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Binaphthyl Scaffold: A Class of Versatile Structure in Asymmetric C−H Functionalization

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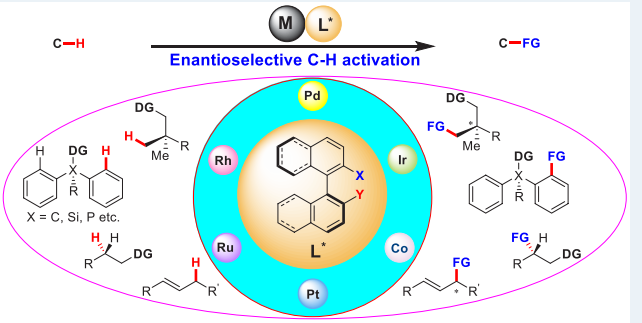
ABSTRACT: Over the past decades, transition metal-catalyzed enantioselective C−H functionalization has emerged as a straightforward and powerful tool for the rapid access to chiral molecules. The enormous advances achieved in this emerging area largely rely on the development of chiral ligands that can enable both high levels of enantiocontrol and efficiency. Chiral ligands bearing binaphthyl scaffolds have been proven to be versatile in asymmetric C−H functionalization due to their availability, unique stereochemical features, and ease of fine-tuning steric and electronic properties. In this Review, we summarized the advance in the applications of chiral ligands on the basis of the binaphthyl scaffold in asymmetric C−H functionalization.



KEYWORDS: *asymmetric C−H activation, binaphthyl scaffold, chiral ligand, transition metal, enantioselectivity*

1. INTRODUCTION

The development of efficient approaches to access enantiopure compounds has stimulated great interest in asymmetric synthesis.[1−3] Over the past decades, transition metal-catalyzed enantioselective C−H activation has emerged as a novel strategy to enrich the synthetic disconnections of organic molecules to desirable enantiomers.[4−11] The greatest hindrance to asymmetric C−H functionalization is to find a suitable catalytic system for the control of chemo- and stereoselectivity. To this end, the chiral ligands that bind to transition metals to provide the steric and electronic environment in the C−H activation process are crucial.

In recent years, enormous progress of transition metal-catalyzed enantioselective C−H activation reactions have been achieved by the employment of different chiral ligands. Several different types of chiral ligands have been developed for asymmetric C−H activation (Figure 1). For example, mono-*N*-protected amino acids (MPAAs), prepared from commercially available amino acids, could serve as the efficient chiral ligands in Pd(II)-catalyzed enantioselective C−H functionalization.[12−14] Naturally occurring amino acids could be used directly as catalytic transient chiral auxiliaries with aldehyde substrates to form the imine directing groups *in situ*, delivering the chiral aldehydes in high yields and high enantioselectivities.[15,16] Chiral cyclopentadienyl motifs (Cp^x), as an important and unique

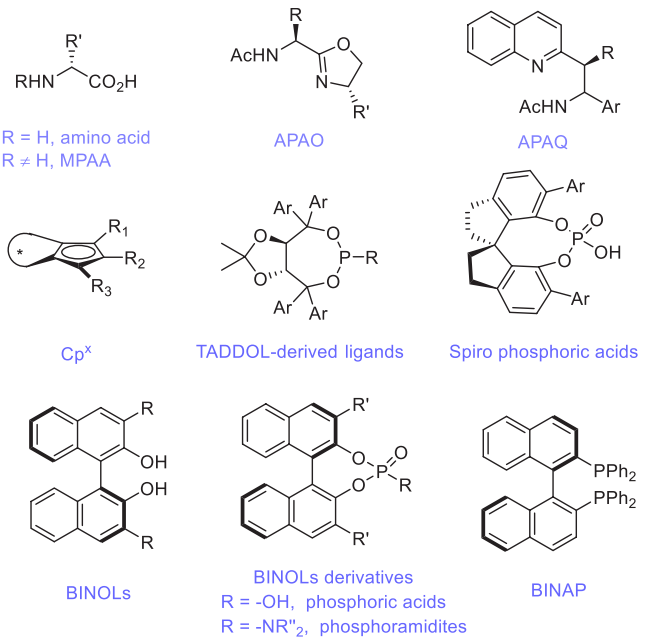


Figure 1. Selected privileged chiral ligands for asymmetric C−H activation.

