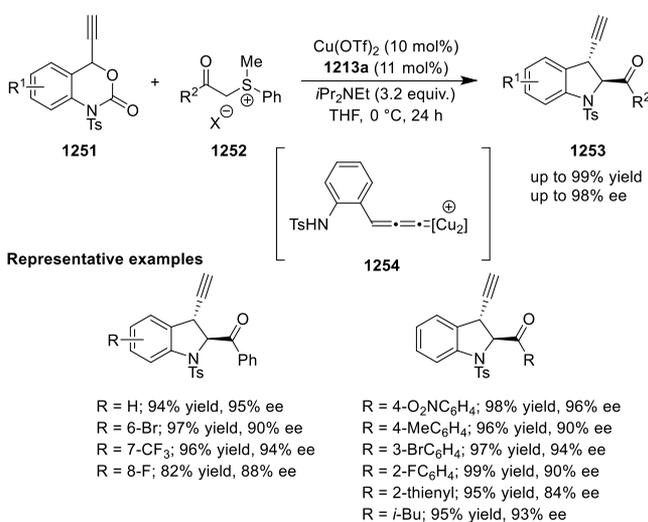
Zhou has applied ligand **1213a** in the first highly enantioselective Cu-catalyzed azide–alkyne cycloaddition (CuAAC) via desymmetrization of oxindole-based 1,5-heptadiynes **1248** to furnish chiral quaternary oxindoles **1250** bearing a 1,2,3-triazole moiety (Scheme 367). A range of azides and oxindoles were demonstrated to perform well in the reaction providing the products in good yields of up to 82% and excellent enantioselectivities of up to 98% *ee*, with the construction of all-carbon quaternary stereogenic centers.⁴³⁷

Li and Xiao reported the first decarboxylative $[4 + 1]$ cycloaddition of propargylic carbamates **1251** with sulfur ylides (Scheme 368). A range of ethynyl benzoxazinones **1251** with varying aryl substitution patterns were subjected to the reaction with sulfonium salts **1252**, bearing different ketonic moieties, in the presence of $\text{Cu}(\text{OTf})_2$ and chiral Ph-PyBOX ligand **1213a** to yield chiral indolines **1253** in high yields of up to 99% and with excellent enantioselectivities of up to 98% *ee*. The proposed mechanism for the reaction involves a key Cu-allenylidene intermediate **1254**, which undergoes a formal $[4 + 1]$ cycloaddition with the *in situ* formed sulfur ylide.⁴³⁸

Scheme 367. Enantioselective Cu-Catalyzed Azide–Alkyne Cycloaddition *via* Desymmetrization of Oxindole-Based 1,5-Heptadiynes

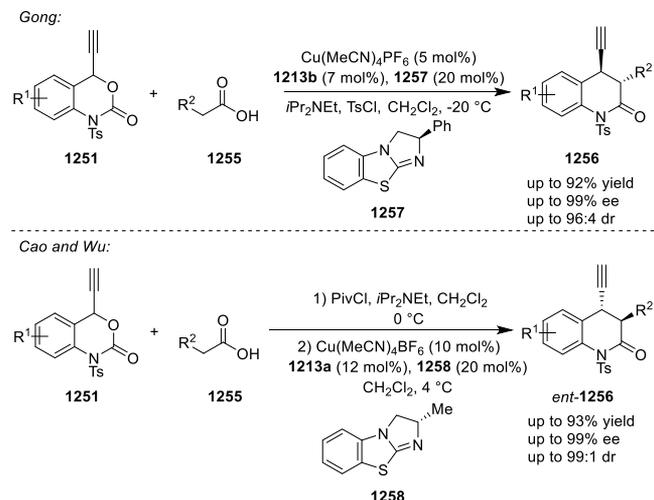


Scheme 368. Asymmetric Decarboxylative [4 + 1] Cycloaddition of Propargylic Carbamates with Sulfur Ylides



Gong⁴³⁹ and Cao and Wu⁴⁴⁰ independently reported the use of ethynyl benzoxazinones **1251** in a similar Cu-catalyzed [4 + 2] annulation of the same copper allenylidene intermediate **1254** with *in situ* generated carboxylic acid/nucleophilic Lewis base derived enolates. Gong utilized *i*Pr-PyBOX ligand **1213b** to achieve high levels of stereoinduction of up to 99% ee, while Cao and Wu utilized Ph-PyBOX **1213a**, also achieving enantioselectivities of up to 99% ee (Scheme 369). Interestingly, Cao and Wu reported the opposite absolute stereochemistry of the quinolinone products **1256** to that reported by Gong (both reports determined the absolute stereochemistry by X-ray crystallographic analysis of the product). The (*R,R*)-PyBOX ligands (Ph **1213a** or *i*Pr **1213b**) were applied in both cases, while the nucleophilic Lewis base catalysts **1257** and **1258**, with opposite senses of stereochemistry were used. In both reports, a switch in the stereochemistry of the nucleophilic Lewis base catalyst led to the formation of the opposite enantiomer, so the nucleophilic Lewis base catalyst controls the absolute stereochemistry of the product of this cascade process. In fact, Gong performed the

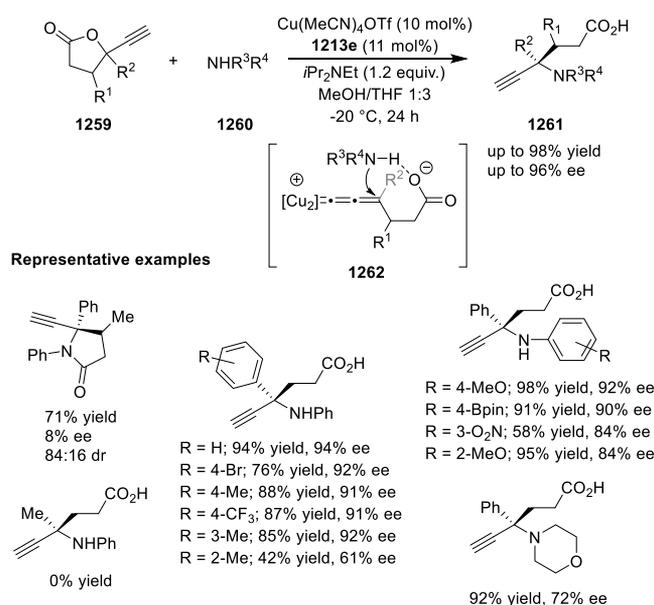
Scheme 369. Asymmetric Cu-Catalyzed [4 + 2] Annulation of Ethynyl Benzoxazinones with *In Situ* Generated Carboxylic Acid/Nucleophilic Lewis Base Derived Enolates



reaction in the presence of an achiral PyBOX ligand, isolating the product quinolinone in a slightly lower 92% ee, but with a much lower diastereoselectivity. Multiple Cu(PyBOX) catalytic systems have been shown to be proficient in the enantioselective [4 + 2] cycloaddition of Cu-allenylidenes (derived from ethynyl benzoxazinones) with multiple synthetic partners.^{441–443}

Kleij has developed a somewhat related Cu-catalyzed asymmetric synthesis of γ -amino acids bearing quaternary stereocenters. Utilizing chiral naphthyl-PyBOX ligand **1213e**, propargylic lactones **1259** undergo an enantioselective Cu-catalyzed amination with a variety of primary amines and one secondary amine **1260** to give the corresponding γ -amino acids **1261** in up to 98% yield and with up to 96% ee (Scheme 370). The proposed mechanism for this transformation involves a similar Cu-allenylidene intermediate **1262** which is nucleophilically attacked by the amine.⁴⁴⁴ Zhang has described a very

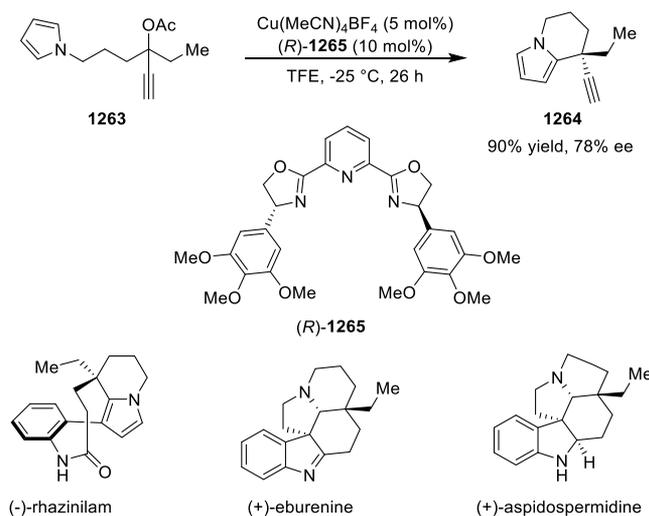
Scheme 370. Cu-Catalyzed Asymmetric Synthesis of γ -Amino Acids



similar Cu(**1213d**)-catalyzed enantioselective synthesis of β -amino alcohols, utilizing cyclic carbonates in place of lactones.⁴⁴⁵

Carrera has utilized the electron rich 3,4,5-trimethoxyphenyl PyBOX ligand (*R,R*)-**1265** in a Cu-catalyzed propargylation of an internal C-nucleophile as the key step in the enantioselective total synthesis of three natural products. Propargyl acetate **1263** was subjected to the reaction, which proceeds through a Cu-allenyldiene intermediate, to give pyrrole **1264** containing the core stereogenic center of (–)-rhazinilam, in 90% yield and 78% *ee* (Scheme 371).

Scheme 371. Asymmetric Cu-Catalyzed Propargylation for the Total Synthesis of (–)-Rhazinilam, Aspidospermidine, and (+)-Eburenine

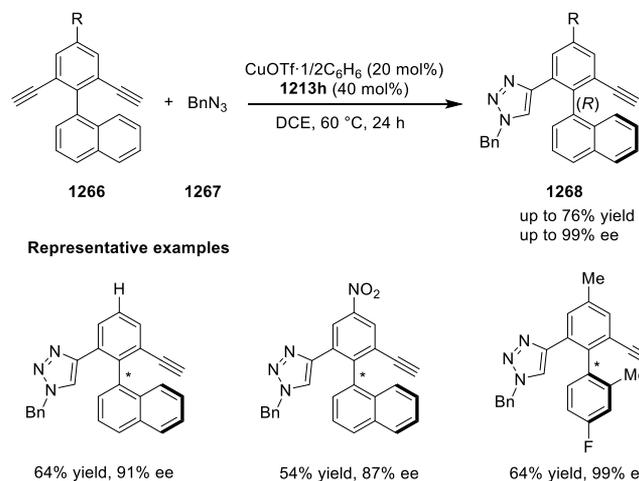


(–)-Rhazinilam was synthesized in six additional steps. Pyrrole **1264** was also taken forward to synthesize (+)-eburenine in five additional steps. (+)-Aspidospermidine was synthesized in one step from (+)-eburenine.⁴⁴⁶

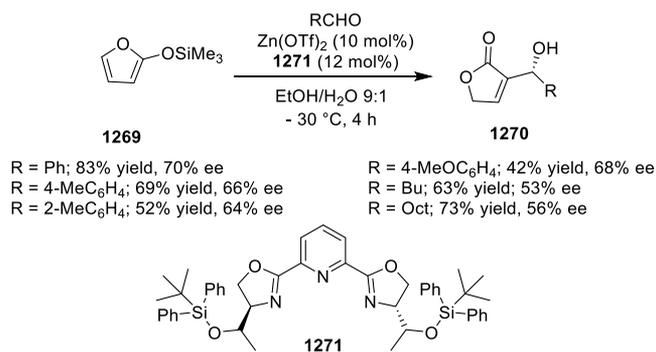
Uozumi has developed an enantioselective CuAAC to construct axially chiral biaryl derivatives by employing the *L*-serine-derived, di-OTBS protected PyBOX ligand **1213h**. The reaction of benzyl azide **1267** with prochiral biaryl dialkynes **1266** led to the formation of 1,2,3-triazoles **1268** bearing axially chiral biaryl groups in up to 76% yield and 99% *ee* (Scheme 372). The reaction was limited to the use of benzyl azide for good enantioselectivity; however, changes to the top aryl ring were well tolerated, as was the use of both naphthalene and *ortho*-substituted benzene rings as the bottom aryl moiety.⁴⁴⁷

Mlynarski applied the highly hindered TBDPS *O*-protected chiral PyBOX ligand **1271** in an unprecedented asymmetric Zn-catalyzed Mukaiyama aldol reaction of 2-(trimethoxysilyloxy)-furans **1269** with various aldehydes (Scheme 373). Some commercially available PyBOX ligands were tested in the reaction with little success, leading the authors to employ a more hindered PyBOX ligand **1271** which proved essential in obtaining decent levels of asymmetric induction. Several chiral α -butenolides **1270** were obtained in good yields of up to 82% and moderate to good enantioselectivities of up to 70% *ee*. A benzoic acid additive (10 mol %) was found to promote the reaction in the case of aryl aldehydes, but was not welcome in the reaction of aliphatic aldehydes.⁴⁴⁸

Scheme 372. Enantioselective CuAAC to Construct Axially Chiral Biaryl Derivatives

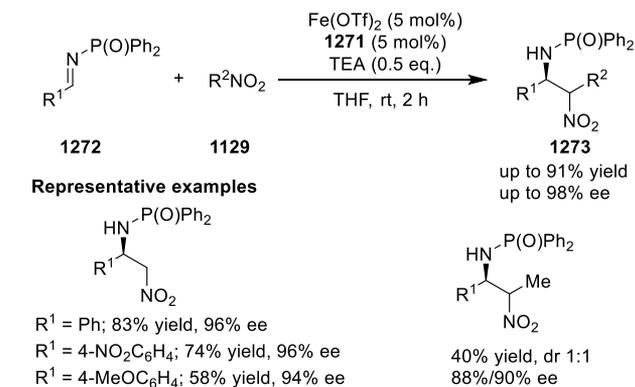


Scheme 373. Asymmetric Zn-Catalyzed Mukaiyama Aldol Reaction of 2-(Trimethoxysilyloxy)-furans



Mlynarski has applied the same chiral PyBOX ligand **1271** in an Fe-catalyzed nitro-Mannich reaction for the enantioselective synthesis of β -nitroamines **1273** (Scheme 374). A wide range

Scheme 374. Fe-Catalyzed Nitro-Mannich Reaction for Enantioselective Synthesis of β -Nitroamines

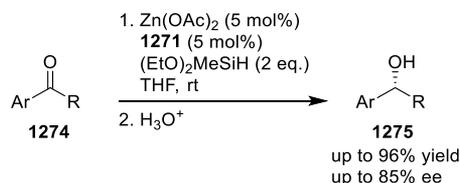


of chiral PyBOX ligands were found to induce good enantioselectivities with the very hindered PyBOX **1271** giving the best results. A range of β -nitroamines **1273** were prepared with good yields of up to 91% and consistently high enantioselectivities of up to 98% *ee*.⁴⁴⁹

Utilizing the same hindered PyBOX ligand **1271**, Mlynarski has developed an enantioselective Zn-catalyzed hydrosilylation

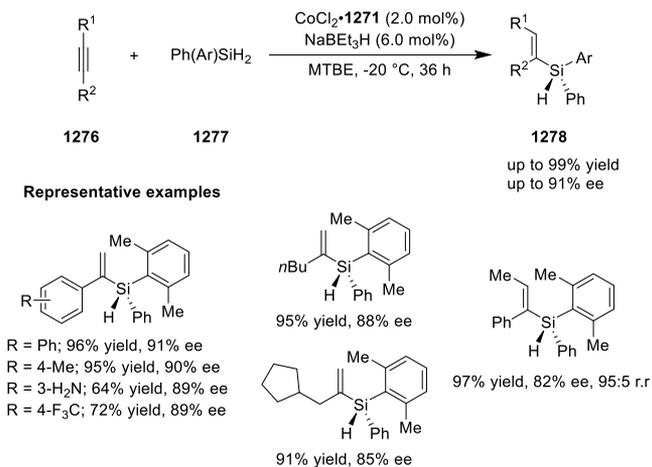
of aromatic ketones **1274** with $(\text{EtO})_2\text{MeSiH}$ (Scheme 375). A range of chiral secondary alcohols **1275** were obtained in good yields up to 96% (generally >99% conv.) and moderate to good enantiomeric excesses of up to 85% *ee*.⁴⁵⁰

Scheme 375. Enantioselective Zn-Catalyzed Hydrosilylation of Aromatic Ketones



Huang utilized **1271** in an asymmetric Co-catalyzed regioselective alkyne hydrosilylation with dihydrosilane **1277**. A range of aryl, alkyl, internal and terminal alkynes **1276** were applied in the hydrosilylation to yield alkenes **1278** bearing silicon stereogenic centers in up to 99% yield and with up to 91% *ee* (Scheme 376). Reactions with terminal alkynes proceeded with high Markovnikov regioselectivity.⁴⁵¹

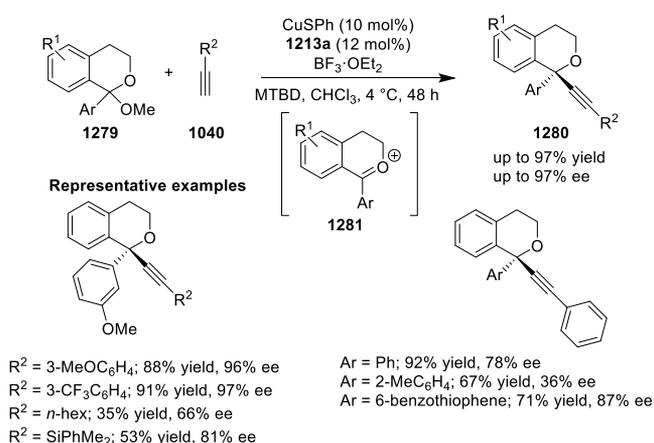
Scheme 376. Asymmetric Co-Catalyzed Regioselective Alkyne Hydrosilylation



Watson has reported a Cu-catalyzed alkylation of oxocarbenium ions **1281** derived from isochroman acetals **1279**, utilizing chiral PyBOX ligand **1213a** to access tetrasubstituted biaryl stereocenters in high enantioselectivities. A range of alkynes **1040** can be added to isochroman oxocarbenium species **1281** bearing a variety of aryl groups to access isochroman ketals **1280** in high yields of up to 97% and enantioselectivities of up to 97% *ee* (Scheme 377). Changes to the substitution on the aryl group of the isochroman acetals **1279** affected the stereoselectivity of the reaction, for example when the 2-methyl substituted substrate was reacted with phenylacetylene, the product was isolated in 36% *ee*. Generally, aryl- and silane-based acetylenes performed well, with alkylacetylenes giving the product with lower enantioselectivities. For example, subjecting *n*-hexaneacetylene to the reaction with the 3-Me-O-substituted isochroman acetal gave the product in only 66% *ee*, as compared to 81% *ee* for -SiPhMe₂ acetylene.⁴⁵²

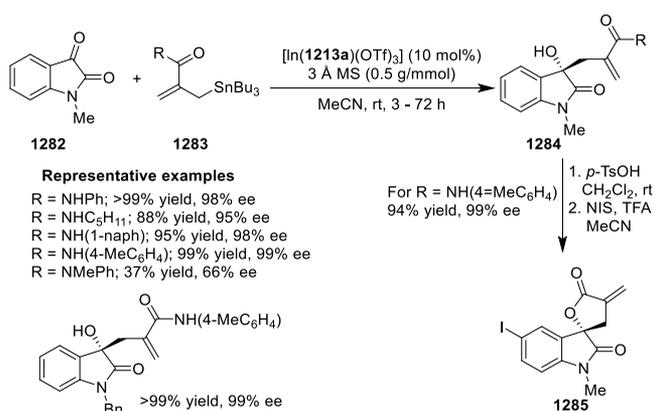
Yoda has described an asymmetric In-catalyzed amide allylation of *N*-methyl isatin **1282** with *N*-substituted- β -

Scheme 377. Asymmetric Cu-Catalyzed Alkylation of Oxocarbenium Ions



amido allyltributylstannanes **1283** to synthesize the corresponding chiral allylated products **1284** in excellent yields of up to >99% and enantioselectivities of up to 99% *ee* (Scheme 378). Further derivatization of the R = NH(4-MeC₆H₄)

Scheme 378. Asymmetric In-Catalyzed Amide Allylation of *N*-Methyl Isatin

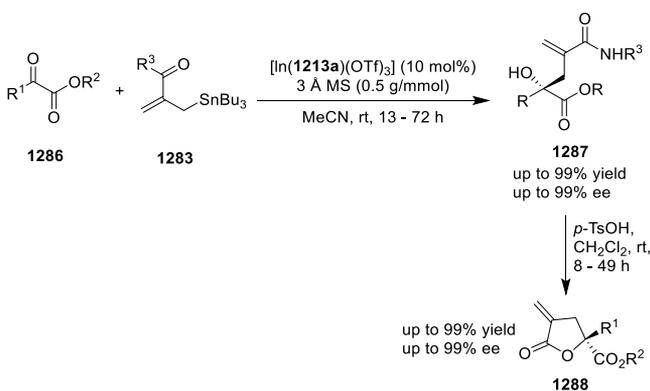


product, by means of an acid promoted cyclization followed by C₅-iodination, led to the formation of an antineoplastic spiro-fused 2-oxindole/*R*-methylene- γ -butyrolactone **1285**, retaining the high optical purity of 99% *ee*.⁴⁵³ A follow-up report by Yoda expanded the substrate scope to isatins bearing different *N*-protecting groups and C₅-substitution, retaining the excellent yields and enantioselectivities from the previous report.⁴⁵⁴

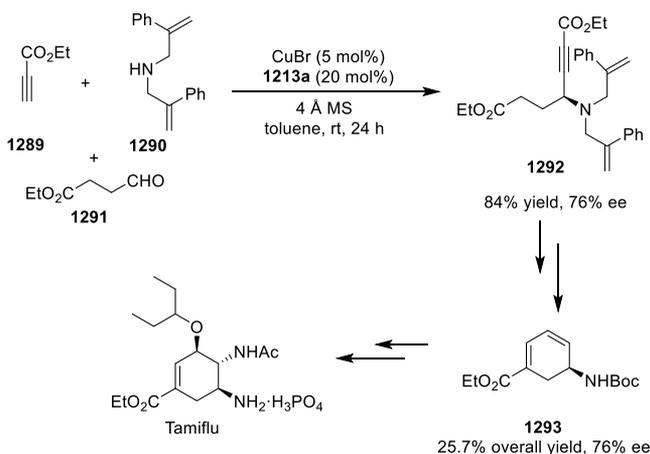
Yoda further explored the In-catalyzed amide allylation with the allylation/lactonization of α -keto esters **1286** for the enantioselective synthesis of ester-functionalized α -methylene- γ -butyrolactones **1288** in excellent yields of up to 99% and enantiomeric excesses of up to 99% (Scheme 379). Following the [In(**1213a**)(OTf)₃]-catalyzed allylation of α -keto esters **1286** with allylstannanes **1283**, an acid promoted lactonization of the corresponding amides **1287** gives access to the α -methylene- γ -butyrolactones **1288**.⁴⁵⁵

Watanabe and Shibasaki reported the use of chiral PyBOX ligand **1213a** in an asymmetric Cu-catalyzed A³-coupling reaction for the synthesis of an oseltamivir phosphate precursor **1293** in 84% yield and 76% *ee* (Scheme 380). This propargylic amine **1292** was taken forward to synthesize a

Scheme 379. In-Catalyzed Amide Allylation with Allylation/Lactonization of α -Keto Esters



Scheme 380. Asymmetric Synthesis of Tamiflu

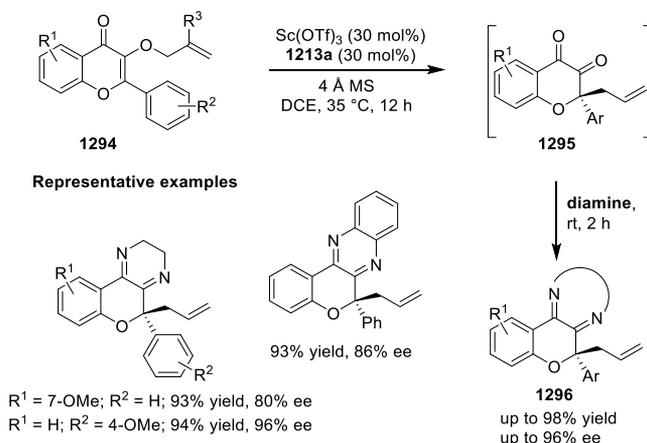


direct precursor of oseltamivir phosphate consisting of 5 purification steps, 25.7% overall yield and an optical purity of 76% *ee*. This sequence represents a formal total synthesis of the antiviral drug Tamiflu.⁴⁵⁶