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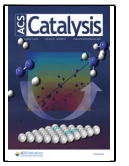

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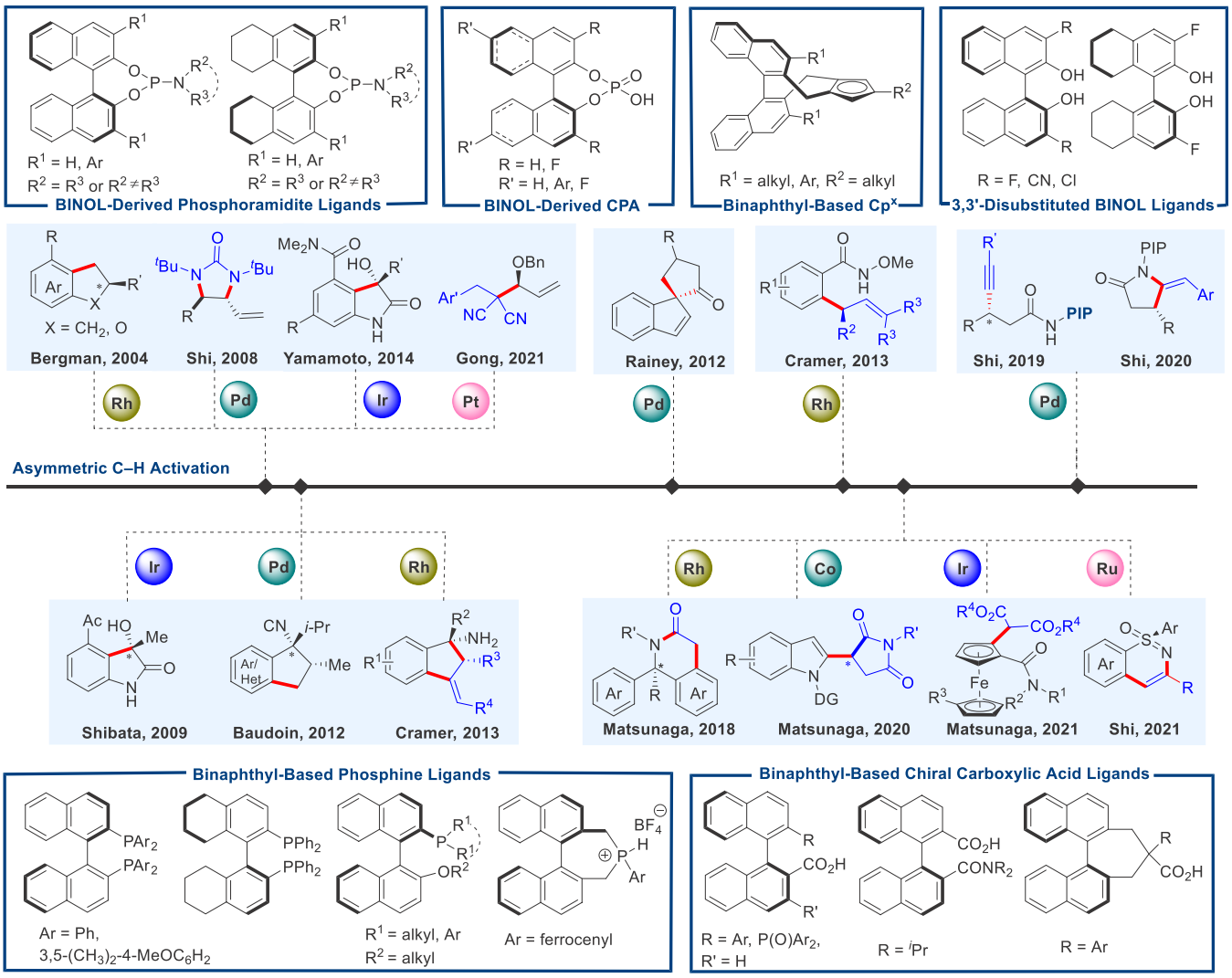

Figure 2. Timeline of the development of chiral binaphthyl scaffold chiral ligands in transition metal-catalyzed asymmetric C−H activation.

catalogue of chiral ligands to bind with transition metals, have also been demonstrated to be applicable to a broad range of transformations on the basis of enantioselective C−H activation.[17−19] At the same time, some new chiral ligands that can offer high levels of efficiency and enantiocontrol were prepared by the elaboration of the above-mentioned architectures. By fine-tuning the core structure of the MPAA ligands, the Yu group[20,21] designed various related bifunctional ligands such as acetyl-protected aminoethyl quinoline (APAQ) and *N*-acyl-protected aminomethyl oxazoline (APAO). Many other commonly used chiral ligands in other asymmetric syntheses have also been broadly used in asymmetric C−H activation reactions, such as TADDOL-derived phosphines, spiro phosphoric acids, BINOLs and their derived phosphoric acids and phosphoramidites, and 2,2′-diphenylphosphino-1,1′-binaphthyl (BINAP).[22,23]

Axially chiral binaphthyl compounds, such as BINAP, BINOLs, and their derivatives, have been recognized as favored ligands due to their wide applications in asymmetric catalysis.[24−26] Especially, chiral 1,1′-binaphthyl backbones can be modified by the introduction of substituents within the framework, thereby influencing both the steric environment and electronic properties of the ligands toward asymmetric transformations. With the development of asymmetric C−H functionalization, binaphthyl chiral ligands show their potential as promising chiral ligands in the enantioselective transformation of C−H bonds. In this Review, we summarized the advances of transition metal-catalyzed asymmetric C−H activation reactions using chiral ligands on the basis of binaphthyl scaffolds by the end of 2021. It was categorized into six parts according to the type of binaphthyl chiral ligands: (i) BINOL-derived phosphoramidites; (ii) binaphthyl-based phosphine ligands; (iii) BINOL-derived phosphoric acids; (iv) binaphthyl-derived chiral cyclopentadienyl ligands; (v) binaphthyl-based chiral carboxylic acids; (vi) 3,3′-disubstituted BINOLs (Figure 2). Some related chiral auxiliaries based on hydrogenated binaphthyl backbones such as H_8−BINOL and H_8−BINAP were also discussed. Notably, trivalent group 9 metal complexes ligated with a binaphthyl-type chiral cyclopentadienyl (Cp^x) ligand have been well explored in enantioselective C−H functionalization, pioneered by Cramer and co-workers.[27−29] A general overview of this type of ligand according to the chiral $Cp^xM(III)$ complexes was also summarized in Section 7 of this Review.

2. BINOL-DERIVED PHOSPHORAMIDITE LIGANDS

In 2000, Feringa and co-workers reported a rhodium(I)-catalyzed asymmetric hydrogenation reaction of dehydroamino

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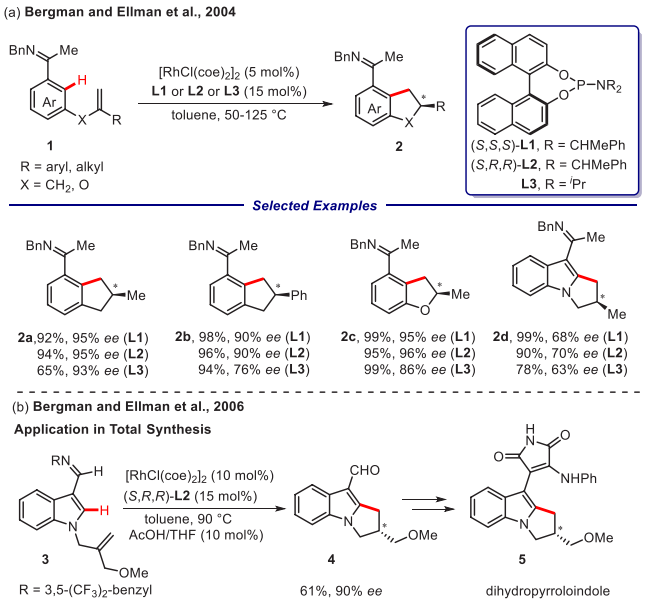
Scheme 1. (a) Rhodium-Catalyzed Enantioselective Intramolecular C(sp²)−H Cyclization of Aromatic Imines; (b) Enantioselective Synthesis of a Bioactive PKC Inhibitor