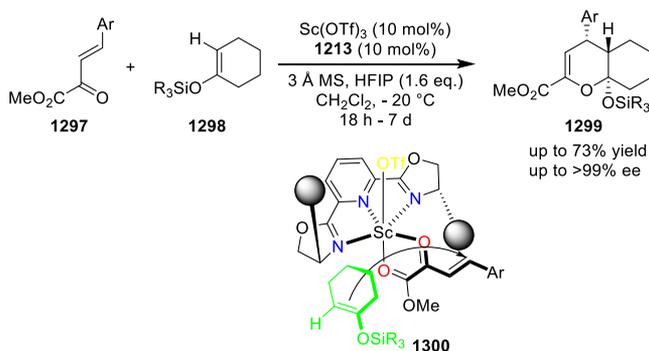
Porco and Schaus have reported the asymmetric Sc-catalyzed rearrangement of 3-allyloxyflavones **1294** for the preparation of chiral 3,4-chromanediones **1295**. For purification purposes, the authors condensed the dicarbonyl products with various diamines to yield the corresponding dihydropyrazines **1296**. Employing chiral PyBOX ligand **1213a**, the dihydropyrazines **1296** could be accessed in high yields of up to 98% and enantioselectivities of up to 96% *ee* (Scheme 381). Mechanistic studies support the intramolecular rearrangement pathway proceeding through a benzopyrylium intermediate.⁴⁵⁷

Desimoni studied the enantioselective formal hetero-Diels–Alder (HDA) reaction of (*E*)-4-aryl-2-oxo-3-butenates **1297** utilizing $\mathbf{1213}\text{-Sc(III)}$ catalysts (Scheme 382). The authors found that these compounds, behaving as α -dicarbonyl derivatives, operate through a bidentate coordination to form rigid complexes that are characterized by a 5-membered structure. The reaction intermediate (as shown in **1300**) gives excellent facial discrimination, determined by the configuration of the PyBOX C_4 -substituent in a tandem Mukaiyama–Michael addition/intramolecular ring closure, which is a formal HDA reaction. This process yields the products **1299** with *trans*–*trans*-fused junctions in bicyclic six to six-membered ring systems in up to 73% yield and >99% *ee*.⁴⁵⁸

Scheme 381. Asymmetric Sc-Catalyzed Rearrangement of 3-Allyloxyflavones for the Preparation of Chiral 3,4-Chromanediones

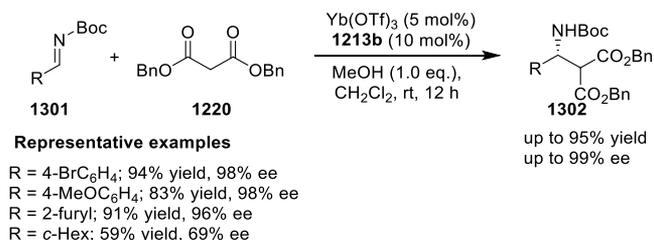


Scheme 382. Enantioselective Formal Hetero-Diels–Alder Reaction of (*E*)-4-Aryl-2-oxo-3-butenates



Karimi and Enders have described a highly efficient Yb(**1213b**)-catalyzed Mannich reaction of malonates with *N*-*tert*-butoxycarbonyl (Boc) imines **1301** to access the corresponding chiral amines **1302** in excellent yields and enantioselectivities (Scheme 383). Using MeOH as an

Scheme 383. Asymmetric Yb-Catalyzed Mannich Reaction of Malonates with *N*-*tert*-Butoxycarbonyl (Boc) Imines

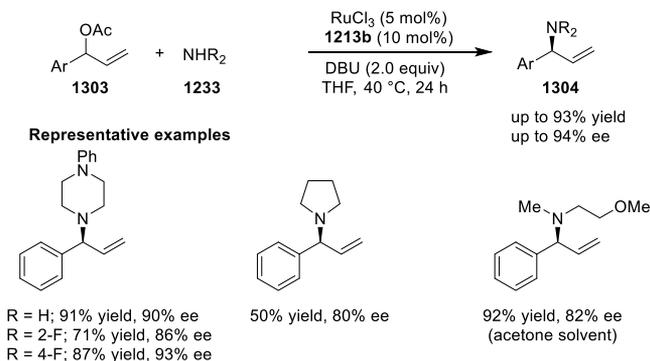


additive, the authors could synthesize a range of chiral amines in up to 95% yield and 99% *ee*. They found the substituent on the *N*-atom of the imine played an important role in the formation of the product, with only *N*-Boc imines allowing the reaction to proceed.⁴⁵⁹

Kawatsura and Itoh have demonstrated a $\text{RuCl}_3/\mathbf{1213b}$ -catalyzed allylic amination of racemic 1-aryl allyl esters **1303** with amines **1233**. Using mainly cyclic secondary amines, they could access enantiomerically enriched allylic amine products **1304** in good yields up to 93% and high enantioselectivities of

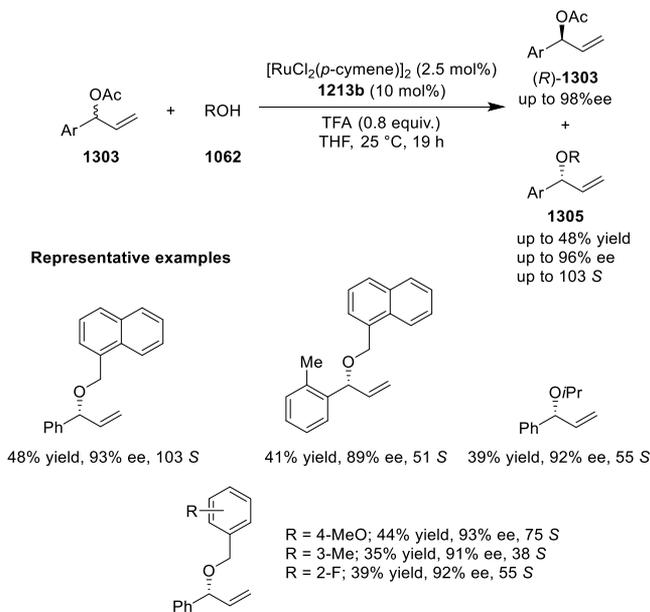
up to 94% *ee* (Scheme 384). The reaction was shown to proceed with perfect regioselectivity for several allyl esters.⁴⁶⁰

Scheme 384. Ru-Catalyzed Asymmetric Allylic Amination of Racemic 1-Aryl Allyl Esters with Amines



Kawatsura has reported a related kinetic resolution of allyl acetates via a Ru-catalyzed asymmetric etherification. A variety of aryl allyl acetates **1303** were subjected to the reaction with alkyl and benzyl alcohols **1062** in the presence of $[\text{RuCl}_2(p\text{-cymene})]_2$ and *i*Pr-PyBOX **1213b** to give the corresponding ethers **1305** in up to 48% yield, 96% *ee* and with selectivity factors (*S*) of up to 103 (Scheme 385). The enantiomerically enriched allyl acetate (*R*)-**1303** could also be isolated in up to 98% *ee*. The reaction proceeded with perfect regioselectivity in all cases.⁴⁶¹

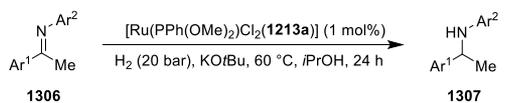
Scheme 385. Kinetic Resolution of Allyl Acetates via a Ru-Catalyzed Asymmetric Etherification



Gamasa and Pizzano have described a Ru-**1213a**-catalyzed hydrogenation and transfer hydrogenation of imines for the asymmetric synthesis of benzylamines. Subjecting diaryl imines **1306** to 1 mol% of the Ru catalyst in *i*PrOH at 60 °C under 20 bar H_2 led to the isolation of enantioenriched benzyl amines **1307** in up to 93% yield and up to 99% *ee* (Scheme 386). Conducting the transfer hydrogenation under N_2 in place of H_2 led to the isolation of the enantioenriched benzyl amines

Scheme 386. Ru-Catalyzed Asymmetric Hydrogenation and Asymmetric Transfer Hydrogenation of Imines

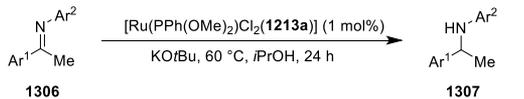
Catalytic hydrogenation:



Representative examples

$\text{Ar}^1 = 4\text{-FC}_6\text{H}_4$; $\text{Ar}^2 = \text{Ph}$; 84% yield, 99% *ee* (*S*)
 $\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4$; $\text{Ar}^2 = \text{Ph}$; 44% yield, 79% *ee* (*S*)
 $\text{Ar}^1 = 3\text{-MeOC}_6\text{H}_4$; $\text{Ar}^2 = \text{Ph}$; 88% yield, 99% *ee* (*S*)
 $\text{Ar}^1 = 2\text{-naphthyl}$; $\text{Ar}^2 = 4\text{-MeOC}_6\text{H}_4$; 80% yield, 99% *ee* (*S*)

Transfer hydrogenation:



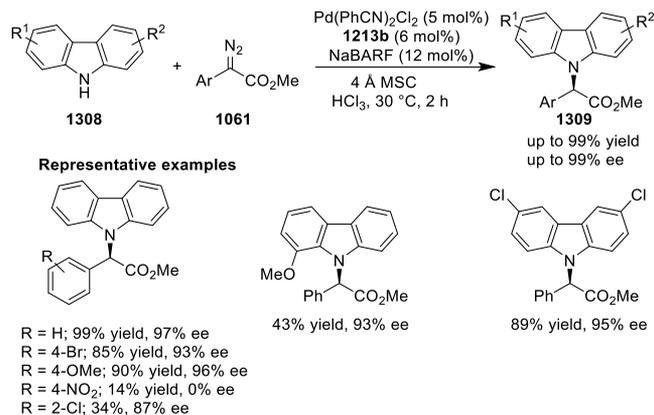
Representative examples

$\text{Ar}^1 = 4\text{-FC}_6\text{H}_4$; $\text{Ar}^2 = \text{Ph}$; 87% yield, 99% *ee* (*S*)
 $\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4$; $\text{Ar}^2 = \text{Ph}$; <5% yield
 $\text{Ar}^1 = 3\text{-MeOC}_6\text{H}_4$; $\text{Ar}^2 = \text{Ph}$; 93% yield, 99% *ee* (*S*)
 $\text{Ar}^1 = 2\text{-naphthyl}$; $\text{Ar}^2 = 4\text{-MeOC}_6\text{H}_4$; 98% yield, 99% *ee* (*S*)

1307 in up to 99% yield and up to 99% *ee*. Overall, the two processes gave similar results. Substrates bearing $\text{Ar}^1 = 4\text{-ClC}_6\text{H}_4$ or $4\text{-BrC}_6\text{H}_4$ did not perform well under catalytic hydrogenation, while they were found to be completely incompatible with transfer hydrogenation.⁴⁶²

Van Vranken has reported an enantioselective Pd-catalyzed carbene insertion into carbazole derivatives **1308** (Scheme 387). While a range of oxazoline-containing chiral ligands were

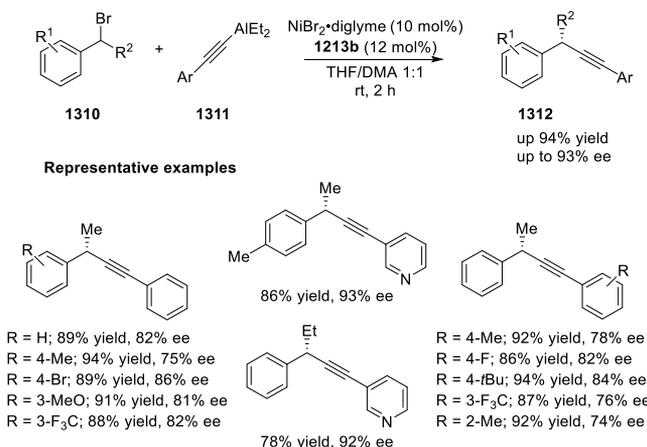
Scheme 387. Enantioselective Pd-Catalyzed Carbene Insertion into Carbazole Derivatives



tested, the *i*Pr-PyBOX ligand **1213b** was found to induce the highest levels of enantioselectivity, giving the chiral amine products **1309** in up to 99% yield and 99% *ee*. Carbenes bearing a strongly electron-withdrawing group were found to perform poorly in the reaction. For example, the reaction of a 4-nitro-substituted carbene with carbazole led to the formation of the product as a racemate.⁴⁶³

Zhou has reported a Ni-catalyzed asymmetric cross-coupling reaction of secondary benzylic bromides **1310** with aryl alkynyl aluminum reagents **1311** (Scheme 388). *i*Pr-PyBOX ligand **1213b** was found to effectively induce good to high levels of enantioselectivity, leading to the isolation of a range of internal alkyne products **1312** in up to 94% yield and with up to 93% *ee*. Other PyBOX and BOX ligands were tested in the reaction, but these did not give comparable levels of stereoinduction. A

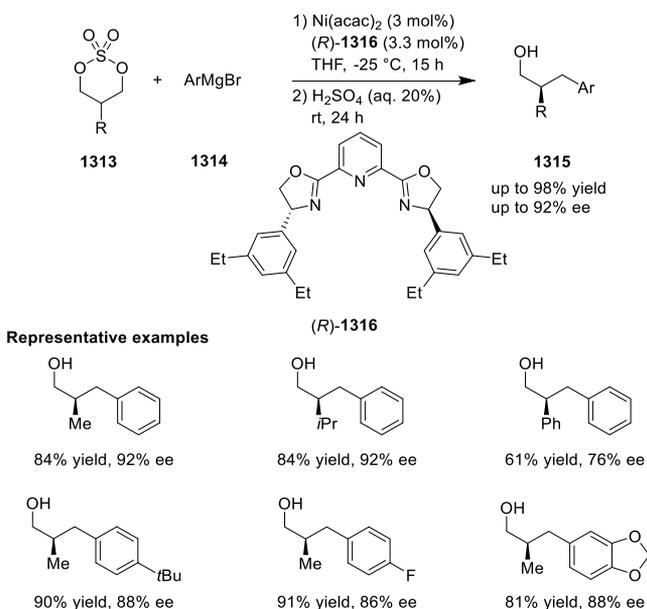
Scheme 388. Ni-Catalyzed Asymmetric Cross-Coupling Reaction of Secondary Benzylic Bromides with Aryl Alkynyl Aluminum Reagents



range of aryl groups were well tolerated on the alkyl bromide coupling partner, while aryl and heteroaryl groups performed well on the alkynyl aluminum partner.⁴⁶⁴

Morken has applied 3,5-EtC₆H₃-PyBOX ligand **1316** in the development of an asymmetric Ni-catalyzed Kumada cross-coupling of symmetric cyclic sulfates **1313**. A range of aryl Grignard reagents **1314** were successfully coupled with the cyclic sulfates **1313** to give, following acid hydrolysis, chiral alcohols **1315** in up to 98% yield and with high enantioselectivities up to 92% ee (Scheme 389).⁴⁶⁵

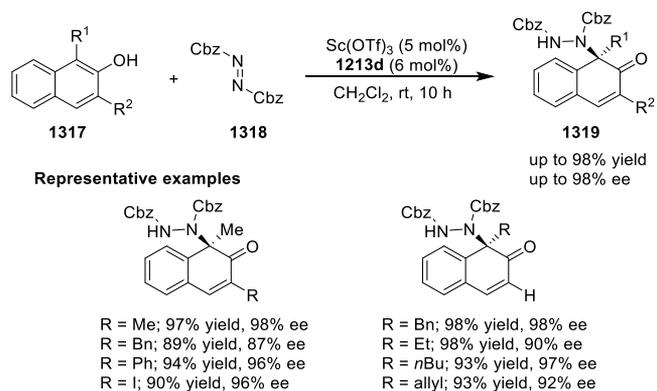
Scheme 389. Asymmetric Ni-Catalyzed Kumada Cross-Coupling of Symmetric Cyclic Sulfates



Luan achieved an asymmetric dearomatization of naphthols **1317** via a Sc-catalyzed electrophilic amination reaction with DEAD **1318**. A series of chiral PyBOX ligands were screened, but only ligand **1213d** gave high levels of asymmetric induction. Both monosubstituted 2-naphthols and disubstituted 1,3-naphthols performed well in the reaction, allowing access to the products **1319** in up to 98% yield and 98% ee

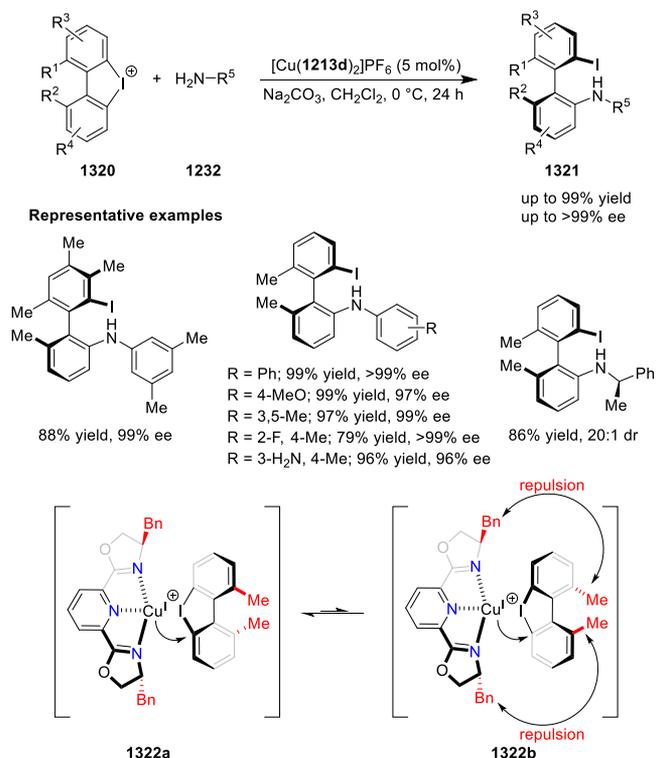
with a wide substrate scope and at gram scale (Scheme 390).⁴⁶⁶

Scheme 390. Asymmetric Dearomatization of Naphthols via a Sc-Catalyzed Electrophilic Amination Reaction with DEAD



Fu and Gu have also utilized Bn-PyBOX ligand **1213d** in a Cu-catalyzed asymmetric ring-opening reaction of diaryliodonium salts **1320** with amines **1232** (Scheme 391).

Scheme 391. Cu-Catalyzed Asymmetric Ring-Opening Reaction of Diaryliodonium Salts

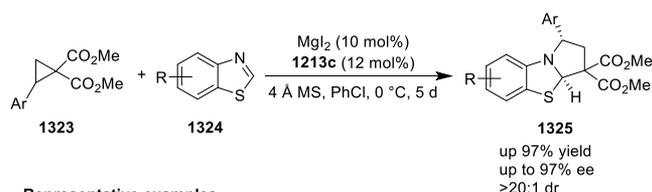


Diaryliodonium salts **1320** exist in two rapidly interconverting conformers. The interaction of the two conformers with the Cu(**1213d**) species leads to the formation of **1322a** and **1322b**. **1322b** is sterically disfavored due to the steric interaction between the Bn-group of the ligand and the methyl group of the diaryliodonium salt. Thus, **1322b** rapidly converts to **1322a** and undergoes the ring-opening reaction with the Cu(**1213d**) species, selectively establishing axial chirality. Base

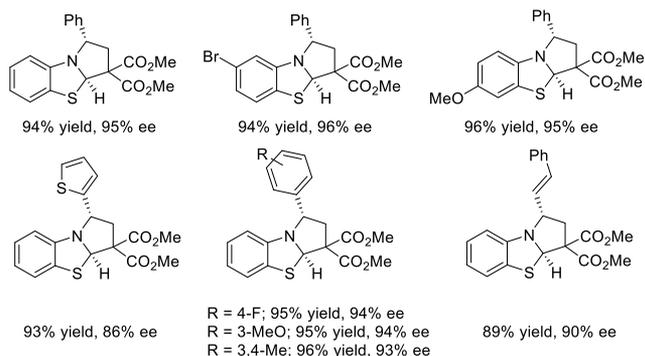
promoted coordination of the amine with the Cu-species, followed by reductive elimination leads to the formation of the products **1321**. A range of di-*o*-substituted diaryliodonium salts **1320** were successfully reacted with a range of aryl and benzylic amine **1232** giving the axially chiral products **1321** in up to 99% yield and >99% *ee*. It should be noted that the reaction works equally well when indanyl PyBOX ligand (*R,S*)-**1327** (below) is utilized.⁴⁶⁷ Further mechanistic insights, and an improved experimental procedure, in which the amine is added slowly via a syringe pump, leading to an expanded substrate scope (benzylic and aliphatic amines) were subsequently reported by Gu.⁴⁶⁸

You has described a MgI₂/1213c-catalyzed asymmetric dearomative [3 + 2] cycloaddition of benzotriazoles **1324** with cyclopropane-1,1-dicarboxylates **1323** (Scheme 392). By

Scheme 392. Mg-Catalyzed Asymmetric Dearomative [3 + 2] Cycloaddition of Benzotriazoles with Cyclopropane-1,1-dicarboxylates



Representative examples

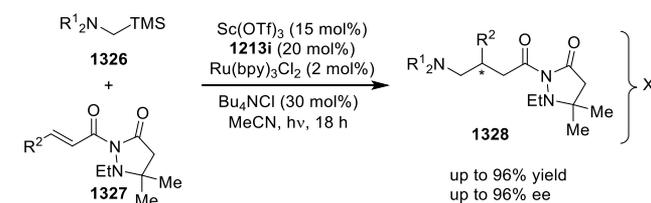


subjecting a range of aryl- and alkene-substituted cyclopropanes **1323** to the reaction with a range of benzotriazoles **1324** in the presence of 4 Å MS at 0 °C for 5 days, the polycyclic products **1325** containing two stereocenters were isolated in excellent yields of up to 97%, with excellent enantioselectivities of up to 97% *ee* (only one example <90% *ee*) and all >20:1 dr. Conducting the reaction with both the enantiomerically pure (*S*)- and (*R*)-enantiomers of the cyclopropane **1323** showed that the catalyst preferentially reacts with the (*R*)-enantiomer. The results also suggested that this transformation is a simple kinetic resolution and not a dynamic kinetic resolution, with >2.0 equiv of the racemic cyclopropane required to achieve a high yield.⁴⁶⁹

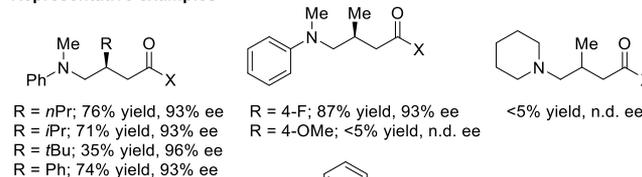
Yoon has reported an asymmetric α -amino radical conjugate addition by the merging of photoredox catalysis and Lewis acid catalysis. Following a screen of isomers of chiral PyBOX ligand **1213c** they found that the *i*Bu-containing PyBOX ligand **1213i** in combination with Sc(OTf)₃ and Ru(bpy)₃Cl₂, provided a system that was optimal for catalyzing the reaction and achieving high levels of stereoreduction. A range of chiral amines **1328** were synthesized in good yields of up to 96% and enantioselectivities of up to 96% *ee* (Scheme 393). Aryl amines

appeared to perform best in the reaction, while the Michael acceptor bearing an auxiliary group X was required.⁴⁷⁰

Scheme 393. Asymmetric α -Amino Radical Conjugate Addition



Representative examples

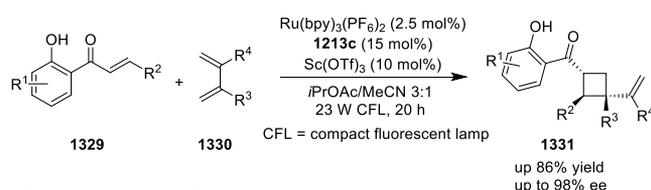


1213i

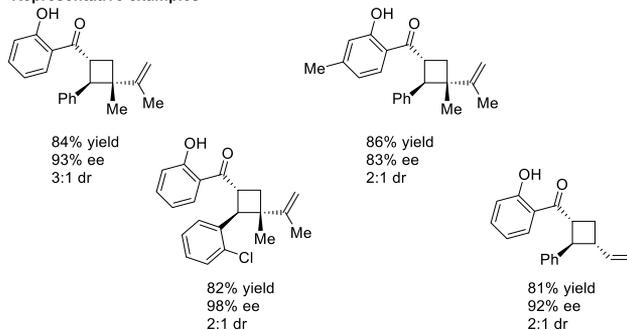
Yoon subsequently described a chiral Lewis acid-catalyzed triplet energy transfer strategy for the asymmetric [2 + 2] cycloaddition of 2'-hydroxychalcones **1329** with dienes **1330**. They discovered that the coordination of a Sc(OTf)₃-**1213c** complex to the 2'-hydroxychalcone substrates **1329** significantly decreased their triplet state energy, giving access to enantioselective reactions of the electronically excited states. A range of 2'-hydroxychalcones **1329** were subjected to the [2 + 2] cycloaddition with a small range of dienes **1330**, in the presence of Ru(bpy)(PF₆)₂ as the photosensitizer, to yield chiral cyclobutanes **1331** in high yields of up to 86%, excellent enantioselectivities of up to 98% *ee* and low diastereoselectivities of up to 4:1 dr (Scheme 394).⁴⁷¹

A later report by Yoon expanded the scope of the [2 + 2] cycloaddition to include styrene substrates in place of the

Scheme 394. Chiral Lewis Acid-Catalyzed Triplet Energy Transfer Strategy for the Asymmetric [2 + 2] Cycloaddition of 2'-Hydroxychalcones with Dienes

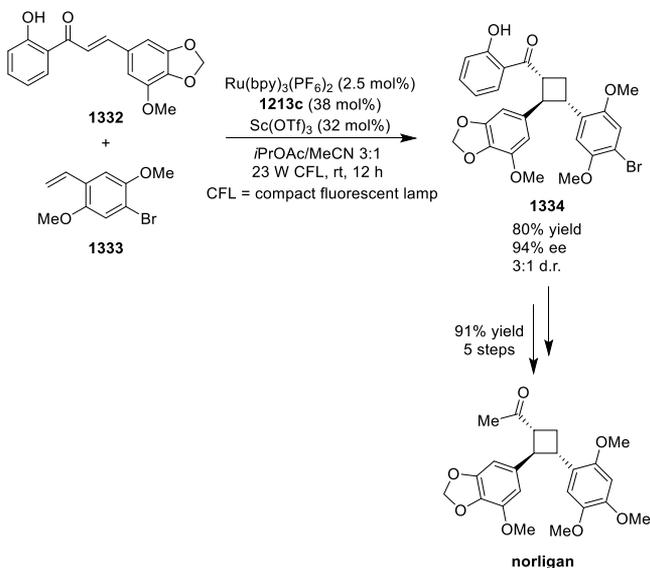


Representative examples



dienes **1330**, maintaining the high levels of enantioselectivity. This strategy was applied in the total synthesis of norlignan, a diaryl cyclobutane natural product (Scheme 395).⁴⁷²

Scheme 395. Asymmetric Total Synthesis of Norlignan



Overall, PyBOX ligands are some of the most used bis(oxazoline) ligands in asymmetric catalysis. They have been combined with a range of metal catalysts to induce excellent levels of stereoselectivity. The tridentate and planar PyBOX ligands appear to be particularly useful in Cu-catalyzed asymmetric transformations, such as propargylation and cycloaddition reactions. However, they have also been applied *inter alia* in the chemistries of Pd, Ni, Ru, Fe, Sc, and In. Notably, the application of these ligands in asymmetric photoredox catalysis is an important step forward. We predict there will be further developments in this area.

3.2.13. Bis(oxazoline) Ligands with Pyridine Linkers and Disubstituted Oxazoline Rings. PyBOX ligands derived from disubstituted amino alcohols are commonly applied in a wide range of transformations in asymmetric catalysis (Figure 66).

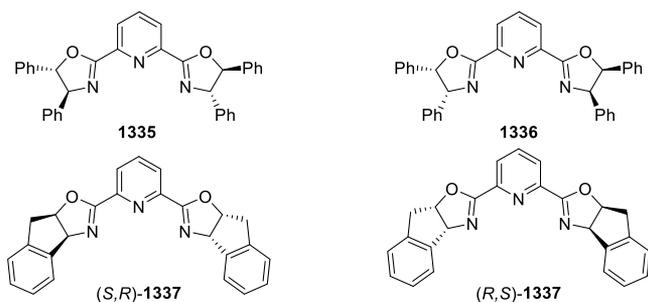
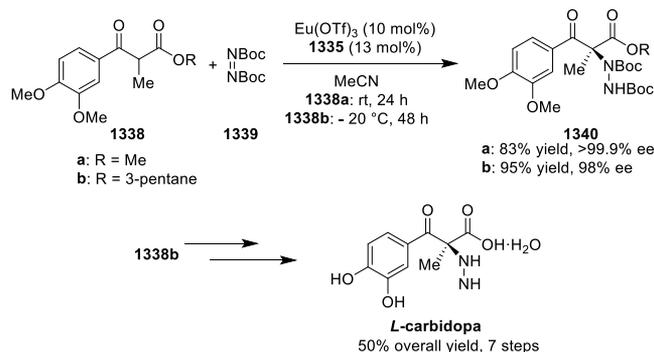


Figure 66. PyBOX ligands derived from disubstituted amino alcohols.

Vallribera has reported an enantioselective synthesis of L-carbidopa in 7 steps from β -keto ester **1338b**. The synthesis involves a key Eu-catalyzed α -amination of acyclic β -keto esters, utilizing diphenyl-PyBOX ligand (*R,R*)-**1335**. Mono-substituted PyBOX ligands **1213a–b** were found to give the product **1340a** with good enantioselectivities, although lower than (*R,R*)-**1335**. β -Ketoesters **1338a–b** were reacted with di-

tert-butyl azodicarboxylate **1339** in the presence of $\text{Eu}(\text{OTf})_3$ and **1335** to yield the chiral amines **1340a** and **1340b** in 83% and 95% yields, respectively, and >99.9% and 98% ee (Scheme 396). Chiral amine **1340b** was brought forward to synthesize

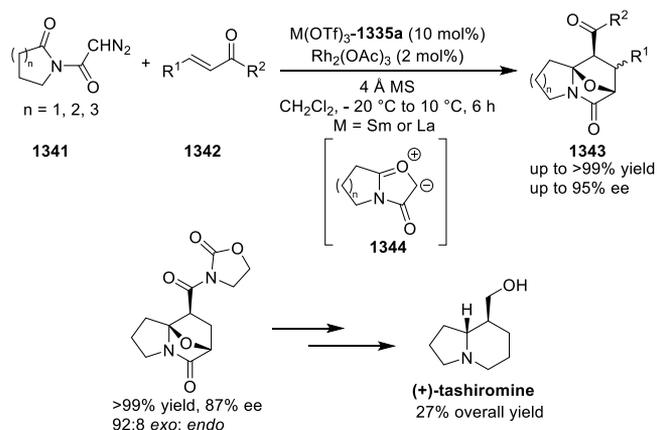
Scheme 396. Asymmetric Synthesis of L-Carbidopa via an Enantioselective Eu-Catalyzed α -Amination of Acyclic β -Keto Esters



L-carbidopa in a 50% overall yield.⁴⁷³ Sodupe and Vallribera later applied this methodology to the asymmetric synthesis of fluorous L-carbidopa precursors with similarly high enantioselectivities of up to 99% ee.⁴⁷⁴

Suga has described the chiral Lewis acid-catalyzed asymmetric cycloaddition of carbonyl ylides, employing chiral PyBOX ligand **1335**, for the synthesis of indolizidine alkaloids. The carbonyl ylides **1344** were first derived from various sized ($n = 5, 6, 7$) *N*-diazoacetyl lactams **1341** in the presence of $\text{Rh}_2(\text{OAc})_4$, followed by the chiral Lewis acid-catalyzed cycloaddition with the appropriate dienophile **1342**, to yield the corresponding heterocycle **1343** ($n = 5, 6, 7$) in up to >99% yield and 95% ee (Scheme 397). This methodology was applied to the asymmetric total synthesis of the indolizidine alkaloid (+)-tashiromine in 27% overall yield.⁴⁷⁵

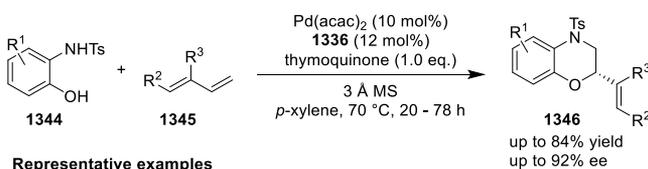
Scheme 397. Chiral Lewis Acid-Catalyzed Asymmetric Cycloaddition of Carbonyl Ylides



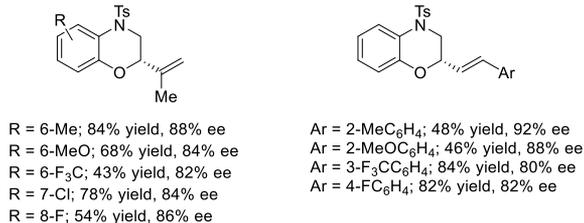
Gong has reported a Pd-catalyzed regioselective asymmetric aminohydroxylation of 1,3-dienes **1345** with *N*-tosyl-2-amino-phenols **1344**. Employing chiral PyBOX ligand **1336**, the corresponding 3,4-dihydro-2*H*-1,4-benzoxazine **1346** was formed with perfect regioselectivity for a range of substrates in up to 84% yield and 92% ee (Scheme 398). The reaction proceeds via a cascade aminopalladation (aza-Wacker)/

asymmetric allylation sequence, with the ligand **1336** chelating in a bidentate-mode throughout.⁴⁷⁶

Scheme 398. Pd-Catalyzed Regioselective Asymmetric Aminohydroxylation of 1,3-Dienes with *N*-Tosyl-2-aminophenols

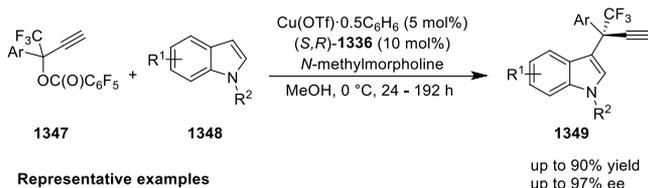


Representative examples

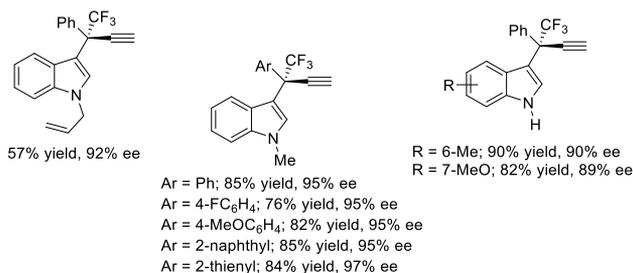


Nishibayashi has described an enantioselective Cu-catalyzed propargylation of indoles **1348** with CF₃-substituted propargylic esters **1347** for the construction of all-carbon quaternary stereocenters. Employing chiral PyBOX ligand (*S,R*)-**1336** in the Cu(OTf)₂·0.5C₆H₆-catalyzed process, a range of propargylic esters **1349** bearing different aryl groups were reacted with a range of indoles **1348** for the enantioselective synthesis of propargylic indoles **1349** in excellent yields of up to 90% yield and with up to 97% ee (Scheme 399).⁴⁷⁷

Scheme 399. Enantioselective Cu-Catalyzed Propargylation of Indoles



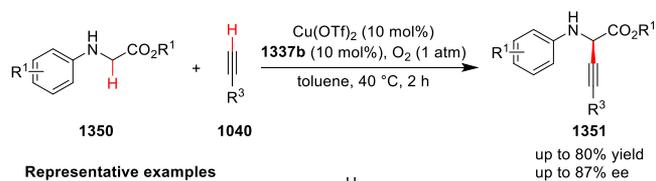
Representative examples



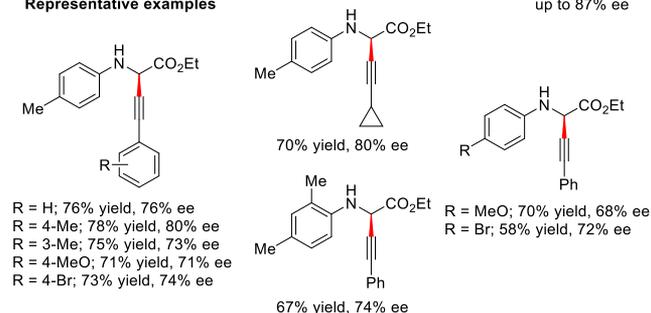
Liu has described a Cu-catalyzed asymmetric dehydrogenative C_(sp³)H–C_(sp)H cross-coupling employing O₂ as the terminal oxidant. Following a screen of multiple oxazoline-based chiral ligands, indanyl PyBOX ligand (*R,S*)-**1337** was found to induce moderate to high levels of enantioselectivity in the Cu-catalyzed cross-coupling of *N*-aryl glycine esters **1350** (C_(sp³)H) with terminal alkynes **1040** (C_(sp)H) to give the enantioenriched α-amino esters **1351** in up to 80% yield and with up to 87% ee (Scheme 400). A range of aryl and alkyl

alkynes **1040** were well tolerated in the reaction giving access to enantioenriched non-natural α-amino acids.⁴⁷⁸

Scheme 400. Cu-Catalyzed Asymmetric Dehydrogenative C_(sp³)H–C_(sp)H Cross-Coupling

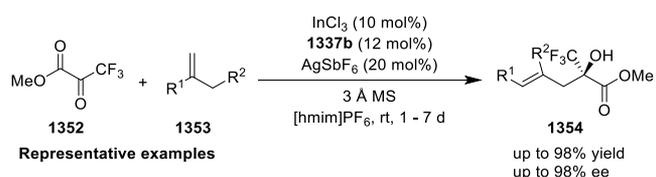


Representative examples

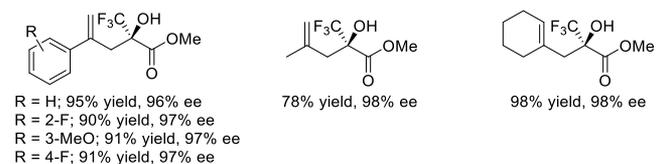


Loh has reported a chiral In(II)-(R,S)-**1337** complex-catalyzed asymmetric ketone-ene reaction of trifluoropyruvate **1352** conducted in the ionic liquid [hmin]PF₆. Subjecting a range of alkenes **1353** to the reaction led to the isolation of the corresponding tertiary allylic alcohols **1354** in high yields of up to 98% and excellent enantioselectivities of up to 98% ee (Scheme 401). The chiral In(II)-(R,S)-**1337** complex in the ionic liquid was recycled up to seven times with retention of high yields and enantioselectivities.⁴⁷⁹

Scheme 401. In-Catalyzed Asymmetric Ketone-ene Reaction of Trifluoropyruvate

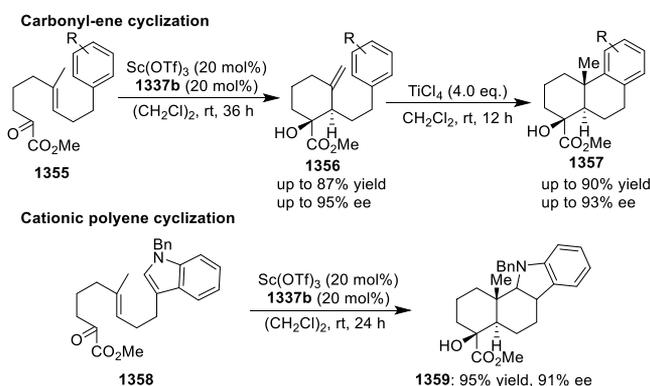


Representative examples



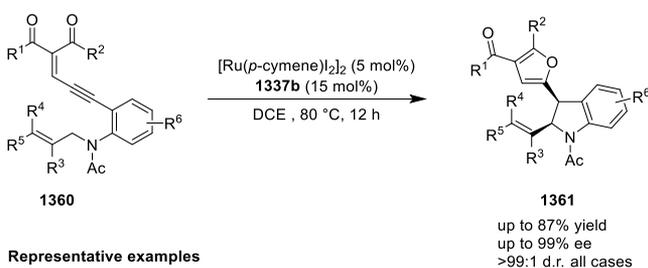
Loh has described a study on the asymmetric carbonyl-ene and cationic polyene cyclization reactions of 1,5-keto-olefins **1355** with Sc(III)-(R,S)-**1337** complexes. First, promoting the cyclization of 1,5-keto-olefins **1355** with a Sc(III)-(R,S)-**1337** complex led to the isolation of carbonyl-ene product **1356** in high yields up to 87% and enantioselectivities up to 95% ee (Scheme 402). Treatment of the ene-product **1356** with TiCl₄ led to formation of the polyene-products **1357** without much loss in enantioselectivity. Subjecting substrates with terminator groups which are more nucleophilic, like furan, indole or tetrasubstituted alkenes, to the reaction conditions led to formation of the polyene-products **1359** in high yields and enantioselectivities without the need for TiCl₄.⁴⁸⁰

Scheme 402. Asymmetric Carbonyl-ene and Cationic Polyene Cyclization Reactions



Zhu has reported a highly enantioselective intramolecular allylic C–H insertion reaction. Using indanyl PyBOX ligand (*R,S*)-1337 in this Ru-catalyzed process, a variety of *N*-allylic enynones **1360** were transformed into di-*syn*-substituted indolines **1361** in just one step, giving the products in up to 87% yield, with excellent enantioselectivities up to >99% *ee*, and in all cases with diastereoselectivities of >99:1 *dr* (Scheme 403).⁴⁸¹

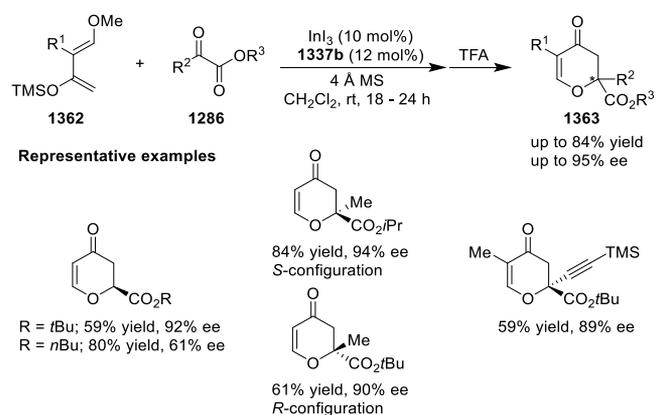
Scheme 403. Enantioselective Intramolecular Allylic C–H Insertion Reaction



Loh has applied (*R,S*)-1337 in an In-catalyzed HDA reaction of Danishefsky-type dienes **1362** with α -carbonyl esters **1286**. A variety of substrates were successfully applied in the reaction to give the corresponding chiral 2,3-dihydro-4-pyranones **1363** in high yields up to 84% and enantioselectivities up to 95% *ee* (Scheme 404). Products containing both tertiary and quaternary stereocenters could be isolated with similarly good results.⁴⁸²

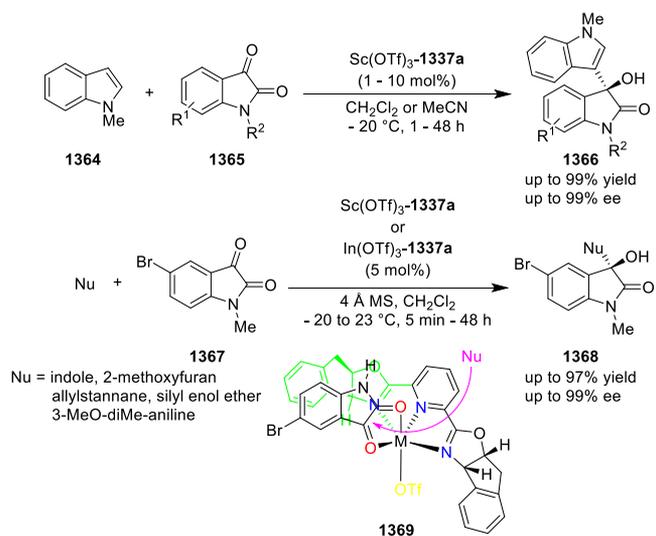
Franz has reported an asymmetric synthesis of 3-hydroxy-2-oxindoles **1366** via the Friedel–Crafts alkylation of indoles **1364** and electron-rich arenes with isatins catalyzed by Sc(III)-

Scheme 404. In-Catalyzed HDA Reaction of Danishefsky-type Dienes with α -Carbonyl Esters



and In(III)-(*S,R*)-1337 complexes. Other PyBOX ligands tested were found to induce only moderate to good enantioselectivities. The product oxindoles **1366** were isolated in up to 99% yield and 99% *ee* for a range of substrates (Scheme 405). The catalysts were also found to promote

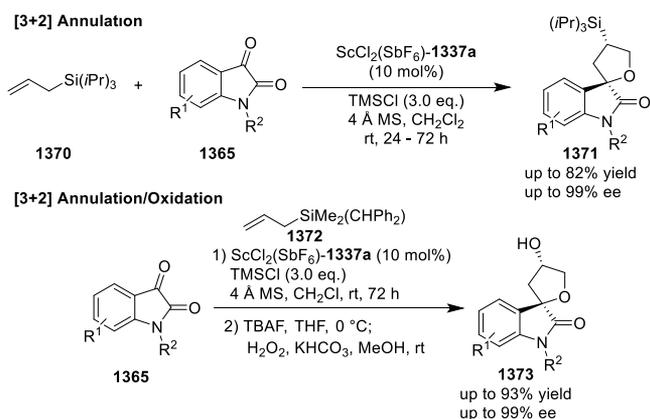
Scheme 405. Asymmetric Synthesis of 3-Hydroxy-2-oxindoles



asymmetric allylation and aldol reactions of isatins in up to 97% yield and 99% *ee*. An octahedral model **1369** for this process is invoked to explain the sense of stereoinduction. If the isatin amide carbonyl group is bound to the apical position of the complex, the nucleophile is forced to attack the *Si*-face. This study into the activity of both Sc(III) and In(III) complexes provides a useful guide for further research in this area.⁴⁸³ Franz has extended this work to include *N*-methylpyrrole⁴⁸⁴ and allylsilanes⁴⁸⁵ as nucleophiles.

Franz has described another extension of this work wherein allyl silanes based on a bulky –Si(*i*Pr)₃ moiety is used as nucleophiles in an asymmetric [3 + 2] annulation with isatins. Various isatin derivatives **1365** react with allylsilanes **1370**, which bear a bulky silyl-group, in an ScCl₂(SbF₆)-(*S,R*)-1337-catalyzed nucleophilic addition/1,2-silyl migration/annulation to give a range of spirooxindoles **1371** in up to 82% yield and 99% *ee* (Scheme 406). Subjecting allyl silane **1372**, bearing an –SiMe₂(CHPh₂) group, to the annulation reaction conditions

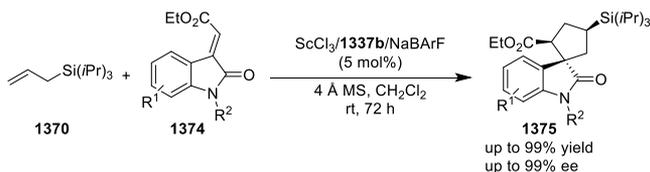
Scheme 406. Asymmetric [3 + 2] Annulation of Isatins with Allyl Silanes



followed by C–Si oxidation affords the corresponding secondary alcohols **1373** in excellent yields and enantioselectivities.⁴⁸⁶

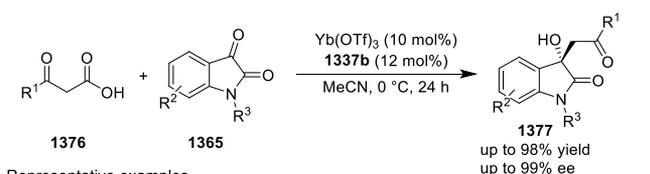
Franz has extended this carboannulation methodology to include alkylidene oxindoles **1374** as electrophiles, utilizing a $\text{ScCl}_3/(R,S)\text{-1337}/\text{NaBARF}$ catalytic system, to give the corresponding spirooxindoles **1375** in up to 99% yield and 99% ee (Scheme 407).⁴⁸⁷

Scheme 407. Asymmetric [3 + 2] Annulation of Alkylidene Oxindoles with Allyl Silanes

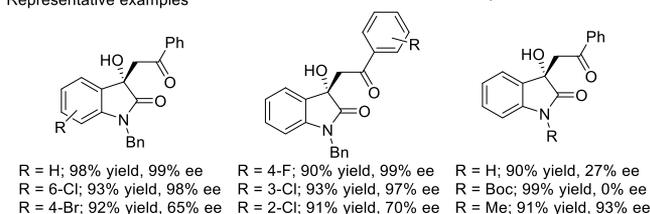


Wang has described a related Yb-catalyzed decarboxylative asymmetric addition of β -ketoacids **1376** to isatins **1365**, employing chiral PyBOX ligand $(R,S)\text{-1337}$. A range of 3-hydroxy-oxindoles **1377** were synthesized in up to 98% yield and 99% ee (Scheme 408). The same stereochemical model is used to explain the outcome of this reaction as in Franz's previous example, with the opposite enantiomer of the ligand giving *Re*-face attack in this instance.⁴⁸⁸

Scheme 408. Yb-Catalyzed Decarboxylative Asymmetric Addition of β -Ketoacids to Isatins

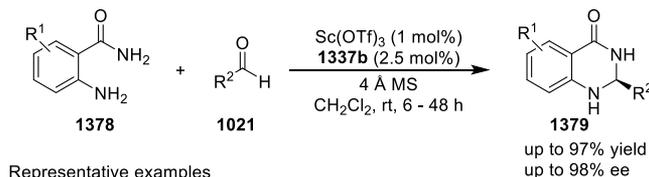


Representative examples

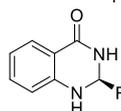


Kesavan has reported a highly enantioselective $\text{Sc}(\text{OTf})_3\text{-}(R,S)\text{-1337}$ -catalyzed intramolecular amidation of imines for the synthesis of a range of 2,3-dihydroquinazolinones **1379** in high yields of up to 97% and excellent enantiomeric excesses of up to 98% (Scheme 409). Aryl aldehydes **1021** were reacted with *ortho*-amide-substituted aniline derivatives **1378** with high to excellent enantioselectivities in all reported cases.⁴⁸⁹

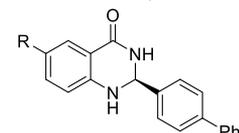
Scheme 409. Enantioselective Sc-Catalyzed Intramolecular Amidation of Imines