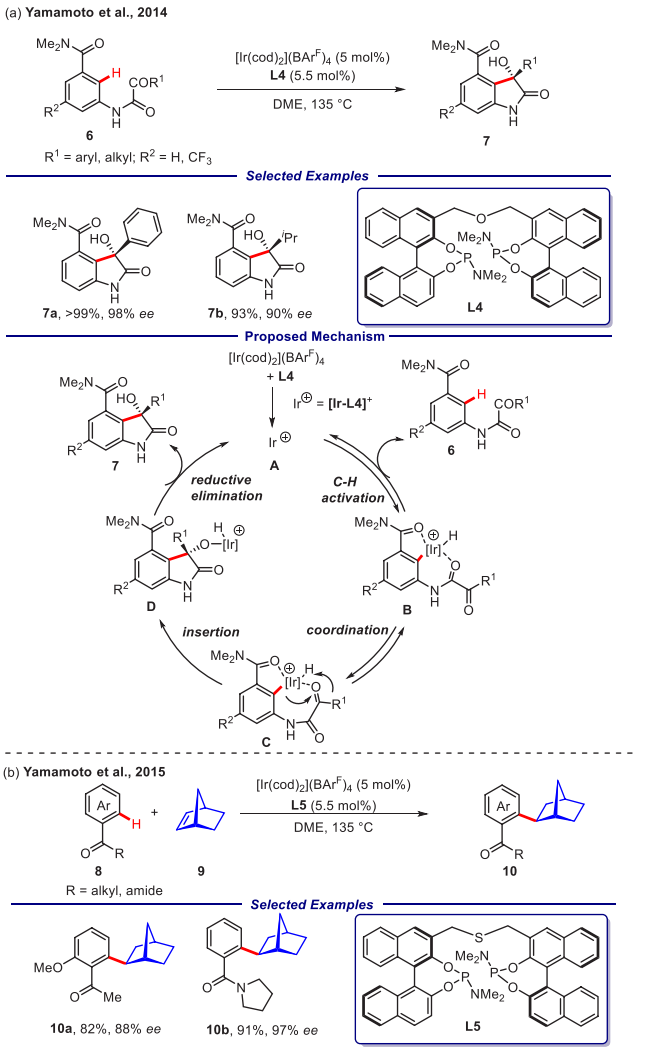


acids and itaconic acids.[30] In this catalysis, the BINOL-derived phosphoramidite ligand was employed as a ligand, which exhibited a faster reaction rate and better enantioselectivity than the corresponding bidentate ligand. Soon after, this type of BINOL-derived phosphoramidite ligand was successfully applied in Rh-, Ru-, and Ir-catalyzed asymmetric hydrogenation of olefins, ketones, and imines.[31,32] Apart from the hydrogenation reaction, the application of such ligands in enantioselective C−H activation has been well established. In this section, the relative works will be thoroughly and extensively discussed.

BINOL-derived phosphoramidite ligands were first employed in asymmetric C(sp²)−H functionalization. In 2004, Bergman and co-workers reported the rhodium-catalyzed enantioselective intramolecular C(sp²)−H cyclization assisted by an imine directing group (DG) using a BINOL-derived phosphoramidite ligand (Scheme 1a).[33] The optimal ratio of chiral ligand/Rh is 1.5 or 1, indicating that the active catalyst contains only one BINOL-derived phosphoramidite ligand. Moreover, the authors proposed that the improved reaction rate with BINOL-derived phosphoramidite ligand was due to their reduced σ donation and enhanced π acceptor ability. In a following study, this catalysis provided an efficient way to get access to the key intermediate (**4**) used for the synthesis of dihydropyrroloindole **5** (Scheme 1b).[34]

In 2014, Yamamoto and co-workers used an O-linked bidentate BINOL-derived phosphoramidite ligand **L4** for iridium-catalyzed highly enantioselective intramolecular hydroarylation of α-ketoamides **6** (Scheme 2a).[35] A proposed reaction mechanism was described. Intermediate **B** was generated by C−H activation of ketoamides **6** and subsequent insertion of the carbonyl group into the aryl−Ir bond, producing intermediate **D**. Finally, cyclized product **7** was obtained by reductive elimination of intermediate **D** and the regeneration of the active iridium species **A**. Apart from using BINOL-derived phosphoramidite ligands to achieve asymmetric intramolecular cyclization reactions, these chiral ligands could also be applied to intermolecular versions. In 2015, the Yamamoto group extended

Scheme 2. (a) Iridium-Catalyzed Enantioselective Intramolecular Hydroarylation of Ketones; (b) Iridium-Catalyzed Enantioselective Intermolecular Hydroarylation of Bicycloalkenes



this methodology to the enantioselective intermolecular hydroarylation of bicycloalkenes using S-linked bidentate BINOL-derived phosphoramidite ligand **L5** (Scheme 2b).[36] A broad range of chiral hydroarylated products were obtained in good yields and high enantioselectivities. The S-linked bidentate BINOL-derived phosphoramidite ligand was demonstrated to be key for the enhancement of enantioselectivity in this transformation. Subsequently, a similar strategy was applied to accomplish asymmetric alkylation of aniline derivatives as well, giving the desired products with high yields and excellent enantioselectivities.[37]