Representative examples



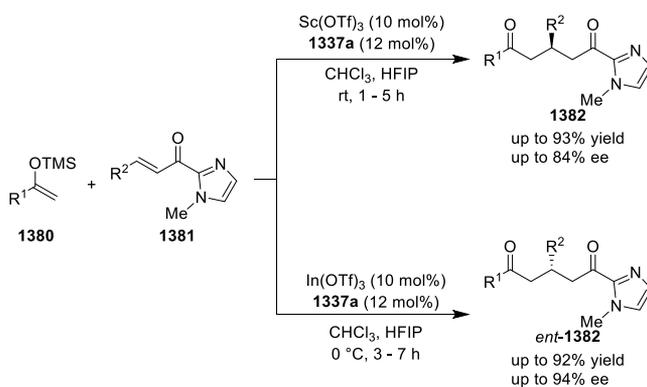
R = C₆H₅; 94% yield, 98% ee
R = 2-naphthyl; 92% yield, 98% ee
R = 3-FC₆H₄; 91% yield, 98% ee
R = 4-CNC₆H₄; 88% yield, 90% ee



R = Cl; 97% yield, 96% ee
R = F₃CO; 95% yield, 94% ee

Singh has reported a $\text{Sc}(\text{III})$ - and $\text{In}(\text{III})$ -catalyzed Mukaiyama–Michael addition of silyl enol ethers **1380** to α,β -unsaturated 2-acyl imidazoles **1381**. Utilizing indanyl PyBOX ligand $(S,R)\text{-1337}$, the enantioselectivity of the process could be switched by using either $\text{Sc}(\text{OTf})_3\text{-}(S,R)\text{-1337}$ or $\text{In}(\text{OTf})_3\text{-}(S,R)\text{-1337}$ as the catalyst. In the reaction catalyzed by $\text{Sc}(\text{OTf})_3\text{-}(S,R)\text{-1337}$, a range of aryl-substituted silyl enol ethers **1380** were tolerated, as were a range of aryl groups on the Michael acceptors **1381**, to yield the enantioenriched 1,5-carbonyl products **1382** in up to 93% yield and with up to 84% ee (Scheme 410). The reaction catalyzed by $\text{In}(\text{OTf})_3\text{-}(S,R)\text{-1337}$

Scheme 410. Enantiodivergent Sc(III)- and In(III)-Catalyzed Mukaiyama–Michael Addition of Silyl Enol Ethers

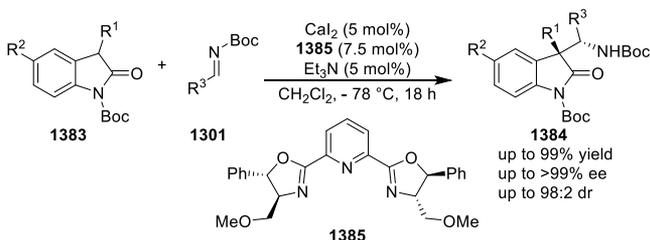


1337 gave similar, but opposite results, leading to the formation of the products *ent*-**1382** in up to 92% yield and with higher levels of enantioselectivity of up to 94% ee. The larger ionic radius of $\text{In}(\text{III})$, which leads to the formation of a bipyramidal trigonal complex in the key intermediate, as compared to $\text{Sc}(\text{III})$, which leads to the formation of an octahedral complex intermediate, was presented as an explanation for the observed switch in enantioselectivity.⁴⁹⁰

Singh has also employed (*S,R*)-**1337** in the Sc(III)- and Er(III)-catalyzed Mukaiyama–Michael addition of silyloxyfurans to the same α,β -unsaturated 2-acyl imidazoles.⁴⁹¹

Kobayashi has described a Ca-catalyzed reaction of oxindoles **1383** with *N*-Boc imines **1301** for the asymmetric synthesis of 3-tetrasubstituted oxindoles **1384**. Utilizing chiral PyBOX ligand **1385**, a range of oxindoles **1383** and imines **1301** were successfully subjected to the reaction to give the corresponding chiral amine products **1384** in up to 99% yield, >99% *ee*, and 98:2 *anti/syn* dr (Scheme 411). A DFT study of

Scheme 411. Asymmetric Ca-Catalyzed Reaction of Oxindoles with *N*-Boc Imines



the CaCl_2 -**1385** complex and the corresponding oxindole enolate complex suggested the formation of a C_2 -symmetric complex with all three nitrogen atoms coordinated to the metal center. The distance between the Ca and O (of the methoxy groups) suggested a weak coordination of O to Ca, and a stereochemical model **1386** in which the $-\text{CH}_2\text{OMe}$ moiety of the ligand shields the *Re*-face of the enolate was proposed (Figure 67).⁴⁹²

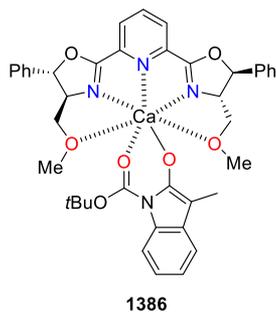


Figure 67. Stereochemical model for the asymmetric Ca-catalyzed reaction of oxindoles with *N*-Boc imines.

Singh has reported the use of *gem*-diPh-*i*Pr PyBOX ligand **1387** in several enantioselective catalytic transformations (Figure 68).

They reported an asymmetric synthesis of coumarin derivatives **1390** via a Zn(II)-**1387**-catalyzed Michael addition of 4-hydroxycoumarin **1388** with 2-enolpyridine *N*-oxides **1389** in up to 99% yield and 97% *ee* (Scheme 412). PyBOX ligands without *gem*-disubstitution did not perform well in the

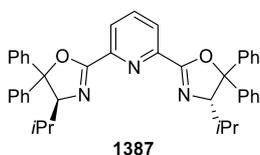
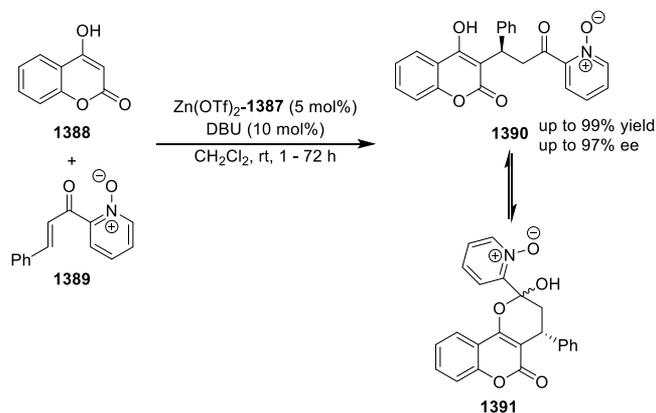


Figure 68. PyBOX ligand **1387**.

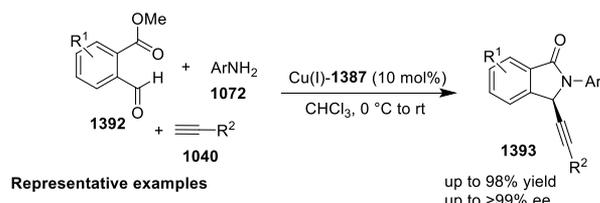
Scheme 412. Asymmetric Synthesis of Coumarin Derivatives



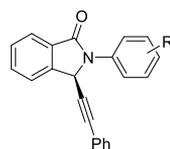
transformation. The coumarin products **1390** were found to be in equilibrium with both diastereomeric forms of cyclized **1391**. Washing the products of the reaction with ethyl acetate significantly increased their enantiomeric purity up to >99.9% *ee*.⁴⁹³ The scope of this reaction was further extended to include aliphatic cyclic 1,3-diketones⁴⁹⁴ and silyl enol ethers⁴⁹⁵ as the nucleophiles with similar results.

Singh also reported a Cu(I)-**1387**-catalyzed asymmetric alkynylation/lactamization cascade for the synthesis of chiral isoindolinones **1393**. The three component reaction of various methyl-2-formylbenzoate derivatives **1392** with aryl amines **1072** and alkynes **1040** proceeds through an A^3 -coupling to give, following intramolecular lactamization of the intermediate chiral amine, the corresponding isoindolinones **1393** in high yields of up to 98% and enantiomeric excesses of up to >99% (Scheme 413).⁴⁹⁶ Singh further employed this methodology in the asymmetric synthesis of medicinally relevant target compounds.⁴⁹⁷

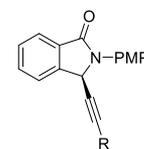
Scheme 413. Cu(I)-Catalyzed Asymmetric Alkynylation/Lactamization



Representative examples



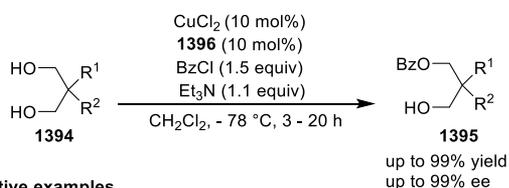
R = H; 89% yield, 95% *ee*
R = 4-O₂CMe; 90% yield, 97% *ee*
R = 2-O₂CMe; 54% yield, 70% *ee*



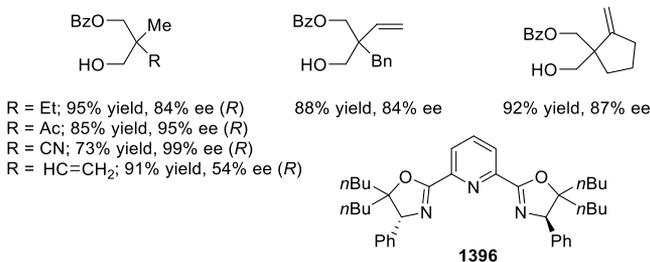
R = 4-MeC₆H₄; 87% yield, 96% *ee*
R = 4-CF₃C₆H₄; 81% yield, >99% *ee*
R = (CH₂)₃Me; 81% yield, 82% *ee*

Kang has reported a desymmetrization reaction of 2,2-disubstituted 1,3-propanediols for the synthesis of all-carbon quaternary stereocenters. Utilizing *gem*-dibutyl CuCl_2 -**1396**, an asymmetric benzoylation of one of the two alcohols was achieved by reacting various 1,3-propanediols **1394** with benzoyl chloride under basic conditions to give the desymmetrized products **1395** in up to 99% yield and 99% *ee* (Scheme 414). A stereochemical model **1397** was proposed

Scheme 414. Desymmetrization of 2,2-Disubstituted 1,3-Propanediols



Representative examples



to explain the asymmetric induction in the reaction (Figure 69). If the tridentate chiral PyBOX ligand sits equatorial in the

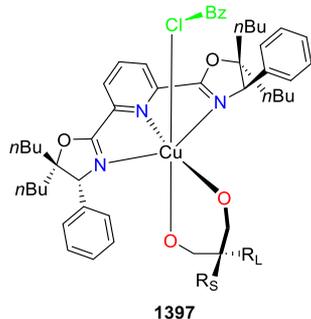


Figure 69. Stereochemical model for the desymmetrization of 2,2-disubstituted 1,3-propanediols.

octahedral complex, the benzoyl chloride axial and the diol axial and equatorial, the smaller R-group on the diol is most likely to occupy the space near the 4-Ph group of the oxazoline ring. The benzoyl cation is then attacked by the equatorial alcohol group to give the desymmetrized products. As a result, substrates with lower levels of steric differentiation between the two R-groups gave lower enantioselectivities, for example in the case of R¹ = Me, R² = -CH=CH₂, the product was obtained in only 54% ee.⁴⁹⁸

Overall, PyBOX ligands with disubstituted oxazoline rings appear to be more useful in asymmetric lanthanide-metal-catalyzed processes than their monosubstituted counterparts. They have also been applied in a range of Sc- and In-catalyzed processes.

3.2.14. Bis(oxazoline) Ligands with Modified Pyridine Linkers. Less common modifications to the chiral PyBOX ligand structure are pyridine ring-based modifications. Johnson has applied 4-halogenated chiral *t*Bu-PyBOX ligands **1398a–b** in dynamic kinetic asymmetric reactions of strained cyclopropane rings (Figure 70).

For example, they applied chlorinated chiral PyBOX ligand **1398a** in a dynamic kinetic asymmetric [3 + 2] cycloaddition of racemic cyclopropanes **1399** bearing electron-rich donor groups, such as *p*-methoxybenzene, and aldehydes **1021**. A range of chiral tetrahydrofurans **1400** were synthesized in the MgI₂-catalyzed process in up to 92% yield and 94% ee (Scheme

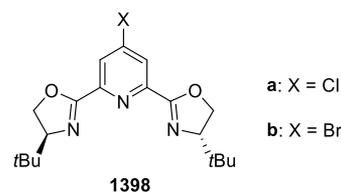


Figure 70. 4-Halogenated PyBOX ligands.

415). A range of alkyl and aryl aldehydes **1021** performed well in the reaction, with the lowest enantiomeric excess obtained

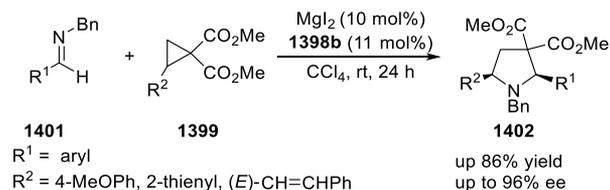
Scheme 415. Dynamic Kinetic Asymmetric [3 + 2] Cycloaddition of Racemic Cyclopropanes



for the *iso*-propyl aldehyde of 82%. A range of ligands with pyridine ring substitution were tested, with the halogenated substrates giving the best results. For comparison, the halogenated *t*Bu-PyBOX ligand **1213c** gave the product in 62% yield and 91% ee, compared to 74% yield and 92% ee with ligand **1398a** for the same substrate.⁴⁹⁹

Johnson subsequently extended the dynamic kinetic [3 + 2] annulation to *N*-benzyl-(*E*)-aldimines **1401** utilizing brominated chiral PyBOX ligand **1398b** under similar conditions to the previous reaction. Chiral 2,5-*cis*-pyrrolidines **1402** were synthesized from cyclopropanes **1399** bearing electron-rich donor groups and aryl aldimines **1401** in up to 86% yield and 96% ee (Scheme 416). Mechanistic studies suggest that the

Scheme 416. Dynamic Kinetic [3 + 2] Annulation to *N*-Benzyl-(*E*)-aldimine with Cyclopropanes

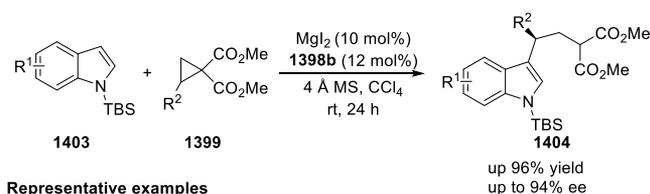


aldimine reacts through the (*E*)-isomer, and that isomerization to the (*Z*)-isomer is not a pathway that furnishes the major 2,5-*cis*-disubstituted products.⁵⁰⁰

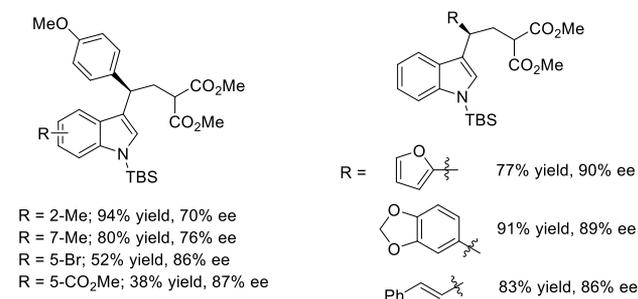
Johnson has further described a MgI₂-catalyzed dynamic kinetic Friedel–Crafts alkylation of indoles with cyclopropanes for the asymmetric synthesis of 3-substituted indoles. A range of *N*-TBS protected cyclopropanes **1403** were reacted with racemic substituted cyclopropanes **1399** in the presence of Br-modified chiral PyBOX ligand **1398b** to give the chiral 3-substituted indoles **1404** in up to 96% yield and 94% ee (Scheme 417).⁵⁰¹

Yoon has applied dimethylamino-substituted *s*-Bu-PyBOX ligand **1408** in the asymmetric photocatalytic [3 + 2] cycloaddition of aryl cyclopropyl ketones **1405** with alkenes **1406** for the synthesis of enantioenriched cyclopentanes **1407**. Employing Gd(OTf)₃ as the Lewis acid in this process, a range of substituted and spirocyclic cyclopentanes **1407** were accessed in up to 95% yield and with up to >99% ee (Scheme

Scheme 417. Mg-Catalyzed Dynamic Kinetic Friedel–Crafts Alkylation of Indoles with Cyclopropanes

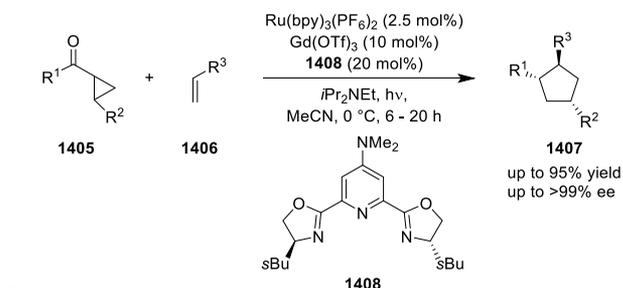


Representative examples

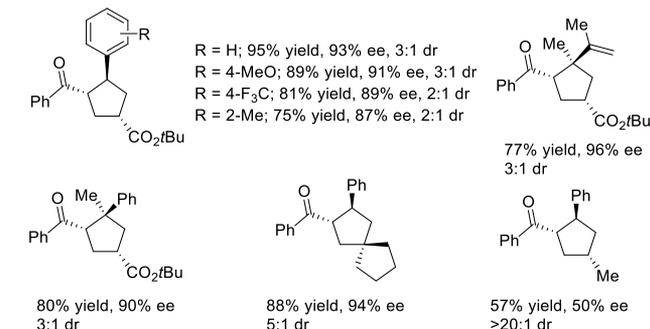


418). Generally, the diastereoselectivity of the reaction was relatively low, giving the products in 2:1 to 5:1 dr, with two examples >20:1 dr⁵⁰²

Scheme 418. Asymmetric Photocatalytic [3 + 2] Cycloaddition of Aryl Cyclopropyl Ketones with Alkenes

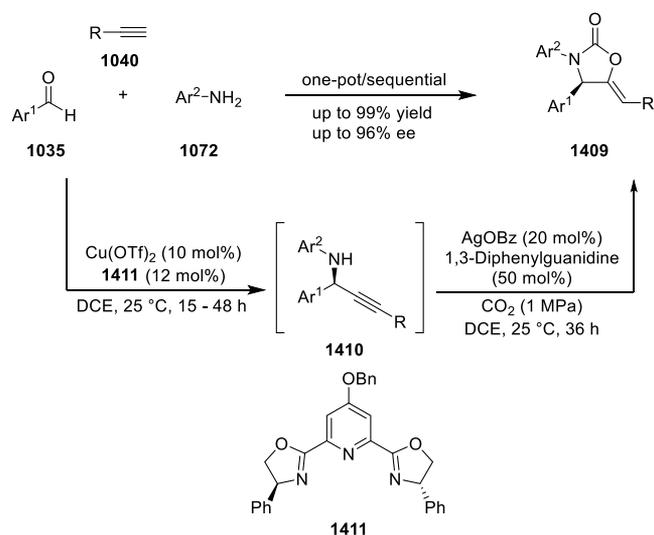


Representative examples



Zhou has reported a one-pot/sequential tandem asymmetric A³-coupling/carboxylation/cyclization for the enantioselective synthesis of 2-oxazolidinones 1409. Employing the novel -OBn substituted Ph-PyBOX 1411, aryl aldehydes 1035, mostly aryl alkynes 1040 and aniline derivatives 1072 were successfully reacted in the Cu-catalyzed A³-coupling/Ag-catalyzed carboxylation sequence to access a range of chiral 2-oxazolidinones 1409 in up to 99% yield and with excellent enantioselectivities up to 96% ee (all examples reported were >90% ee) (Scheme 419). An interesting ligand-accelerating effect was found for the cyclization step. The cyclization occurs without the presence of the ligand 1411 or Cu(OTf)₂, but the rate of the reaction and subsequent yield of the isolated

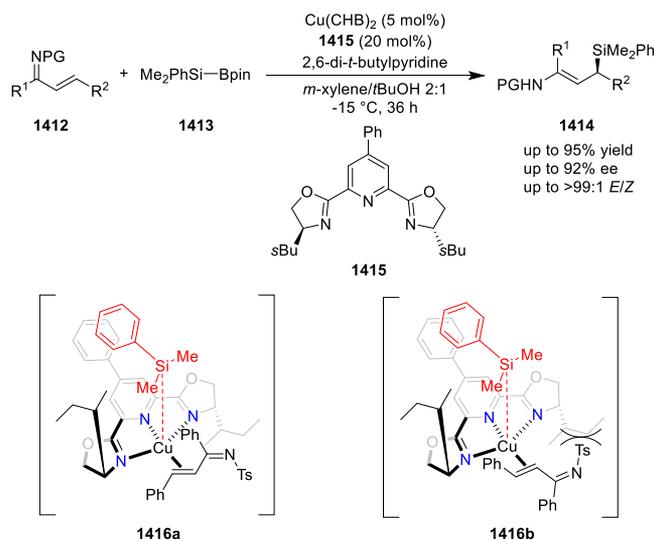
Scheme 419. One-Pot/Sequential Tandem Asymmetric A³-Coupling/Carboxylation/Cyclization



product was found to increase dramatically when the ligand was present, and more so when Cu(OTf)₂ was also present. More interesting still, the presence of excess aniline was found to increase the rate of the cyclization step. Thus, the leftover reagents from the first step were found to promote the upstream cyclization.⁵⁰³

Loh and Xu have utilized the Ph-derivative of the *s*-Bu-PyBOX ligand 1415 in a Cu-catalyzed enantioselective 1,4-protosilylation of α,β -unsaturated ketimines 1412. A range of aryl-substituted ketimines 1412, bearing a variety of protecting groups on *N*, were successfully employed in the reaction for the synthesis of (*E*)-allyl silanes 1414 in up to 95% yield, with up to 92% ee and excellent *E/Z* selectivity of up to >99:1 (Scheme 420). The choice of chiral ligand, bearing Ph-substitution on the pyridine ring, was based on the formation of a favorable π – π interaction between the Si-Ph moiety and the pyridine-Ph moiety in the transition state. The enantioselectivity is rationalized by the disfavored steric interaction between the *N*-PG of the substrate with one of

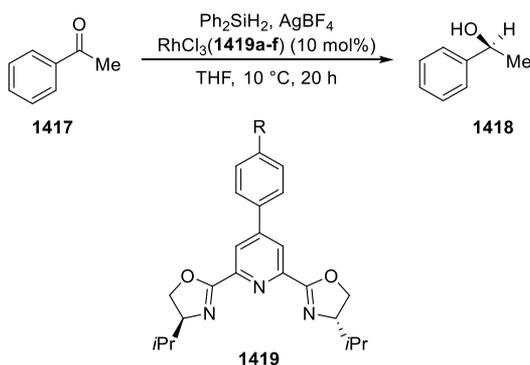
Scheme 420. Cu-Catalyzed Enantioselective 1,4-Protosilylation of α,β -Unsaturated Ketimines



the *s*-Bu groups of the ligand in **1416b**, forcing the ketimine to approach as in **1416a** with the *N*-PG pointing away, for selective delivery of the silyl group.⁵⁰⁴

Jayashankaran has also employed the novel 4-substituted pyridine ring-modified chiral PyBOX ligands in asymmetric catalysis. A range of modified *i*Pr-PyBOX ligands of the type **1419** bearing a substituted aryl ring in the 4-position of the pyridine ring were screened in the Rh-catalyzed hydrosilylation of aromatic ketones with Ph₂SiH. Acetophenone **1417** was chosen as a model substrate and subjected to the reaction with various preprepared Rh-catalysts [RhCl₃(**1419a–f**)] (Table 13). While all the ligands induced good levels of enantiocon-

Table 13. Rh-Catalyzed Hydrosilylation of Aromatic Ketones with Ph₂SiH



entry	1419	R	yield (%)	% ee
1	a	H	88	90
2	b	OMe	90	78
3	c	CN	96	75
4	d	Et	94	98
5	e	Cl	89	84
6	f	CO ₂ Et	78	73

trol, ligand **1419d** bearing a 4-EtC₆H₄ group at the 4-position of the pyridine ring gave the best result, yielding the alcohol **1418** in 94% yield and 98% ee (entry 4). A variety of aromatic ketones were subjected to the hydrosilylation using [RhCl₃(**1419d**)] as the catalyst to afford the corresponding alcohols in up to 94% yield and 99% ee.⁵⁰⁵

The modification of the pyridine ring of the PyBOX scaffold offers an opportunity to alter the electronic properties of these ligands. It is clear from the reports described in this Review that this can be a successful strategy for increasing the levels of stereoselection in a particular transformation, and this should be considered by researchers in the future.

3.2.15. Bis(oxazoline) Ligands with Phenyl Linkers.

Nishiyama has pioneered the development of *N,C,N*-tridentate bis(oxazoline) ligands linked by a phenyl-anion unit (PheBOX).⁵⁰⁶ These ligands form strong C–M (M = metal) covalent bonds that stabilize the resulting chiral ligand–metal complexes. The most widely applied PheBOX-complexes in asymmetric catalysis are the Rh-complexes like **1420** and **1421**, although other metals have also been used like Ru, Pt, Pd, and Ni (Figure 71).

While a range of PheBOX analogues with different phenyl- and oxazoline-ring substitution patterns have been developed, the standard PheBOX metal complexes are more abundantly reported. For example, Nishiyama has developed a diastereo- and enantioselective **1420a**-catalyzed reductive coupling of

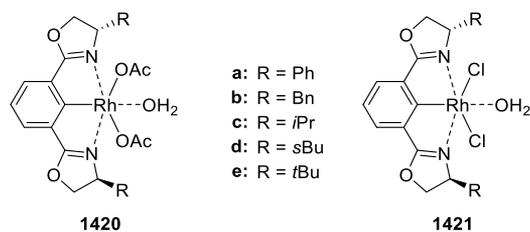
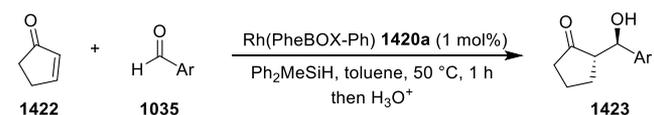


Figure 71. Rh(PheBOX) complexes.

cyclopentenone **1422** with aromatic aldehydes **1035** to yield a range of *anti*-alcohols **1423** in up to 90% yield, with up to 95:5 dr and 93% ee. The outcome of the reaction was sensitive to substitution on the aryl ring of the aldehyde **1035**, for example, *p*-anisaldehyde gave the alcohol in only 65% ee (Scheme 421).⁵⁰⁷

Scheme 421. Diastereo- and Enantioselective Rh-Catalyzed Reductive Coupling of Cyclopentenone with Aromatic Aldehydes



Representative examples

- Ar = Ph; 90% yield, 95:5 dr, 85% ee
- Ar = 1-Naphthyl; 90% yield, 94:6 dr, 90% ee
- Ar = 4-MeCOC₆H₄; 62% yield, 85:15 dr, 90% ee
- Ar = 4-F₃CC₆H₄; 70% yield, 79:21 dr, 91% ee
- Ar = 4-O₂NC₆H₄; 68% yield, 70:30 dr, 93% ee
- Ar = 4-MeOC₆H₄; 72% yield, 88:12 dr, 65% ee
- Ar = 3-MeCOC₆H₄; 49% yield, 79:21 dr, 82% ee
- Ar = 3-MeOC₆H₄; 81% yield, 93:7 dr, 87% ee
- Ar = 2-MeCOC₆H₄; 68% yield, 94:6 dr, 68% ee

Some other enones were tested, with cyclic enones giving the corresponding alcohols **1424–1427** with better enantioselectivities than the only acyclic example, methylvinyl ketone, which gave the *anti*-alcohol **1426** with 80:20 dr and 57% ee (Figure 72).

The possible transition state **1428** was proposed to explain the stereochemical outcome of the reaction, in which the *Re*-face of the enolate, which forms following hydride addition to the enone, attacks the *Re*-face of the aldehyde to avoid a steric interaction with one of the oxazoline-Ph groups (Figure 73).

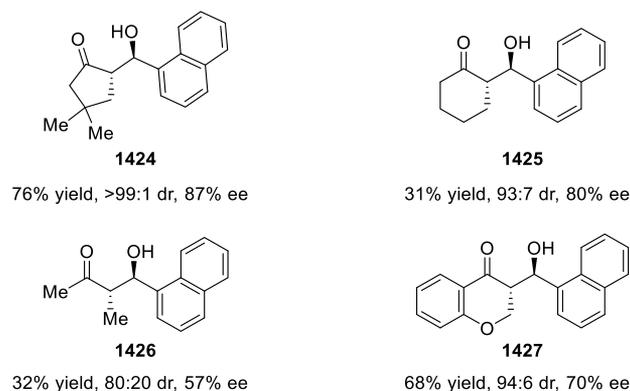


Figure 72. Products of the Rh-catalyzed reductive coupling of various enones with naphthaldehyde.

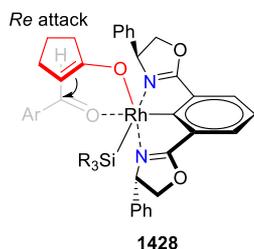
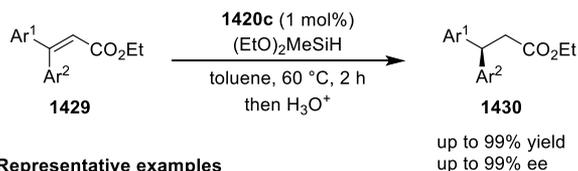


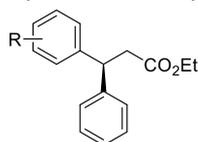
Figure 73. Stereochemical model for the Rh-catalyzed reductive coupling of cyclopentenone with aromatic aldehydes.

Nishiyama also developed the asymmetric hydrosilylation of α,β -unsaturated esters **1429** catalyzed by *i*Pr-PheBOX-Rh **1420c**. Under optimized conditions, a range of enantioenriched, diaryl propanoates **1430** were accessed in up to 99% yield and with up to 99% *ee* with all reported examples isolated with >95% *ee* (Scheme 422). The reaction of heteroaromatic substrates did not proceed smoothly under the optimized conditions.⁵⁰⁸

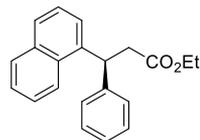
Scheme 422. Rh-Catalyzed Asymmetric Hydrosilylation of α,β -Unsaturated Esters



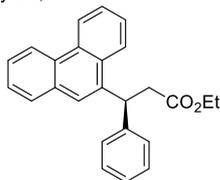
Representative examples



R = 4-Me; 90% yield, 98% *ee*
 R = 4-Cl; 90% yield, 98% *ee*
 R = 4-F₃C; 95% yield, 97% *ee*
 R = 3-MeO; 94% yield, 97% *ee*
 R = 2-Me; 92% yield, 97% *ee*



96% yield, 99% *ee*

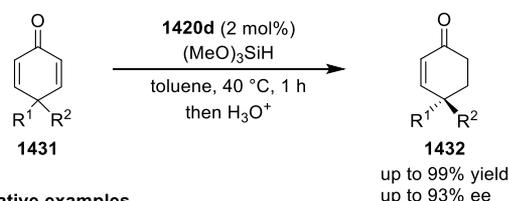


99% yield, 95% *ee*

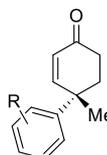
Nishiyama has applied *s*Bu-PheBOX-Rh **1420d** in the asymmetric hydrosilylation of cyclohexadienones **1431** with asymmetric induction at remote quaternary centers. A small range of nonspirocyclic products **1432** were accessed in up to 99% yield and with up to 81% *ee*, generally only giving moderate levels of enantioselectivity (<80% *ee*) (Scheme 423). Spirocyclic cyclohexadienones were found to perform better in this process giving the enantioenriched products in up to 99% yield and with 93% *ee* with most examples giving high levels of enantioselectivity >80% *ee*.⁵⁰⁹

A possible transition state **1433a** was proposed to explain the stereochemical outcome of this hydrosilylation, with stereoreduction at a nonreacting quaternary center (Scheme 424). The Rh–H bond sits in the equatorial position with bond formation occurring on the *Re*-face of the enone, due to the steric repulsion of the oxazoline-*s*Bu-group and the cyclohexadienone, as shown in **1433b**. The steric environment of the γ -position (Ph and Me) is differentiated due to steric repulsion of the bulky trimethoxysilyl group with the Ph-group of the cyclohexadienone, as shown in **1433c**.

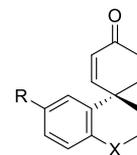
Scheme 423. Rh-Catalyzed Asymmetric Hydrosilylation of Cyclohexadienones



Representative examples

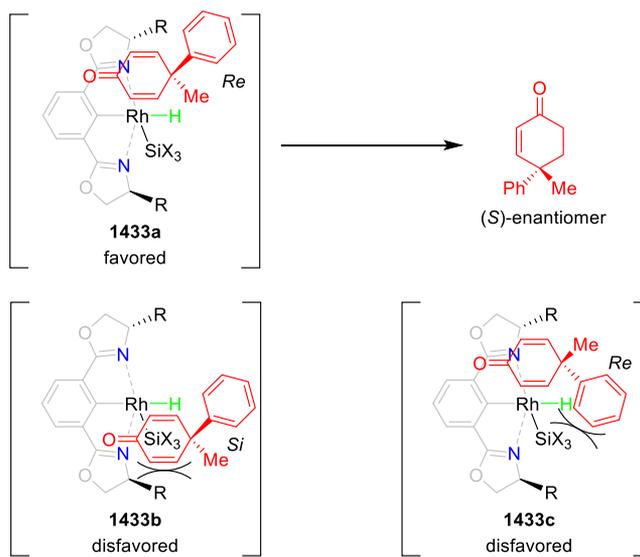


R = H; 82% yield, 77% *ee*
 R = 4-Me; 95% yield, 77% *ee*
 R = 4-MeO; 92% yield, 81% *ee*
 R = 4-F₃C; 92% yield, 65% *ee*
 R = 3-Me; 95% yield, 71% *ee*
 R = 2-Me; 99% yield, 70% *ee*



X = CH₂; R = H; 89% yield; 93% *ee*
 R = MeO; 88% yield, 93% *ee*
 X = O; R = H; 89% yield; 88% *ee*
 R = Cl; 88% yield, 84% *ee*
 X = S; R = H; 94% yield; 82% *ee*
 R = Me; 91% yield, 81% *ee*

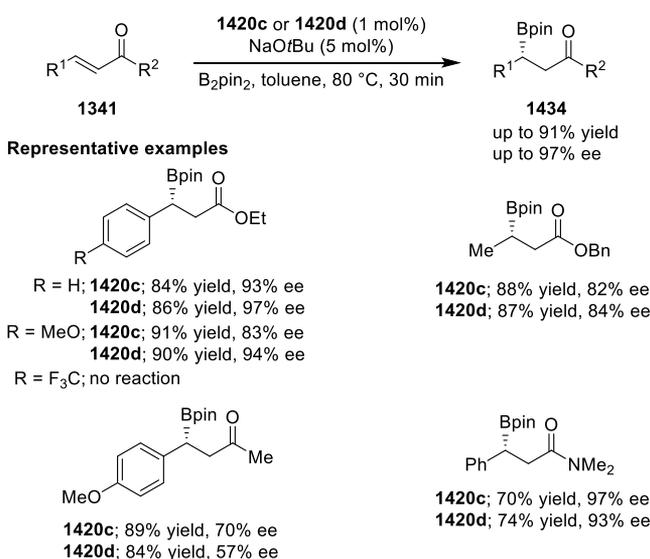
Scheme 424. Stereochemical Model for Rh-Catalyzed Asymmetric Hydrosilylation of Cyclohexadienones



The asymmetric β -borylation of α,β -unsaturated esters, amides and ketones **1341** with *i*Pr- and *s*Bu-PheBOX-Rh catalysts **1420c** and **1420d** was reported by Nishiyama. Enantioenriched esters **1434** were formed in this transformation with a number of examples isolated in up to 91% yield and with up to 97% *ee* (Scheme 425). Methyl ketones did not perform well, with two examples isolated in up to 89% yield and with up to 70% *ee*. Finally, a single dimethylamide example was isolated in 70% yield and with 97% *ee* (**1420c**) and 74% yield and with 93% *ee* (**1420d**). When the reaction was run with (*Z*)-ethyl cinnamate as the substrate and **1420c** as the catalyst, the borylated product was isolated as the same (*S*)-enantiomer, as in the reaction with (*E*)-ethyl cinnamate (84% yield, 95% *ee*), in 70% yield and with 93% *ee*. While a stereochemical model for this transformation was proposed, it did not take the outcome of the reaction with the (*Z*)-alkene into account.⁵¹⁰

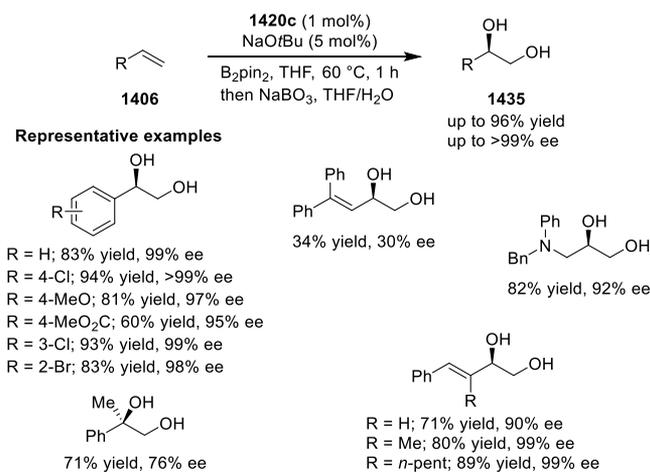
Nishiyama continued to explore asymmetric borylation reactions of alkenes and reported the *i*Pr-PheBOX-Rh

Scheme 425. Asymmetric β -Borylation of α,β -Unsaturated Esters, Amides, and Ketones



1420c-catalyzed diboration/oxidation of unactivated terminal alkenes **1406** for the asymmetric synthesis of 1,2-diols **1435**. A wide range of aryl, alkenyl and aliphatic substituted-alkenes **1406** were successfully transformed into enantioenriched 1,2-diols **1435** in up to 96% yield and with up to >99% ee (Scheme 426).⁵¹¹

Scheme 426. Asymmetric Synthesis of 1,2-Diols



A stereochemical model was proposed to explain the formation of the major (*R*)-enantiomer in this transformation. In transition states **1436a** and **1436b**, the Bpin (B) sits in one of the apical positions (Figure 74). In **1436a**, C–B bond formation on the *Si*-face of the alkene gives the major (*R*)-enantiomer of the product, while transition state **1436b**, with C–B bond formation on the *Re*-face of the alkene, is disfavored due to the steric interaction between the Ph-group of the alkene and one of the oxazoline R-groups. Transition states **1436c** and **1436d** show the Bpin in one of the equatorial positions. Transition state **1436c** shows a disfavored steric interaction as in **1436b**. **1436d** has no disfavored interactions, but C–B bond formation on the *Re*-face of the alkene gives rise to the minor (*S*)-enantiomer of product.

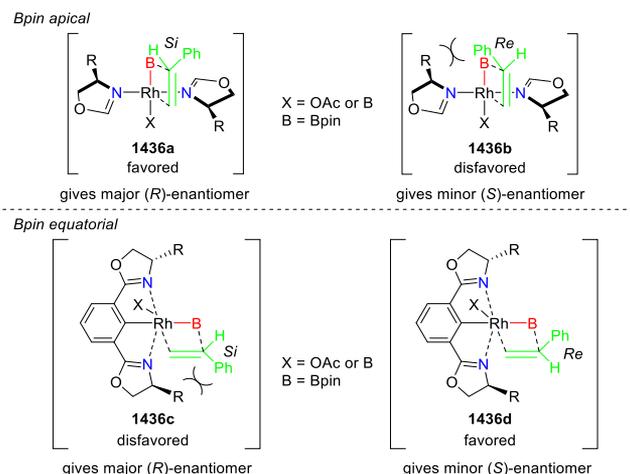
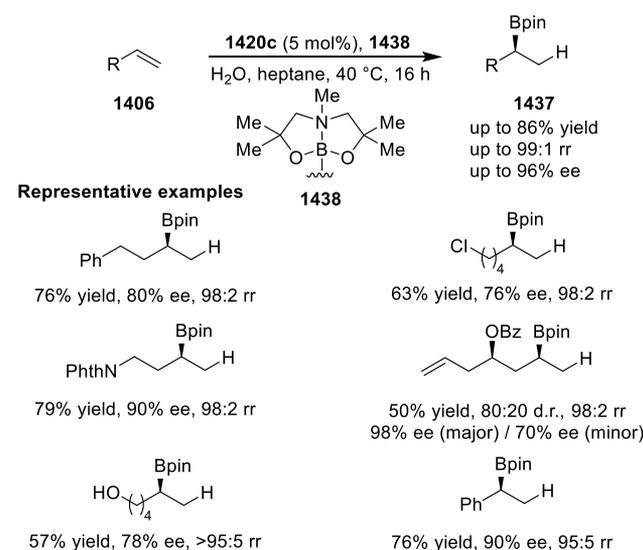


Figure 74. Stereochemical mode for the Rh-catalyzed borylation of alkenes.

Aggarwal built on the work by Nishiyama in the diboration of terminal alkenes and has reported an *i*Pr-PheBOX-Rh **1420c**-catalyzed Markovnikov hydroboration of unactivated terminal alkenes **1406** with a novel borylating reagent **1438** and H₂O as a proton source. Following optimized conditions, the enantioenriched products **1437** were isolated in moderate to good yields up to 86%, with regioselectivities up to 99:1 rr and enantioselectivities up to 96% ee (Scheme 427). Aliphatic and aryl substrates were reported with the process showing good functional group tolerance.⁵¹²

Scheme 427. Rh-Catalyzed Markovnikov Hydroboration of Unactivated Terminal Alkenes



Analogues of the PheBOX ligands have been developed for use in Ru-catalysis. For example, Nishiyama has developed complexes of the type **1439–1442**, bearing PheBOX ligands with dimethyl-substituted bridging-phenyl rings to prevent Ru C–H insertion at these positions (Figure 75).

Nishiyama first applied Ru-complexes **1440–1442** in the asymmetric hydrogenation of ketones. Reactions with Ru-complexes **1440a** and **1442a** were found to give access to enantioenriched alcohols in high yields up to 99% and with up to 98% ee (*S*). For example, ketone **1443** was subjected to the

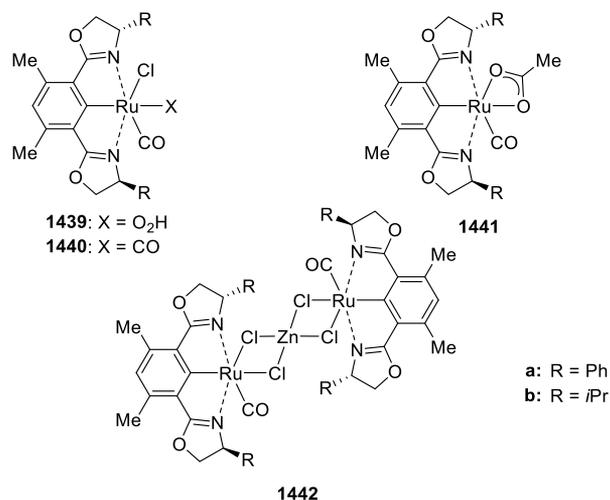
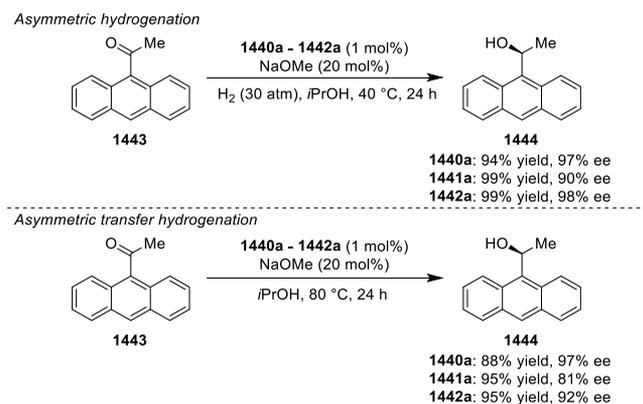


Figure 75. Ru(PheBOX) complexes.

reaction with both complexes to give alcohol **1444** in 94% yield and with 97% *ee* (**1440a**) and in 99% yield and with 98% *ee* (**1442a**) (Scheme 428). These complexes were also applied

Scheme 428. Ru-Catalyzed Asymmetric Hydrogenation and Asymmetric Transfer Hydrogenation of Ketone 1443

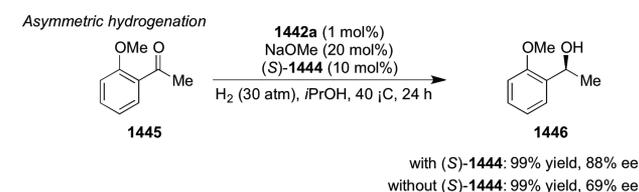


in enantioselective transfer hydrogenation to give the alcohols with overall lower levels of enantioselectivity. For example, the same ketone **1443** was subjected to the transfer hydrogenation in the presence of both complexes to give the alcohol **1444** in 88% yield and with 97% *ee* (**1440a**) and in 95% yield and with 92% *ee* (**1442a**).⁵¹³ In a report earlier that year, complex **1441a** was applied in the same reactions, giving overall lower levels of enantioselectivity to **1440a** and **1442a**.⁵¹⁴

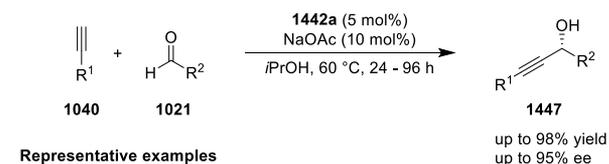
Nishiyama later reported an enhancement of the enantioselectivity in the asymmetric hydrogenation of ketones by including alcohol (*S*)-**1444** as an additive. For example, for the asymmetric hydrogenation of ketone **1445**, catalyzed by complex **1442a**, the enantioselectivity increased from 69% *ee* without the additive to 88% *ee* with the additive. In all but one reported case, an increase in the enantioselectivity was observed (Scheme 429).⁵¹⁵

Nishiyama applied the Ph-PheBOX-Ru complex **1442a** in the asymmetric Ru-catalyzed alkylation of aldehydes **1021**. A range of enantioenriched alcohols **1447** were isolated in up to 98% yield and with up to 95% *ee* (Scheme 430). Aryl alkynes were well tolerated in the reaction, while cyclohexyl and

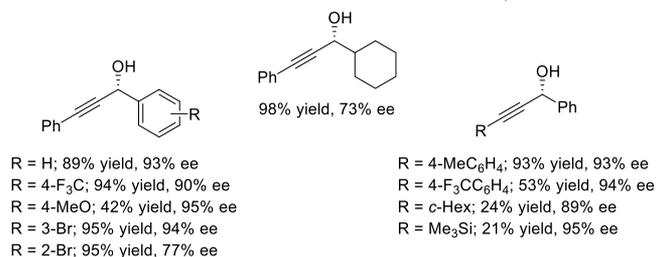
Scheme 429. Ru-Catalyzed Asymmetric Hydrogenation of Ketone 1445



Scheme 430. Asymmetric Ru-Catalyzed Alkynylation of Aldehydes



Representative examples

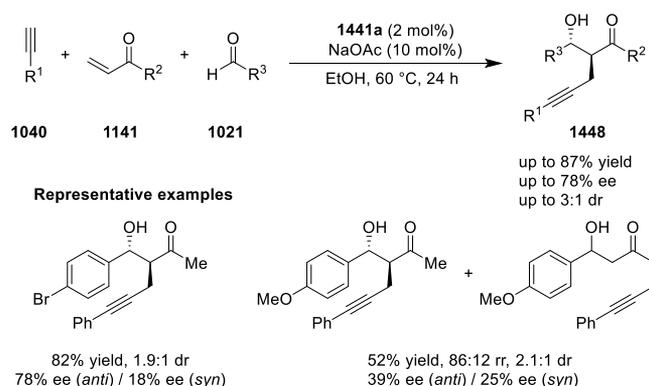


trimethylsilyl alkynes gave the corresponding alcohols in low yields but with high levels of enantioselectivity.⁵¹⁶

Nishiyama later applied Ph-PheBOX-Ru complex **1441a** in the racemic conjugate alkyne addition to α,β -unsaturated carbonyls. A single asymmetric example of an alkyne addition to a β -substituted enone was reported, giving the product in 82% *ee*.⁵¹⁷ This led to the development of the **1441a**-catalyzed enantioselective 3-component coupling reaction of alkynes **1040**, enones **1141**, and aldehydes **1021**. The levels of enantioselectivity for the formation of the isolated products were mostly low to moderate, up to 78% *ee* (Scheme 431). The diastereoselectivity was also low, up to 3:1 *dr*, and in some cases there were regioselectivity issues.⁵¹⁸

Ohshima has reported the asymmetric Rh-catalyzed alkylation of α -keto esters⁵¹⁹ and α -ketiminoesters⁵²⁰ with C₁-symmetric indanyl-PheBOX-Rh complexes **1449a** and **1449b** and C₂-symmetric indanyl-PheBOX-Rh complexes **1450a** and **1450b** (Figure 76).

Scheme 431. Ru-Catalyzed Enantioselective 3-Component Coupling Reaction of Alkynes, Enones, and Aldehydes



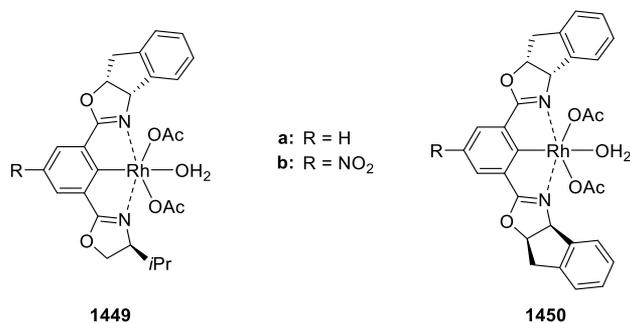
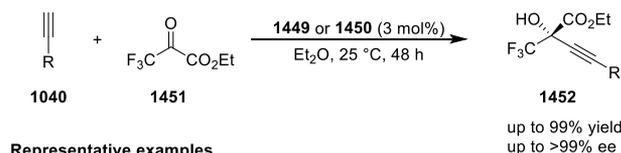


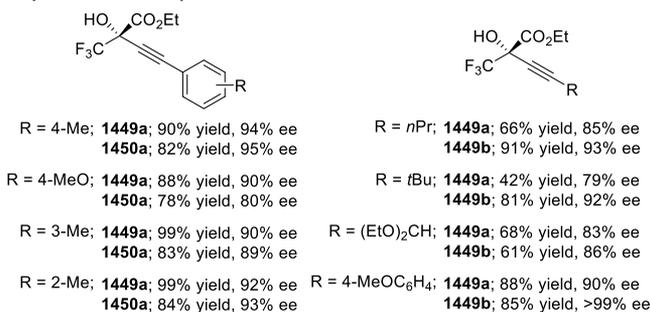
Figure 76. Rh(indanyl-PheBOX) complexes.