BINOL-derived phosphoramidite ligands could also be successfully applied in asymmetric allylic C−H functionalization. In 2008, Shi and co-workers reported the palladium-catalyzed enantioselective intermolecular allylic C−H diamination of terminal olefins using H_8−BINOL-derived phosphoramidite ligand **L6** (Scheme 3a).[38] Di-*tert*-butylaziridinone was used as both the oxidant and nitrogen nucleophile. The substrates containing two terminal double bonds could be easily transformed into chiral diamination products bearing four C−N bonds in one step. It should be noted that this

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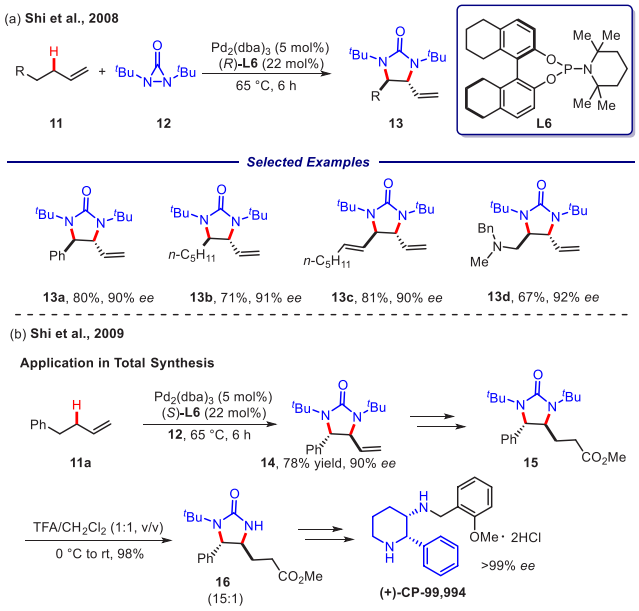
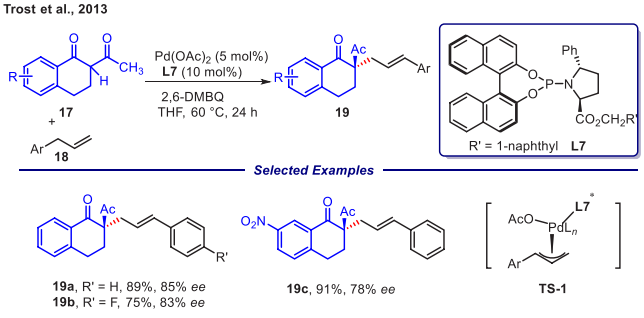
Scheme 3. (a) Palladium-Catalyzed Enantioselective Intermolecular Allylic C−H Deamination of Terminal Olefins; (b) Enantioselective Synthesis of a Bioactive (+)-CP-99,994