Under optimized conditions, enantioenriched tertiary alcohols **1452** could be accessed from α -keto ester **1451** in up to 99% yield and with up to >99% *ee* (Scheme 432).

Scheme 432. Asymmetric Rh-Catalyzed Alkynylation of α -Keto Esters



Representative examples

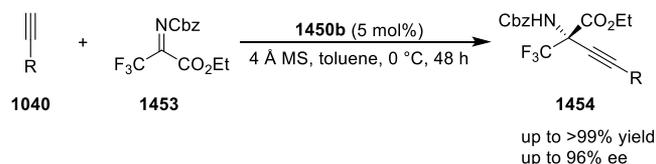


Initially, complexes **1449a** and **1450a** were applied in the reaction with aryl-substituted alkynes. *C*₁-Symmetric **1449a** was found to outperform *C*₂-symmetric **1450a** giving the products in generally higher yields and in most cases, slightly higher enantioselectivities. Nitro-substituted *C*₁-symmetric ligand **1449b** was applied in the reactions of less reactive substrates and was found to drastically improve the isolated yields and enantiomeric excesses of the tertiary alcohol products **1452** when compared to **1449a**. Interestingly, in a competition experiment between benzaldehyde and α -keto ester **1451**, the reaction catalyzed by **1449a** gave no observable alkynylation of the aldehyde.

Later, Ohshima found that the *C*₂-symmetric indanyl-PheBOX-Rh complexes **1450a** and **1450b** outperformed their *C*₁-symmetric counterparts in the asymmetric alkynylation of α -ketiminoester **1453**. Under optimized conditions with nitro-substituted **1450b**, a range of aryl, alkenyl, alkyl and silyl-substituted alkynes **1040** were subjected to this reaction with α -ketiminoester **1453** to give a range of tertiary amines **1454** in up to >99% yield and with up to 96% *ee* (Scheme 433).

A follow-up mechanistic study found that the application of (trimethylsilylethynyl)(PheBOX)Rh complexes **1455a–b** in the alkynylation of α -ketoiminoesters allowed for the alkynylation of less reactive α -ketoiminoesters, for example cyclic *N*-sulfonyl ketiminoester- and α -ketiminophosphonate-

Scheme 433. Asymmetric Rh-Catalyzed Alkynylation of α -Ketiminoesters



derived amines **1456** and **1457** were accessed in high yields of 97% and 98%, respectively, and enantioselectivities of 93% *ee* and 82% *ee*, respectively (Figure 77).⁵²¹

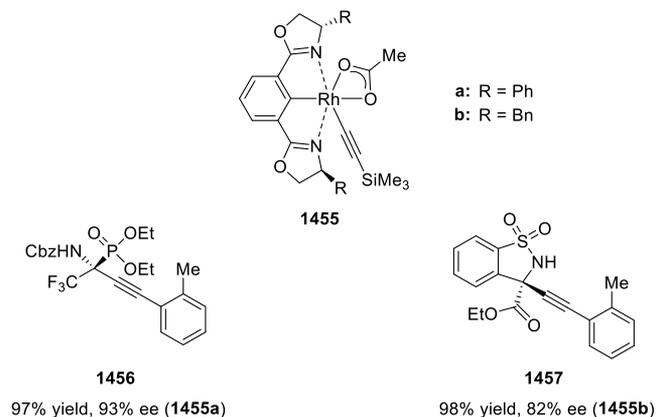
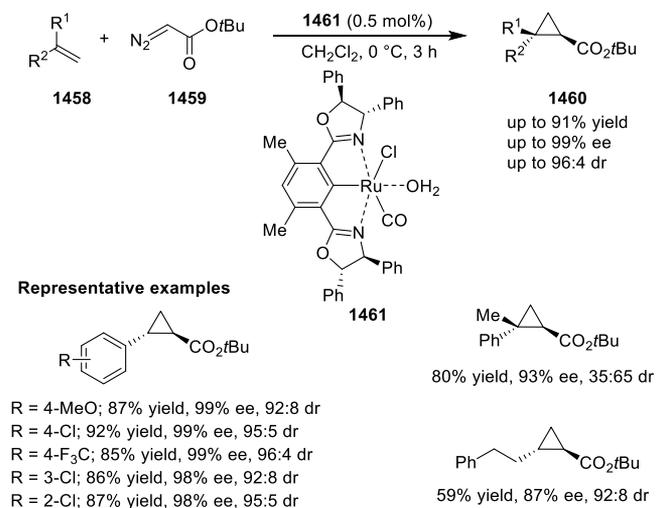


Figure 77. Rh(PheBOX) complex **1455** and cyclic *N*-sulfonyl ketiminoester- and α -ketiminophosphonate-derived amines **1456** and **1457**.

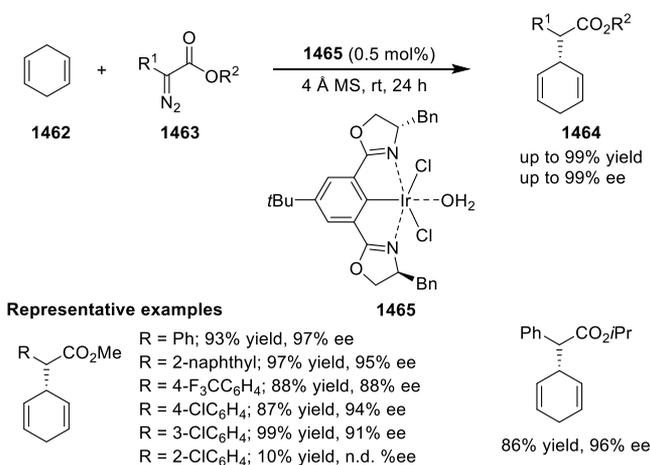
Nishiyama has reported the asymmetric Ru-catalyzed cyclopropanation of terminal alkenes **1458** utilizing diPh-PheBOX-Ru **1461**. A range of *trans*-cyclopropanes **1460** were isolated from the reaction with *tert*-butyl- α -diazoacetate **1459** in up to 91% yield, with up to 96:4 *dr* and 99% *ee* (Scheme 434). Styrene derivatives performed well in the reaction, giving the *trans*-cyclopropanes with high *dr*, while the only reported disubstituted alkene example gave the opposite diastereoselectivity (35:65 *anti/syn*).⁵²²

Scheme 434. Asymmetric Ru-Catalyzed Cyclopropanation of Terminal Alkenes



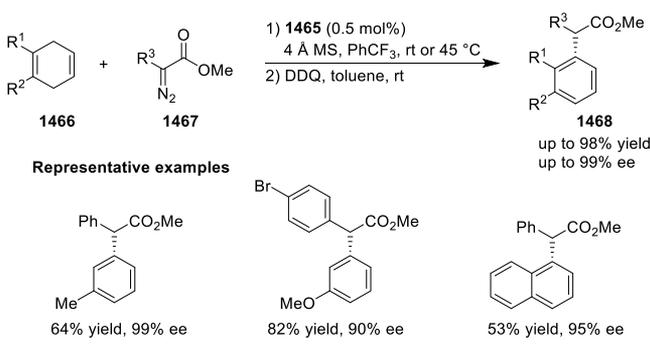
The vast majority of PheBOX applications over the past decade have been in Rh- and Ru-catalyzed transformations. However, Davies and Blakey have reported a PheBOX-Ir-catalyzed asymmetric C–H activation of 1,4-cyclohexadiene **1462** with carbenoids. A range of enantioenriched products were isolated from the reaction catalyzed by *t*Bu-substituted-Bn-PheBOX-Ir complex **1465** in up to 99% yield and with up to 99% *ee* (Scheme 435). The *t*Bu-group in the backbone of the ligand was found to increase the isolated yield of the product without affecting the high levels of enantioselectivity.⁵²³

Scheme 435. Ir-Catalyzed Asymmetric C–H Activation of 1,4-Cyclohexadiene



In the same report, a small range of substituted cyclohexadienes **1466** were also subjected to the site selective C–H activation with subsequent oxidation by DDQ to give a range of enantioenriched α -diarylesters **1468** in up to 98% yield and with up to 99% *ee* (Scheme 436).

Scheme 436. Ir-Catalyzed Asymmetric C–H Activation of Substituted 1,4-Cyclohexadienes



PheBOX ligands have been successfully applied in a whole range of asymmetric transformations of Rh, Ru and Ir. The main disadvantage of these ligands is that the catalysts must be synthesized prior to use. While this will most likely prevent the widespread use of these ligands in asymmetric catalysis, we expect to see future developments, especially in asymmetric Ir-catalysis, which has not been extensively explored.

3.2.16. Bis(oxazoline) Ligands with Dibenzofuran Linkers. Dibenzofuran-4,6-bis(oxazoline) (DBFOX) ligands of the type **1469** and **1470**, which bear a coordinating O atom

in the bridging dibenzofuran moiety, have been developed for a range of applications in asymmetric metal catalysis (Figure 78). In fact, this area was comprehensively reviewed in 2018 by Itoh and Sibi.⁵²⁴ As a result, we will only discuss some recent examples in detail.

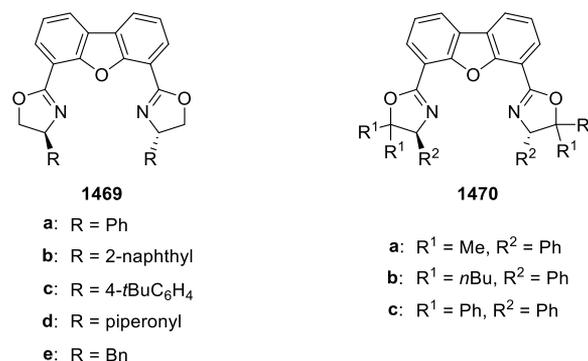


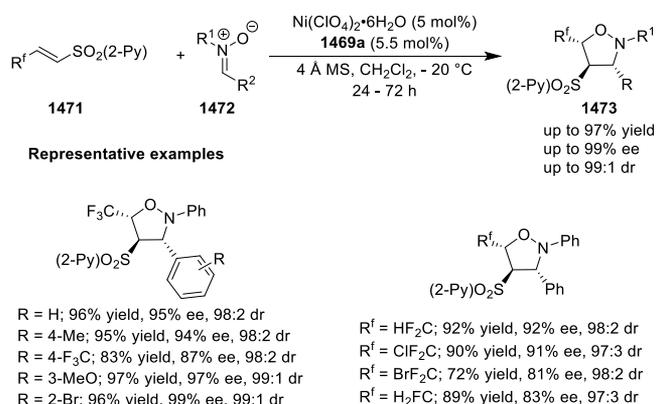
Figure 78. Dibenzofuran-4,6-bis(oxazoline) (DBFOX) ligands **1469**–**1470**.

Since 2008, DBFOX ligands have been employed in, for example, enantioselective Friedel–Crafts of pyrroles,^{525,526} hydride shift/ring closure cascade,⁵²⁷ α -cyanation,⁵²⁸ α -fluorination,^{529–531} and α -hydroxylation of carbonyls,⁵³² enolate protonation⁵³³ and radical conjugate addition⁵³⁴ chemistry, utilizing Zn-, Cu-, Ni- and Mg-catalysis.

Recently, Huang and Shibata reported the catalytic asymmetric 1,3-dipolar cycloaddition of β -fluoroalkylated α,β -unsaturated 2-pyridylsulfones **1471** with nitrones **1472** for the enantioselective synthesis of chiral fluoroalkylated isoxalidinones **1473**, which can be converted into γ -amino alcohols. Under optimized conditions with Ni(ClO₄)₂·6H₂O and Ph-DBFOX **1469a** as the chiral ligand, a range of isoxalidinones **1473** were accessed in up to 97% yield, with up to 99:1 dr and 99% *ee* (Scheme 437). A range of fluoroalkylated groups (R^f) were tolerated in the reaction.⁵³⁵

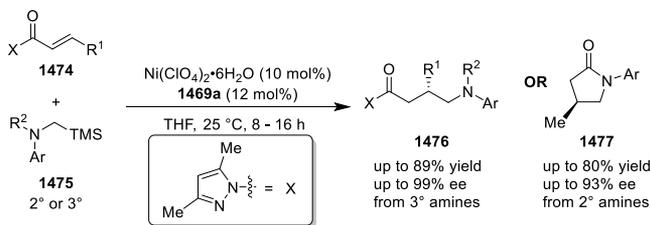
Gong has developed a visible-light-promoted Ni-**1469a**-catalyzed asymmetric radical conjugate addition reaction. The bifunctional Ni-catalyst initiates single electron transfer and provides a chiral environment for effective asymmetric induction. A range of tertiary silylamines **1475** were reacted with α,β -unsaturated *N*-acyl pyrazoles **1474** to give γ -amino

Scheme 437. Asymmetric 1,3-Dipolar Cycloaddition of β -Fluoroalkylated α,β -Unsaturated 2-Pyridylsulfones with Nitrones

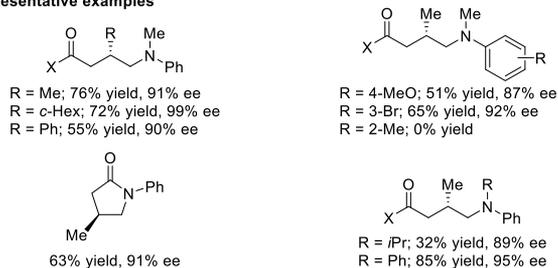


acids **1476** in up to 89% yield and with up to 99% *ee* (Scheme 438). When secondary amines were used in the reaction under

Scheme 438. Visible-Light-Promoted Ni-Catalyzed Asymmetric Radical Conjugate Addition



Representative examples



the optimized conditions, subsequent lactamization occurred to give enantioenriched γ -lactams **1477** in up to 80% yield and with up to 93% *ee*.⁵³⁶

We chose to highlight the recent Ni-catalyzed transformations that the DBFOX ligands have been applied in because the development of asymmetric 3d-transition-metal-catalyzed reactions is an important area in modern organic chemistry. We hope that these ligands can be further applied in this area.

4. TETRADENTATE BIS(OXAZOLINE) LIGANDS

In 2013, Li reported the use of chiral biphosphinobioxazoline ligand **1478** in the asymmetric reduction of α,β -unsaturated ketones **1486** furnishing the product **1487** in up to 89% yield and 97% *ee* (Figure 79, Scheme 439). Interestingly when ^tBuPHOX ligand was used instead in this catalytic transformation only <5% product **1489** was observed. This Ru-catalyst system was also noted to be tolerant of water and air, providing very mild conditions for access to enantioenriched allylic alcohols.⁵³⁷

Gao reported the use of the tetradentate porphyrin inspired ligand **1479** in the Fe-catalyzed asymmetric epoxidation of electron deficient alkenes **1488** (Scheme 440). A range of electronically varied alkenes **1488** were screened using the optimized reaction conditions furnishing the epoxide **1489** in up to 80% yield and 99% *ee*. The utility of this reaction was further tested by carrying out gram-scale epoxidations with no erosion of enantioselectivity observed.⁵³⁸

Ishihara developed a novel sulfonamide-based bis(oxazoline) ligand **1480** and applied it in the inverse-electron-demand hetero Diels–Alder reaction of β,γ -unsaturated α -keto esters **1491** with allyl silanes **1490** (Scheme 441). This methodology gives access to chiral oxanes **1492** rather than cyclic acetals which are the product of the conventional inverse-electron-demand hetero Diels–Alder reaction. A broad substrate scope was carried out furnishing the product **1492** in up to 99% yield and 99% *ee* in a 92:8 *cis/trans* ratio.⁵³⁹ It was also applied in

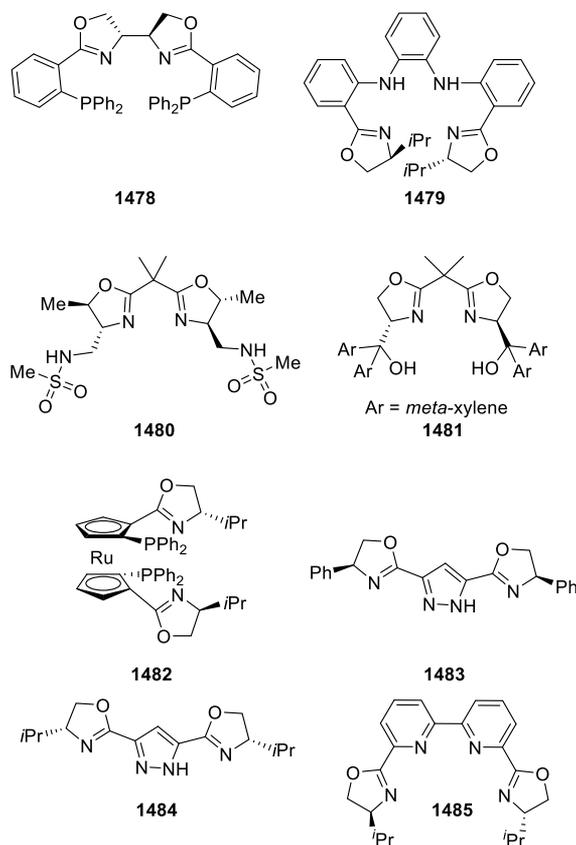
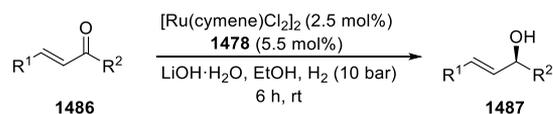
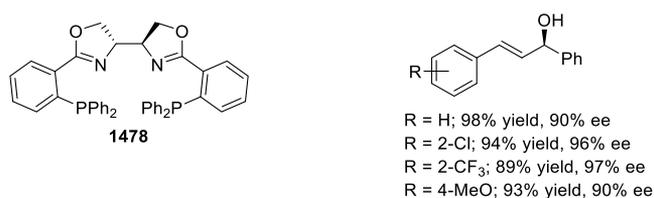


Figure 79. Summary of tetradentate bis(oxazolines) ligands.

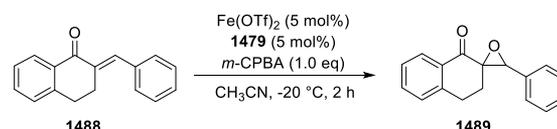
Scheme 439. Ru-Catalyzed Asymmetric Reduction of Ketones



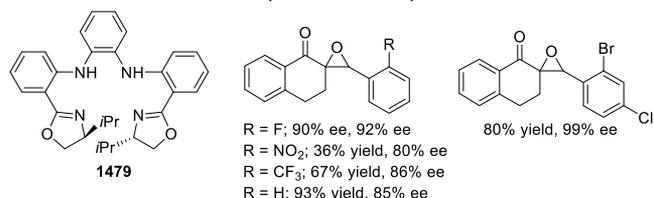
Representative examples



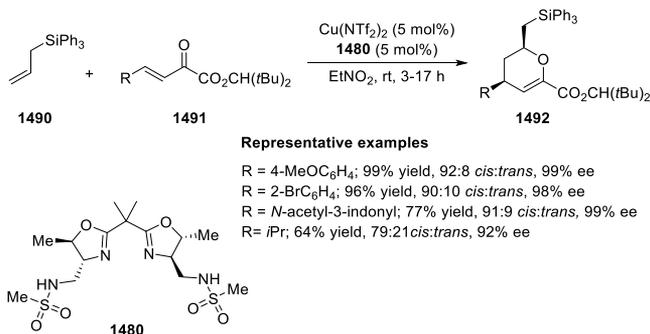
Scheme 440. Fe-Catalyzed Asymmetric Epoxidation



Representative examples

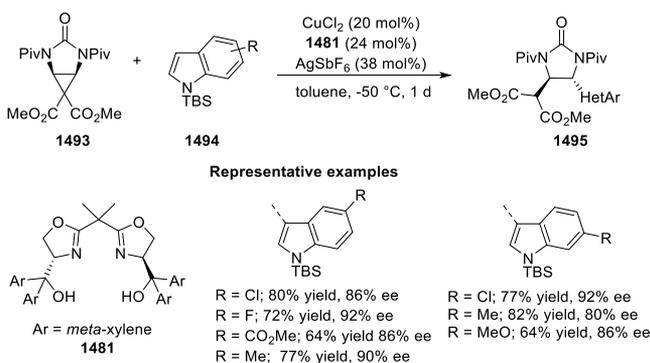


Scheme 441. Cu-Catalyzed Asymmetric Synthesis of Oxanes



the asymmetric Cu-catalyzed Diels–Alder reaction to great effect.⁵⁴⁰

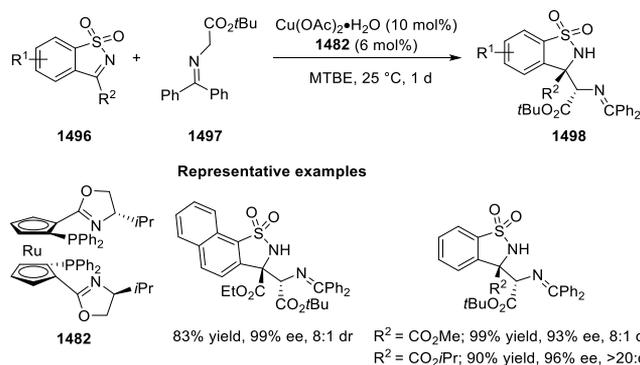
Waser reported the Cu-catalyzed desymmetrization of *meso*-diaminocyclopropanes **1493** in 2018. This modified Friedel–Crafts reaction was originally attempted using BOX ligand **600c** which only furnished the product **1495** in 74% yield, 64% ee, and >20:1 dr. To increase the enantioselectivity the native BOX ligand **600c** was modified in the α -position to furnish a large range of ligands containing bulky alcohols. After screening the structure of the ligand further by fine-tuning the sterics, the Cu complex of ligand **1481** afforded the product **1495** in 80% yield, 86% ee, and >20:1 dr. With the optimized conditions in hand a range of electronically and sterically diverse *N*-TBS indoles **1494** were screened in this catalytic transformation, furnishing the product **1495** in up to 82% yield, 92% ee, and all in >20:1 dr (Scheme 442).⁵⁴¹

Scheme 442. Cu-Catalyzed Desymmetrization of *meso*-Diaminocyclopropanes

Zhang reported the Cu-catalyzed asymmetric Mannich reaction of cyclic ketimines **1496** and glycine Schiff bases **1497**. Planar chiral ferrocene ligands have been widely used in asymmetric catalysis in recent times, however in contrast, ruthenocene based ligands have not been as widely applied in asymmetric catalysis. In this reaction the tetradentate planar-chiral ruthenocene ligand **1482** showed excellent selectivity giving the product in up to 83% yield, 99% ee, and 7:1 dr. The substrate scope highlighted the trend that the ester functionality in the cyclic ketimine **1496** had a large effect on the enantioselectivity. Sterically bulky esters such as an isopropyl ester led to an increase in enantioselectivity and diastereoselectivity (96% ee, >20:1 dr, and 90% yield) compared to methyl esters (99% yield, 93% ee, 8:1 dr). If the cyclic ketimine ester was replaced by a methyl group this caused a pronounced decrease in all selectivity to 26% yield,

8% ee, and 1:1 dr (Scheme 443).⁵⁴² In other publications by Zhang's group, this ligand was applied in the Pd-catalyzed

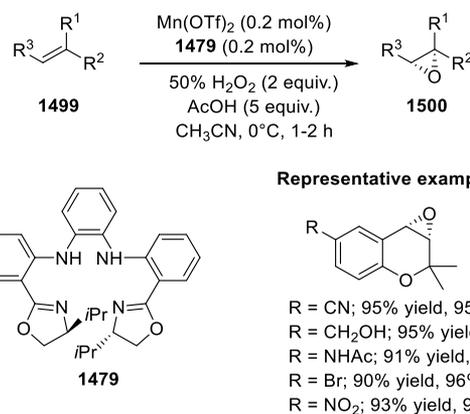
Scheme 443. Cu-Catalyzed Enantioselective Mannich Reaction of Cyclic Ketimines



allylation of amino acid derivatives, *N*-sulfonylimines and in the asymmetric synthesis of chromanols.^{127,543–546}

In 2013 Gao reported the synthesis of ligand **1479** as a porphyrin mimic and subsequently utilized it in the Mn-catalyzed asymmetric epoxidation of alkenes **1499** (Scheme 444). This methodology was applied to a range of alkenes

Scheme 444. Mn-Catalyzed Enantioselective Epoxidation of Alkenes

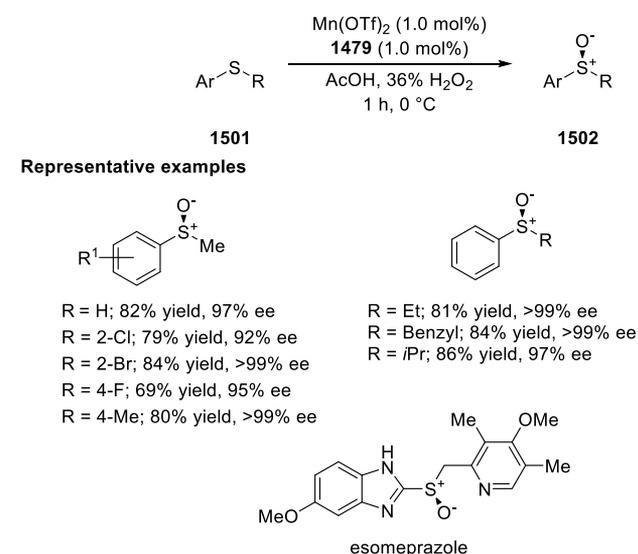


1499 forming the product **1500** in up to 95% yield and >99% ee.⁵⁴⁷ In a follow up publication this methodology was further developed to include a wider substrate scope of cyclic and acyclic alkenes **1499**.⁵⁴⁸

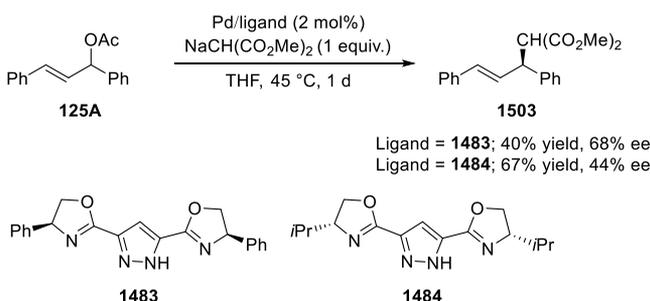
Ligand **1479** was further used by Gao in the Mn-catalyzed asymmetric oxidation of aryl sulfides **1501**. This methodology encompassed a large substrate scope with all aryl methyl sulfides **1501** affording the product **1502** in up to 84% yield and >99% ee (Scheme 445). This methodology was expanded in a subsequent publication and transferred from a batch reaction to a flow set up. This allowed for quicker reactions, the lowering of catalyst loading from 1.0% to 0.5% and for a gram scale synthesis of chiral sulfoxides.^{549,550}

Meyer reported the synthesis of a pyrazole-bridged bis-(oxazoline) ligands **1483/1484** and their application in the Pd-catalyzed allylic alkylation of 1,3-diphenylallyl acetate **125A** (Scheme 446). Interestingly, the active Pd-complex was shown to be a dinuclear palladium species with ligands **1483/1484**. While all Pd complexes of ligands **1483/1484** yielded the

Scheme 445. Mn-Catalyzed Enantioselective Epoxidation of Sulfides



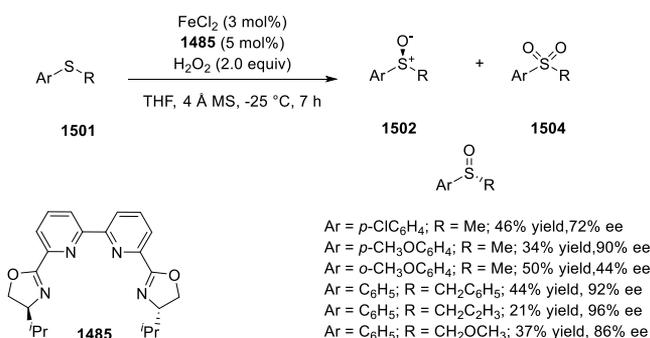
Scheme 446. Pd-Catalyzed Enantioselective Allylic Alkylation



desired product **1503** there was a large variation in the levels of enantioselectivities observed, the phenyl-substituted ligand **1483** gave the product in 40% yield and 68% ee while **1484** did so in 67% yield and 44% ee.⁵⁵¹

In 2017 Ollevier reported the asymmetric oxidation and tandem kinetic resolution of aryl sulfides **1501** to sulfoxides **1502** (Scheme 447). Ligand **1485** was chosen as a porphyrin mimick creating a bioinspired nonhaem Fe^{II} catalyst with FeCl₂. This system was employed and furnished the products in up to 96% ee and 21% yield. This catalysis was shown to be highly sensitive to the nature of the aryl substituents on the

Scheme 447. Fe-Catalyzed Asymmetric Oxidation of Aromatic Sulfides



aryl sulfides. Placing a methyl group in the *ortho*-position drastically diminished the enantioselectivity to 44% ee and 50% yield.⁵⁵²

5. TRIS(OXAZOLINE) AND TETRA(OXAZOLINE) LIGANDS

5.1. Tris(oxazoline) Ligands

Tang, one of the key pioneers in the design, synthesis and applications of metal complexes of trisoxazolines, developed a library of pseudo-C₃-symmetric trisoxazolines **1505**–**1507** (TOX; Figure 80) by a “side arm” approach. The metal

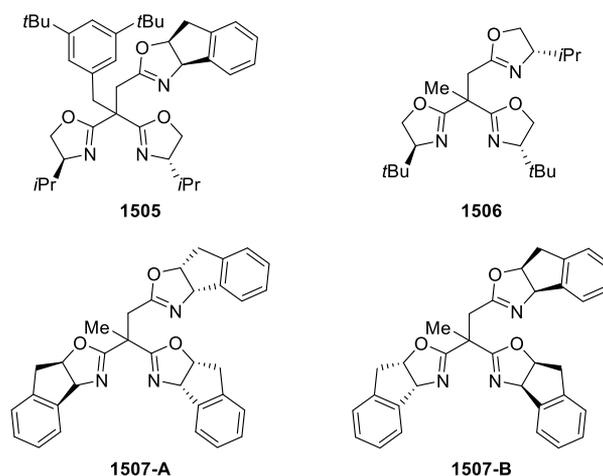
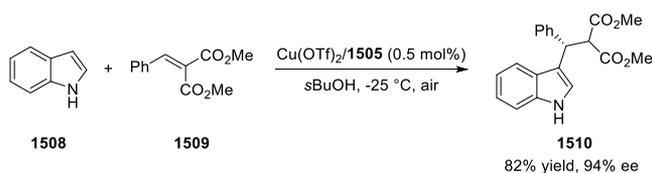
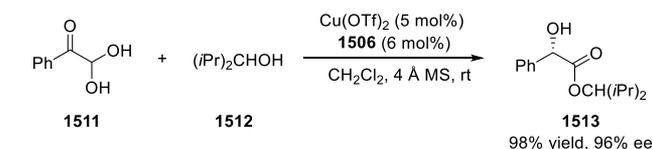


Figure 80. Trisoxazoline ligands (TOX).

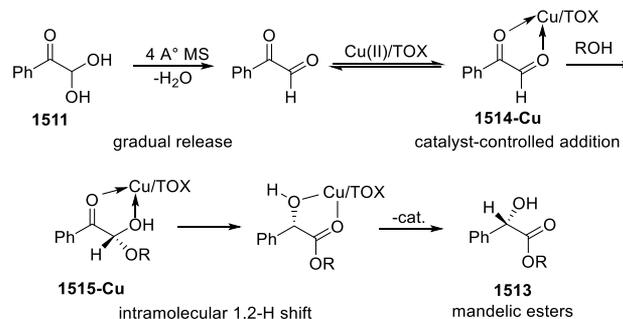
Scheme 448. Asymmetric Friedel–Crafts Alkylation between Indoles and Pyrroles and Alkylidene Malonates



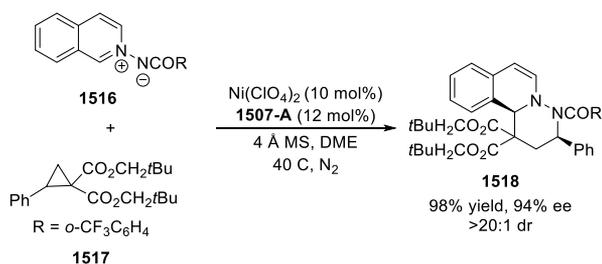
Scheme 449. Asymmetric Intramolecular Cannizzaro Reaction of Aryl and Alkyl Glyoxals with Alcohols



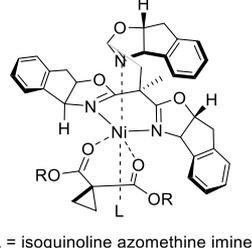
Proposed mechanism



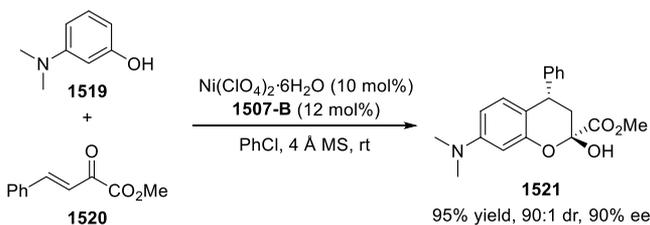
Scheme 450. Ni/In-TOX-Catalyzed Highly Enantioselective Asymmetric [3 + 3] Cycloaddition



Coordination model of Ni(II)/TOX complex



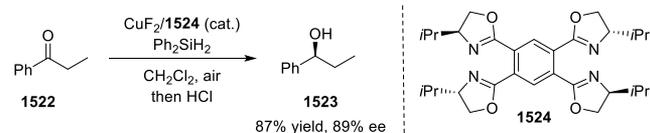
Scheme 451. Ni(II)/TOX-Catalyzed Asymmetric Oxa-[3 + 3]-annulation



complexes of TOX ligands **1505**–**1507** were found to be efficient catalysts for the asymmetric Friedel–Crafts reaction of indole with alkylidene malonate, the asymmetric intramolecular Cannizzaro reaction of aryl and alkyl glyoxals, the asymmetric [3 + 3] cycloaddition of donor–acceptor (D-A)-substituted cyclopropane diesters with aromatic azomethine imines and the asymmetric oxa-[3 + 3]-annulation of oxygenated phenols and 3-aminophenols with β,γ -unsaturated α -keto esters. Compared with the corresponding bisoxazoline ligands, these metal-TOX complexes showed some promising properties, such as better enantioselectivity and stronger tolerance toward water and air.

In 2011, Tang reported a new pseudo-C₃-symmetric heterotrisoxazoline (**1505**), which in combination with

Scheme 452. D₂-Symmetrical Chiral Tetraoxazoline Ligand for Asymmetric Hydrosilylation



Proposed transition state

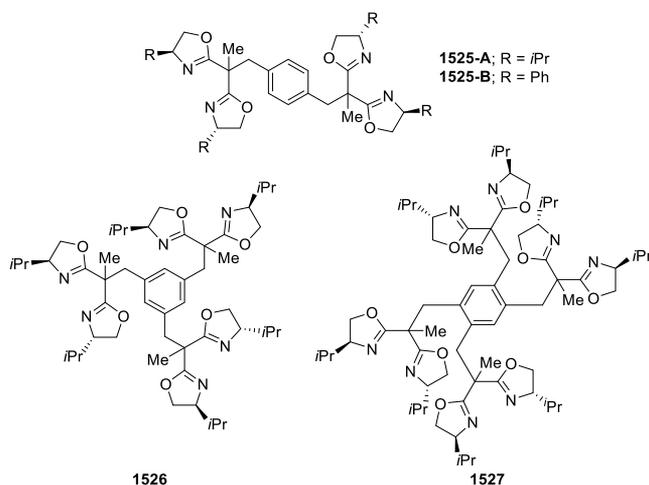
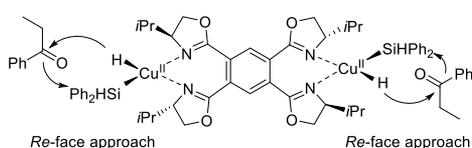
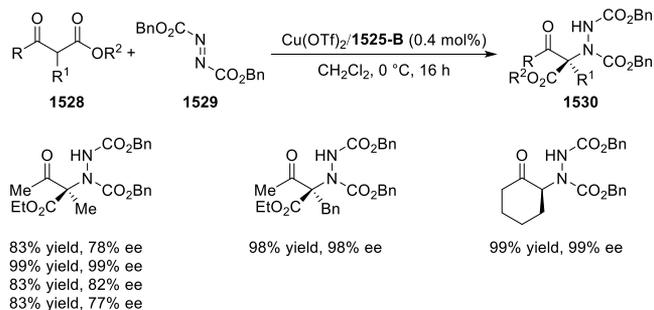


Figure 81. Recyclable oxazoline catalysts.

Cu(OTf)₂ displayed excellent enantioselectivity in the asymmetric Friedel–Crafts alkylation between indoles (**1508**) and pyrroles and alkylidene malonates (**1509**) (Scheme 448).⁵⁵³ Enantioselectivities of up to 94% ee were achieved with only 0.5 mol% of catalyst loading.

Later in 2013, the first asymmetric intramolecular Cannizzaro reaction of aryl and alkyl glyoxals (**1511**) with alcohols (**1512**) was reported with excellent levels of enantioselectivity by using a newly developed congested TOX ligand (**1506**) and Cu(OTf)₂ with a gradual liberation protocol of active glyoxals from glyoxal monohydrates (**1511**) (Scheme 449).⁵⁵⁴ This method allowed a facile entry to the preparation of a variety of α -hydroxy carboxylic acid derivatives (**1513**) with high optical purity (up to 96% ee). The proposed reaction pathway suggested that the chiral induction occurred at the catalyst-controlled face selective addition of alcohols to coordinated glyoxals. The improved stereocontrol with the TOX ligand **1506** over the addition of the alcohol to **1515-Cu** could be described in terms of a more congested environment created around the reactive site with the aid of the extra *t*-butyl oxazoline, while the more typical bisoxazoline (BOX) ligands lack such a side arm regulator.

Scheme 453. Asymmetric α -Hydrazination of β -Keto Esters



In 2013, Tang reported the Ni/In-TOX (**1507-A**)-catalyzed highly enantioselective asymmetric [3 + 3] cycloaddition of donor–acceptor (D–A)-substituted cyclopropane diesters (**1517**) with aromatic azomethine imines (**1516**) (Scheme 450).⁵⁵⁵ A variety of 6,6,6-tricyclic dihydroisoquinoline derivatives (**1518**) were synthesized in up to 98% yields with

Chart 1. Master List of Ligands

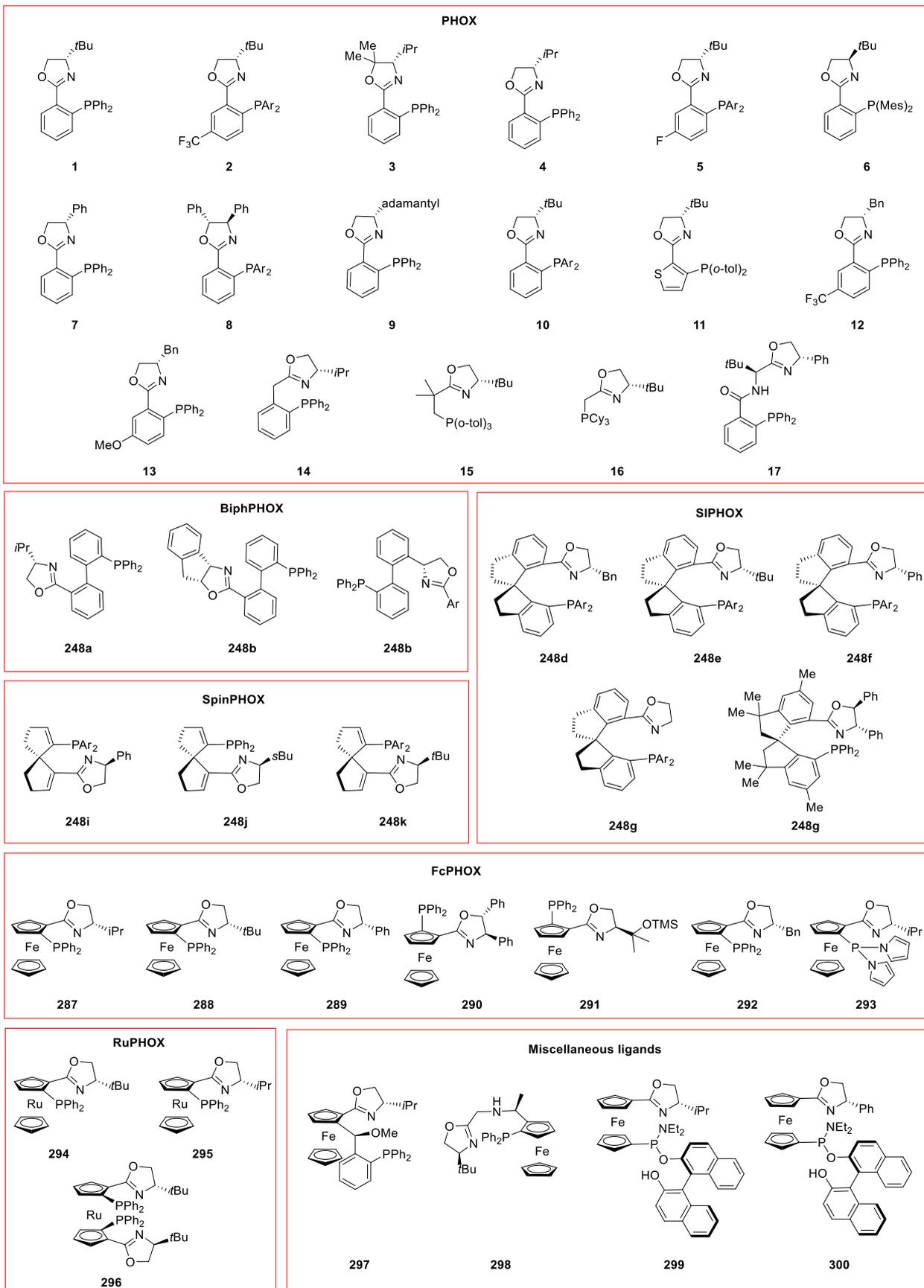
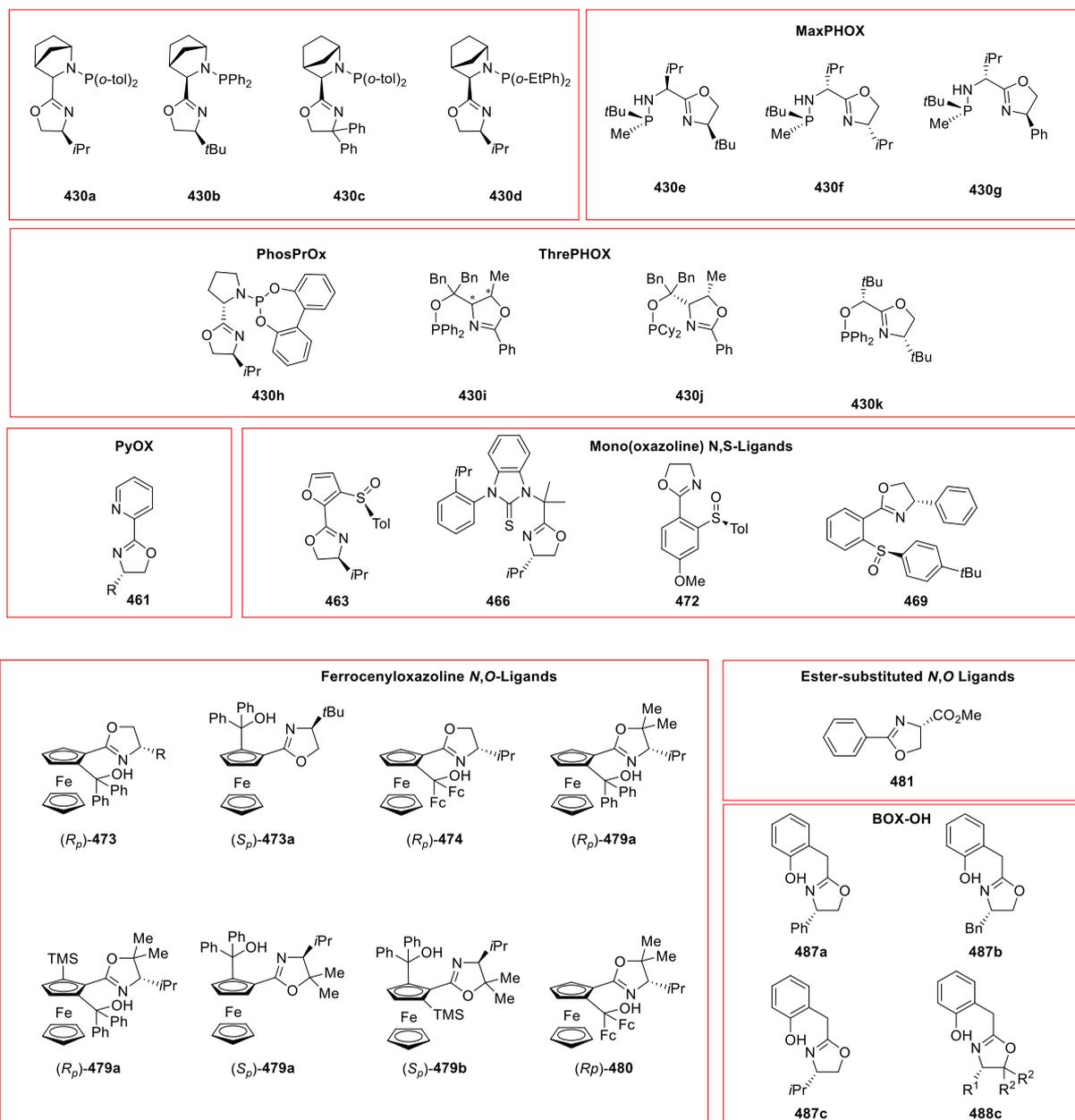


Chart 1. continued



excellent diastereo- and enantioselectivities (>20:1 dr and up to 94% *ee*). Preliminary results and DFT studies suggested that the π - π interaction between the indane group of the ligated side arm and the phenyl group of the cyclopropane plays a vital role in the control of enantioselectivity. On the basis of computational studies, the optimized model of Ni(II)/TOX (**1507-A**) was proposed to be a six-coordinate Ni(II) complex with one molecule of isoquinoline azomethine imine coordinating to the Ni center.