Scheme 4. Palladium-Catalyzed Enantioselective Allylic C−H Alkylation

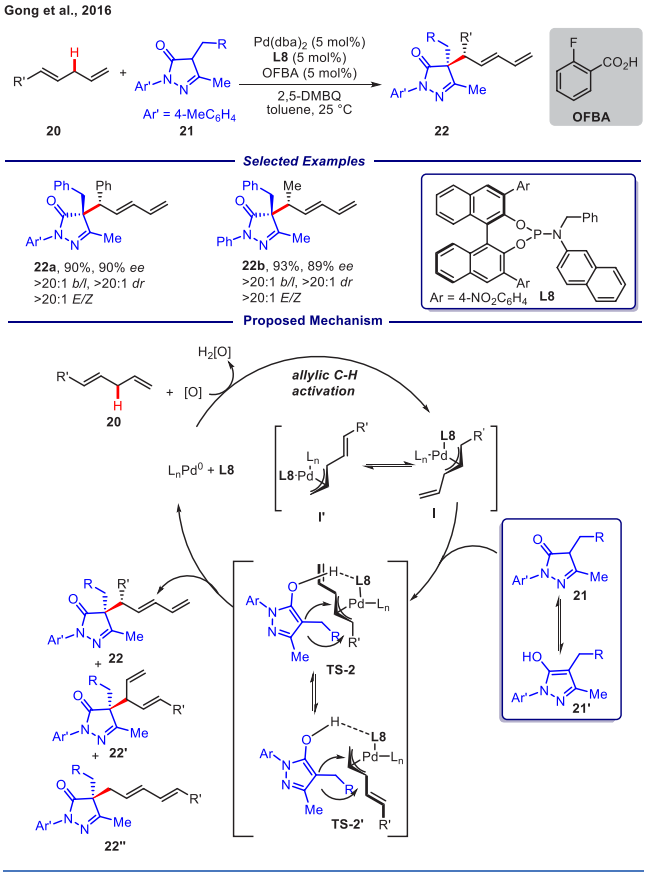


methodology was used as a key step for the synthesis of bioactive (+)-CP-99,994 (2HCl) in 20% overall yield and >99% *ee* (Scheme 3b).[39]

Palladium-catalyzed oxidative asymmetric allylic C−H activation could also be achieved using BINOL-derived phosphoramidite ligands. In 2013, Trost et al. disclosed a palladium-catalyzed enantioselective allylic C−H alkylation reaction of allylarenes (Scheme 4).[40] BINOL-derived chiral phosphoramidite ligand **L7** was demonstrated to be the best ligand in this asymmetric allylic C−H alkylation protocol. As shown in the proposed transition state **TS-1**, the chiral BINOL-derived phosphoramidite ligand **L7** was the only chiral source for enantiocontrol.

Subsequently, palladium-catalyzed asymmetric allylic C−H alkylation of 1,4-dienes **20** with pyrazol-5-ones using chiral BINOL-derived phosphoramidite **L8** as the chiral ligand was reported by the Gong group (Scheme 5).[41,42] A series of the desired chiral *N*-heterocycles with an all-carbon quaternary stereogenic center were obtained in high yields and excellent enantioselectivities. The authors proposed that two chiral vinyl (π-allyl)palladium intermediates **TS-2** and **TS-2′** might be involved, which were responsible for the formation of the

Scheme 5. Palladium-Catalyzed Enantioselective Allylic C−H Alkylation of 1,4-Pentadienes with Pyrazol-5-ones



corresponding branched products **22** and **22′** and a linear product **22′′**.

In 2018, Gong and co-workers reported a palladium-catalyzed asymmetric allylic C−H alkylation of 1,4-dienes **20** with 2,5-diarylthiazol-4(5*H*)-ones to synthesize C5-branched products using chiral BINOL-derived phosphoramidite ligand **L9** (Scheme 6a).[43] The difference in the acidity and steric hindrance of 5-substituted thiazolone could explain the different regioselectivities. 5-Alkylthiazolone was relatively less acidic and less hindered compared to 5-arylthiazolone. Therefore, it attacked the vinyl π-allyl-Pd intermediate by an outer-sphere mechanism to obtain linear products. On the other hand, 5-arylthiazolone with the higher acidity and larger steric hindrance underwent nucleophilic attack via an inner-sphere mechanism to afford the C5-branched products. Subsequently, palladium-catalyzed asymmetric allylic C−H alkylation of cyclic β-ketoesters **24** with 1,4-dienes **20** was achieved using the chiral BINOL-derived phosphoramidite ligand **L10** (Scheme 6b).[44] A broad range of the linear allylic alkylation products were obtained in good to excellent yields and high enantioselectivities. Interestingly, the asymmetric allylic C−H alkylation of 1,4-dienes **20** with azlactones **25** was revealed to provide a C5-branched product by a chiral BINOL-derived phosphoramidite **L11**/palladium catalytic system (Scheme 6c).[45] The experimental studies and DFT calculations suggested that this reaction occurred through the cleavage of allylic C−H via a concerted proton and two-electron transfer step. It should be noted that the nucleophiles are the key to determine the *Z*/*E*- and regioselectivities. In 2020, glycine Schiff bases were also used as prochiral nucleophiles in palladium-catalyzed C5-