In 2018, the first Ni(II)/TOX-catalyzed asymmetric oxa-[3 + 3]-annulation of oxygenated phenols and 3-aminophenols (**1519**) with β,γ -unsaturated α -keto esters (**1520**) was disclosed (Scheme 451).⁵⁵⁶ This method allowed a rapid access to a variety of oxygenated and 7-aminated chromans (**1521**) in excellent yields (up to 95%) with excellent diastereoselectivities (90:1 dr) and enantioselectivities (up to 90% *ee*). The improved functionality tolerance was attributed

to the probable interference of the oxazoline side arm with the coordination of the amino group to the catalyst. Also of note Tang applied the aforementioned TOX ligands in other chemistries such as the asymmetric Nazarov reaction, the enantioselective ring-opening of cyclopropanes and the asymmetric [4 + 3] annulation reaction.^{557–560} Greater detail of TOX ligands and side arm modification strategies for bis(oxazoline) ligand design has been discussed by Tang in the 2014 account.⁵⁶¹

5.2. Tetra(oxazoline) Ligands

In 2010, Li reported a novel D_2 -symmetrical chiral tetraoxazoline ligand (**1524**) and applied it in a Cu-catalyzed asymmetric hydrosilylation of aromatic ketones (**1522**) with diphenylsilane to give optically active secondary alcohols (**1523**) (Scheme 452).⁵⁶² The chiral catalyst showed excellent activities and enantioselectivities in the hydrosilylation of aryl ketones

Chart 1. continued

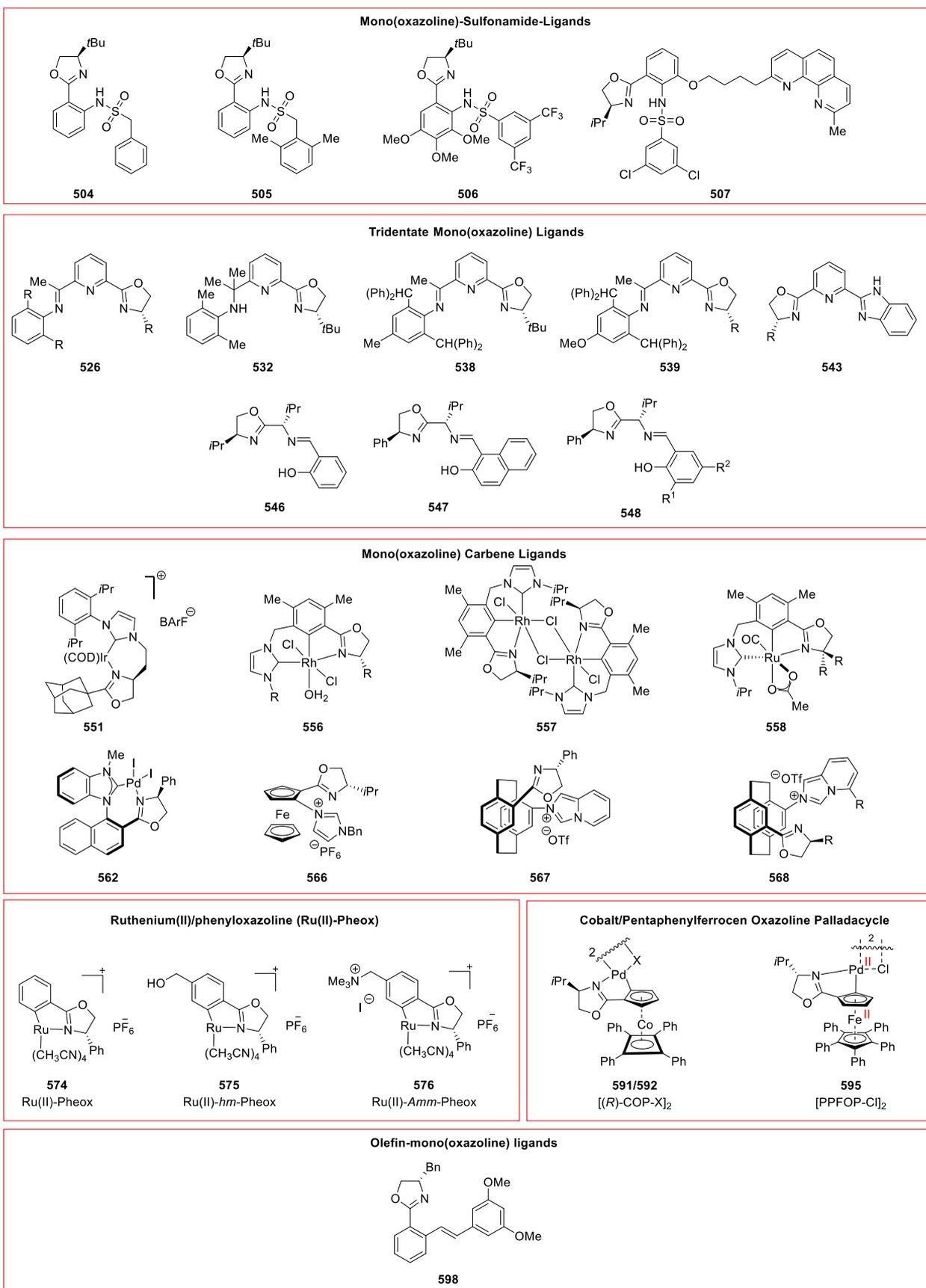


Chart 1. continued

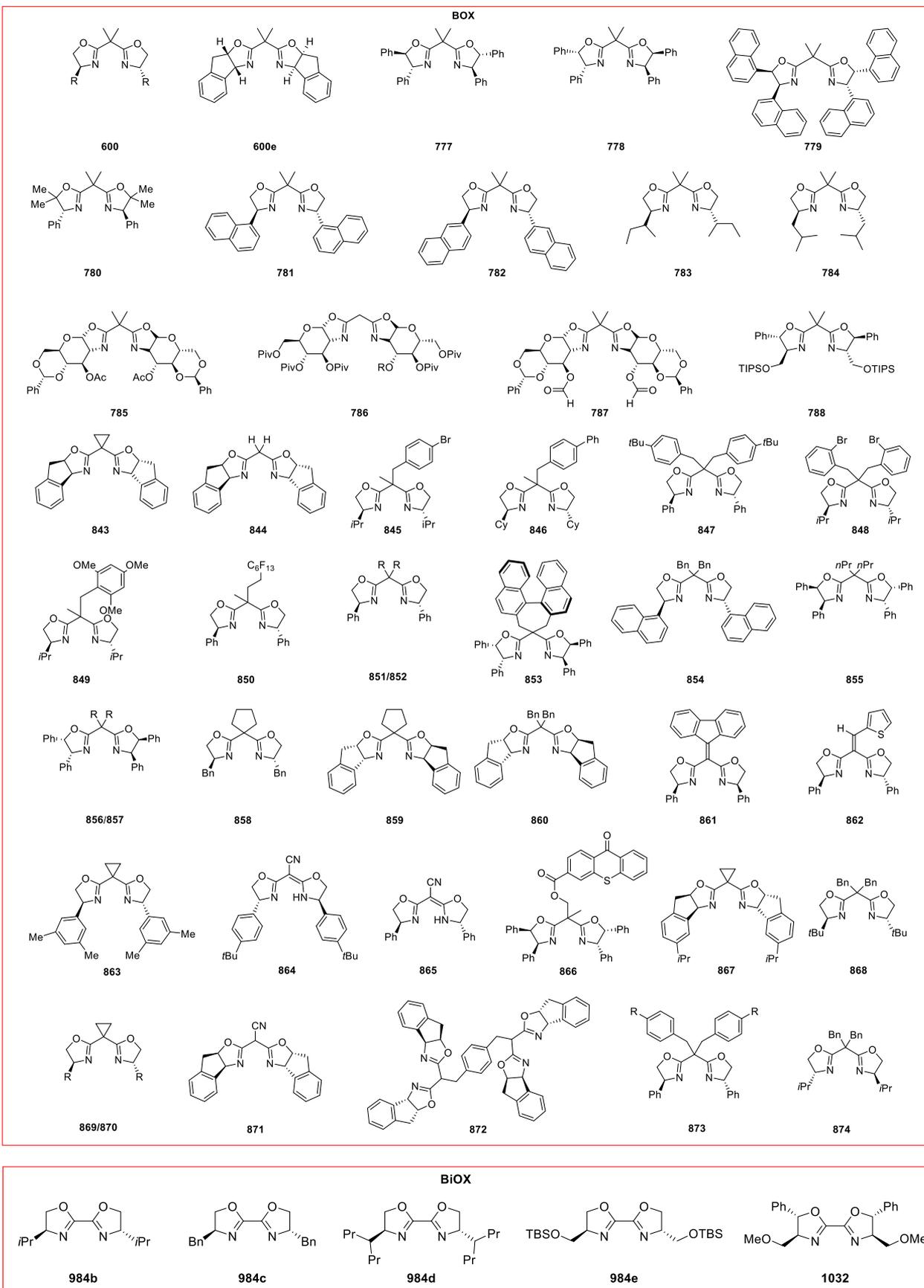


Chart 1. continued

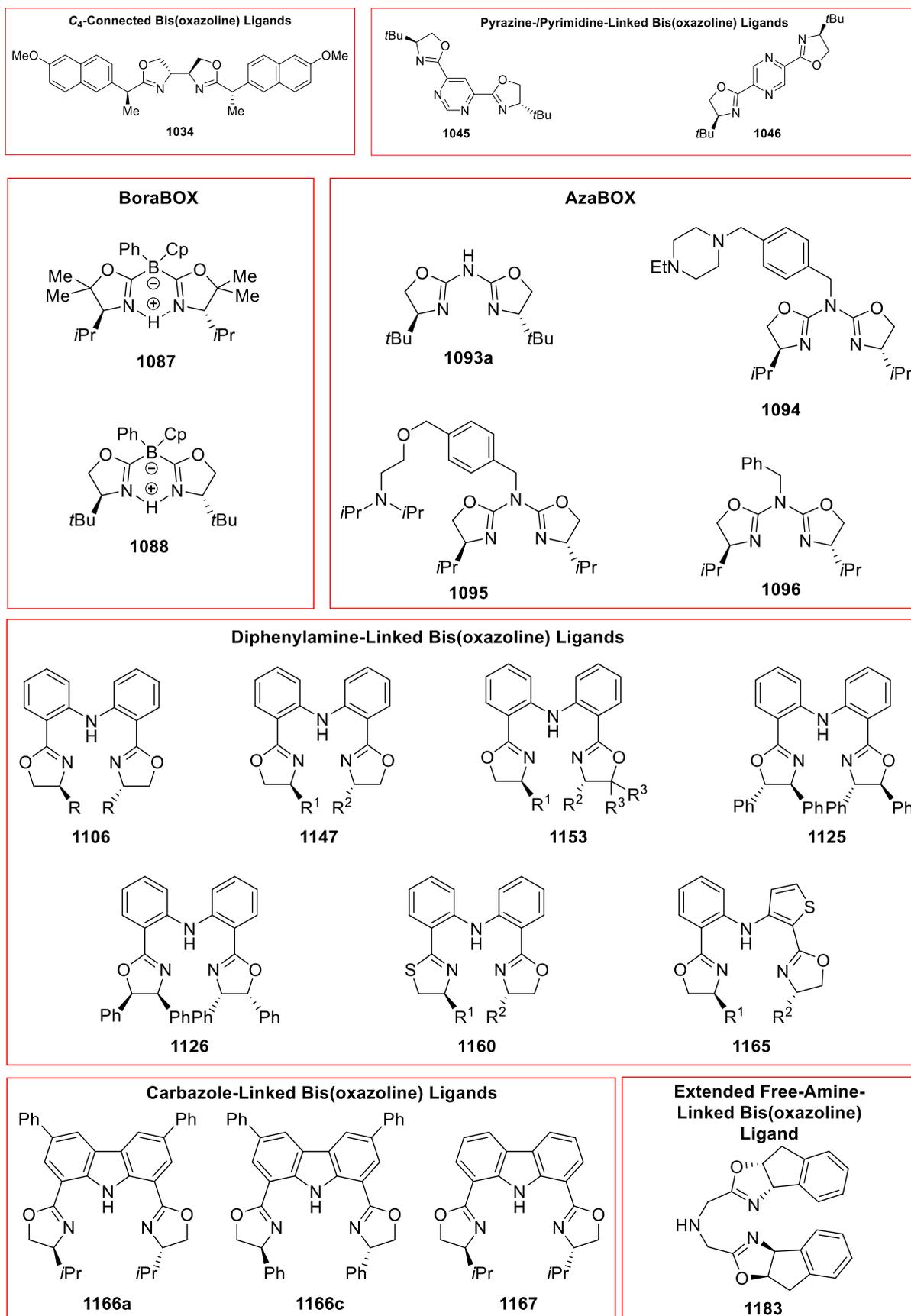
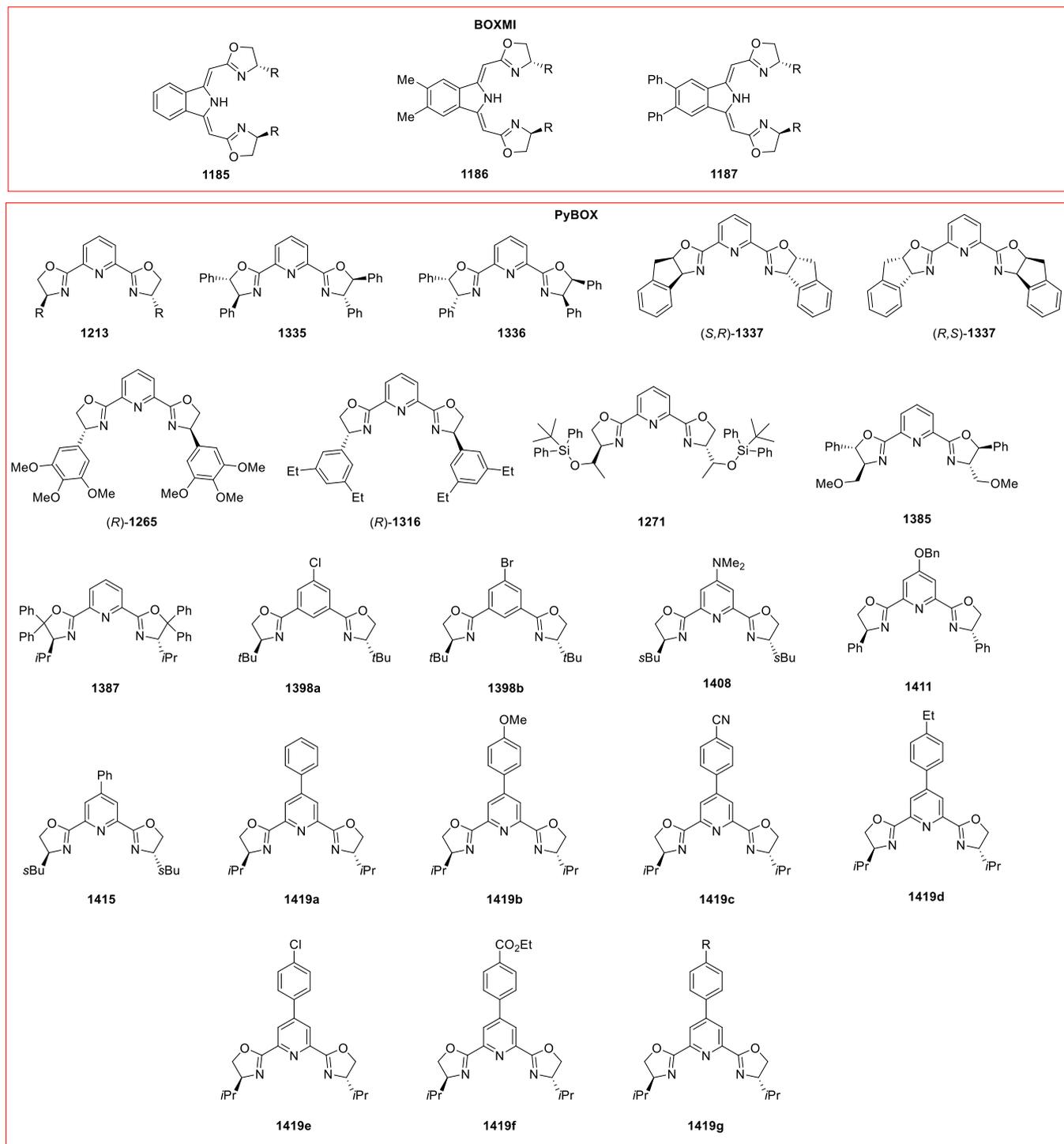


Chart 1. continued



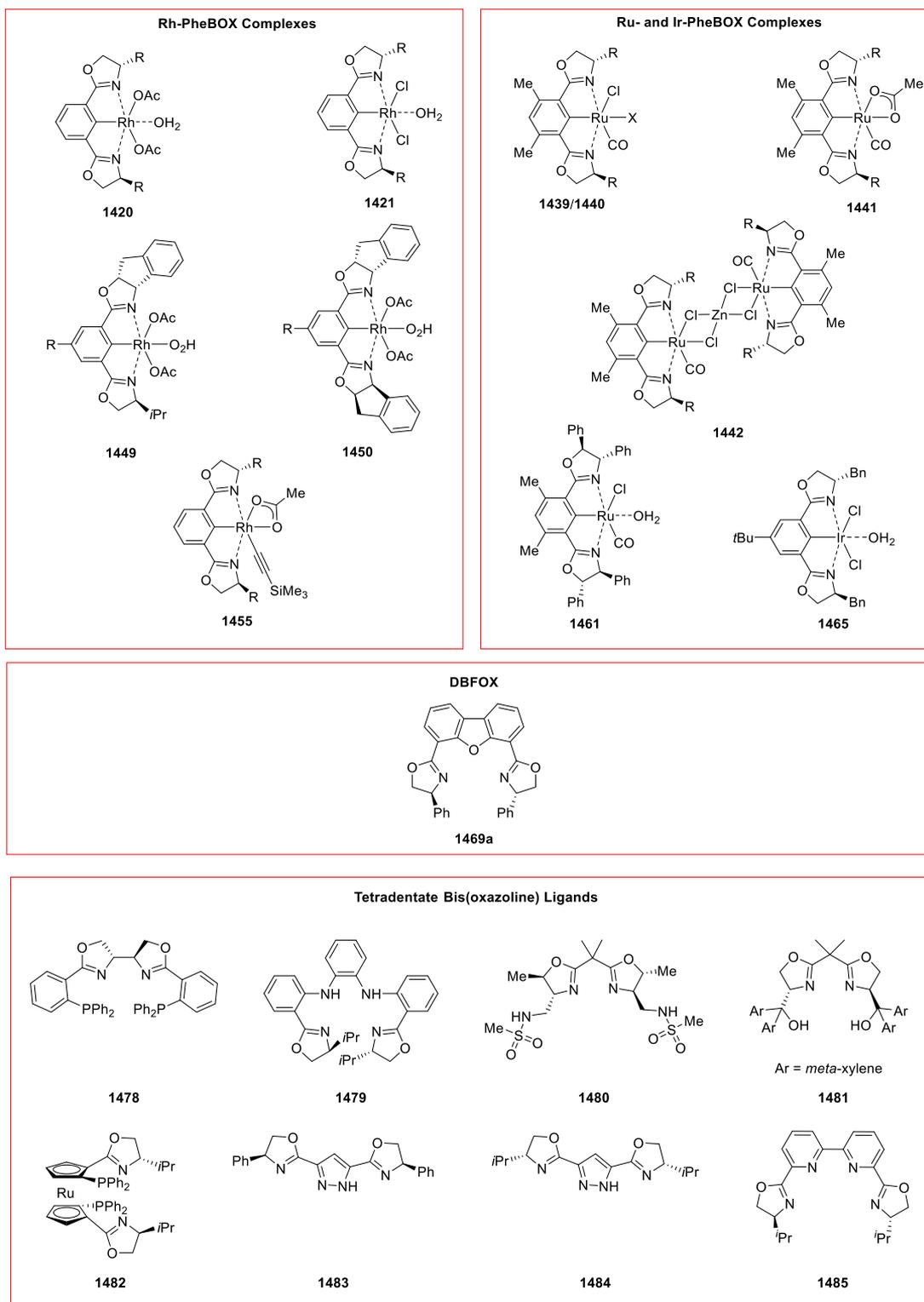
(1522) with up to 89% *ee*. A transition state model was proposed wherein diphenylsilane could only approach the *Re*-face of the aromatic ketones due to steric hindrance leading to the (*S*)-absolute configuration observed for all secondary alcohol products.

Bellemin-Laponnaz reported the synthesis and application of self-supported recyclable oxazoline catalysts **1525–1527** (Figure 81) in the α -hydrazination of β -keto esters **1535**.

Di-, tri- and tetratopic ligands bearing isopropyl substituents **1525-A**, **1526**, and **1527** were synthesized and screened in the α -hydrazination of β -keto esters **1528**, while enantioselectiv-

ities were similar (78–82% *ee*), it was shown that the recyclability of the ligands varied greatly. After five catalytic runs ditopic tetraoxazoline ligand **1525-A** gave the product **1530** in 83% *ee* and 87% yield, tritopic hexaoxazoline ligand **1526** afforded the product in 38% *ee* and <5% yield and tetratopic octaoxazoline ligand **1527** did not give rise to the product **1530** at all. Catalysts were recycled by a solvent swap which allowed them to be decanted from the reaction mixture. It was thought that during the solvent swap Cu was leading to the reduced results for the tri- and tetratopic ligands. When a substrate scope was carried out with **1525-B** enantioselectiv-

Chart 1. continued



ities of up to 99% *ee* and 99% yield were achieved with up to 10 catalytic runs possible with recycled catalysts (Scheme 453).⁵⁶³

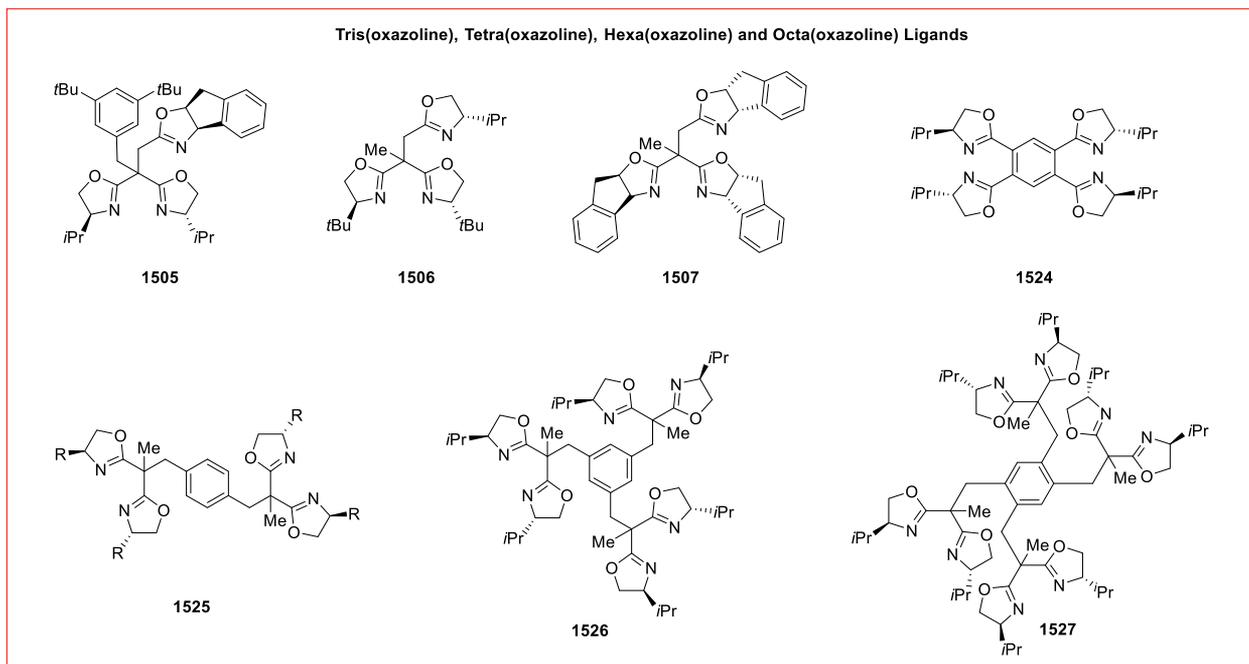
6. CONCLUSION

This Review reports on further developments in the design and application of oxazoline-derived ligands in asymmetric catalysis

over a 10-year period since 2009, when the area was previously reviewed by us.

The exceptionally wide utility of this ligand class in catalytic asymmetric synthesis has continued to be illustrated by the high levels of asymmetric induction in a variety of metal-catalyzed transformations in the review period. Many of the tried and trusted oxazoline-containing ligands like PHOX, BOX, and PyBOX continue to be applied with success to new

Chart 1. continued



transformations, and there are few examples where the levels of enantioselectivities obtained do not reach 99% *ee*. Variation in the ligand structures mainly relies upon small changes to well-established motifs with additional steric or electronic features being modified. Such structural changes to the parent ligands have been aided by mechanistic, spectroscopic, X-ray crystallographic, and computational studies. While there has been a considerable renaissance in metalla-photoredox and metalla-electrocatalysis in recent times, the combination of these methods with metal-catalyzed asymmetric synthesis has remained limited. As society moves toward increased sustainability, organic chemists must keep up, and there is considerable scope for adapting the privileged oxazoline motifs described in this Review to photoredox- and electrocatalytic methodologies. In a similar vein, we have seen a shift toward the development of catalysts based around the earth-abundant 3d transition metals such as cobalt and nickel. 3d Transition metals have been shown to have similar and, in some cases, superior reactivities compared to their more unsustainable, expensive and toxic late-transition-metal counterparts like palladium and rhodium. We hope to see considerable progress in 3d-transition-metal-catalyzed asymmetric synthesis in the coming years, and the use of oxazoline-based ligands in these transformations is a challenge that is just beginning to be addressed.

Although this Review highlights extensive research in the design, synthesis, and application of oxazoline-derived ligands, this topic is far from being exhausted and it is hoped that this Review will again stimulate both the development/design of new ligands and their applications in novel metal-catalyzed asymmetric transformations.

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Notes

The authors declare no competing financial interest.

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Robert Connon received his B.Sc. in Chemistry from University College Dublin in 2015. He was then awarded his Ph.D. degree in 2020, also from University College Dublin, under the supervision of Prof. Pat Guiry. He is currently working as a postdoctoral researcher with Prof. Dr. Lutz Ackermann in the Georg-August-Universität Göttingen, Germany. His current research is focussed on the development of sustainable and asymmetric C–H activation methodologies.

Brendan Roche received his B.Sc. from the University College Dublin in 2015 in Chemistry. He was awarded his Ph.D. degree in 2020 from University College Dublin under the supervision of Prof. Pat Guiry.

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Patrick J. Guiry was born in County Tipperary and studied at University College Dublin (UCD), B.Sc. 1986 and Ph.D. 1990, with Professor Dervilla Donnelly and Professor Sir Derek Barton as Ph.D. supervisors. He carried out postdoctoral research in asymmetric catalysis with John M. Brown FRS (Oxford University). He joined UCD in 1993 and is currently the Director of the CSCB and Full Professor of Synthetic Organic Chemistry since 2006. His research interests include the design, synthesis, and application of novel ligands in asymmetric catalysis, natural product synthesis, and medicinal chemistry. He has supervised 56 Ph.D. students to graduation to date. He was elected a Member of the Royal Irish Academy in 2013 and is an elected member of the UCD Governing Authority and of the Senate of the National University of Ireland. He was the Science Secretary of the Royal Irish Academy from 2016–2020 and is the Vice President of the Institute of Chemistry in Ireland from 2019–present. He was recipient of the Institute of Chemistry of Ireland's Boyle-Higgins Medal in 2014 and the Science Foundation Ireland Mentorship Award in 2020. A keen tennis player, with 18 Irish national titles, he was selected to represent Ireland in 2020 in the Austria Cup (ITF World Team Competition) in Florida, which was unfortunately canceled due to COVID-19.

ACKNOWLEDGMENTS

This publication has emanated from research conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by Science Foundation Ireland (SFI) under Grant No. 12/RC/2275. B.V.R. is grateful for the award of a BiOrbic (Bioeconomy Research Centre) postdoctoral fellowship (16/RC/23889). B.V.R. also thanks the Irish Research Council (IRC) for the award of a postdoctoral fellowship (GOIPD/2015/453).

DEDICATION

Dedicated with respect and admiration to Dr. John Brown FRS, on the occasion of his 80th birthday, and with whom P.J.G. made his first bis(oxazoline) ligand in 1991.

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