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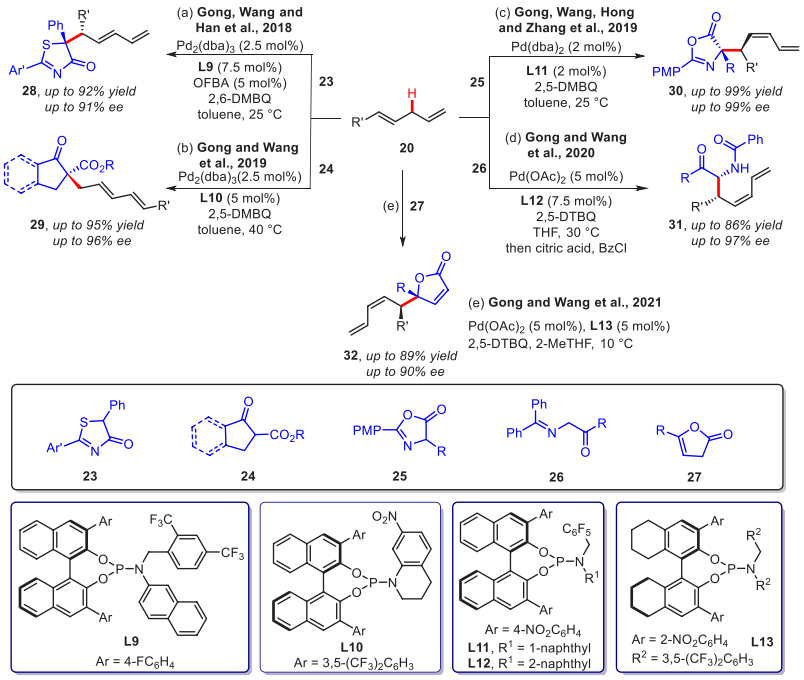
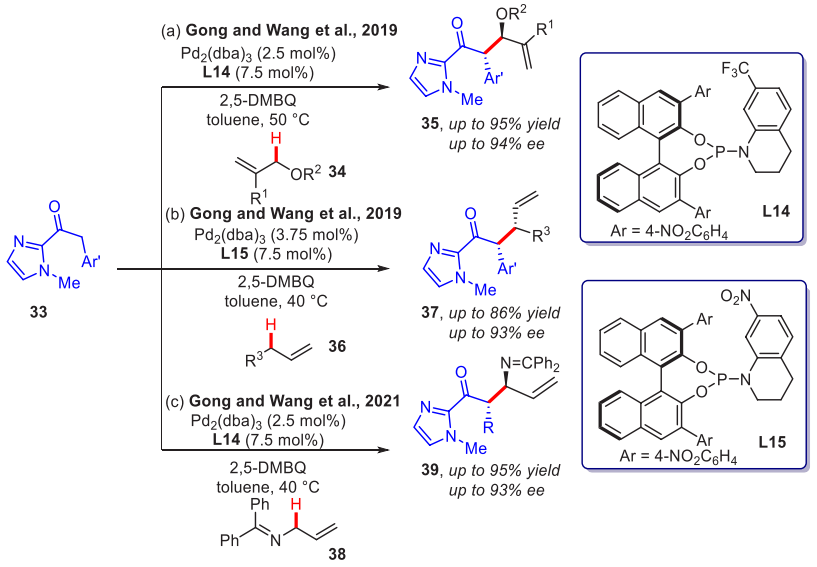
Scheme 6. Palladium-Catalyzed Enantioselective Allylic C−H Alkylation of 1,4-Dienes



Scheme 7. Palladium-Catalyzed Enantioselective Allylic C−H Alkylation of 2-Acylimidazoles



branched allylic C−H alkylation of 1,4-dienes **20** using chiral BINOL-derived phosphoramidite **L12** as the chiral ligand (Scheme 6d).[46] A series of 1,4-dienes were well tolerated to obtain the desired chiral α-amino acid analogues in moderate to high yields and excellent stereoselectivities. In 2021, asymmetric allylic C−H alkylation of 1,4-pentadienes **20** with α-angelica lactones **27** has also been established by the use of a triaxial chiral H_8−BINOL-derived phosphoramidite **L13**/palladium catalytic system (Scheme 6e).[47]

In 2019, a palladium-catalyzed branch-selective and asymmetric allylic C−H alkylation of allyl ethers **34** with 2-acylimidazoles **33** using chiral BINOL-derived phosphoramidite ligand **L14** was demonstrated by the Gong group (Scheme 7a).[48] A series of the desired chiral 2-acylimidazoles **35** were obtained in good yield and excellent enantioselectivity. Notably, this method was used as a key step for the synthesis of a chiral tachykinin receptor antagonist. Shortly after, a C3-branched selectivity was achieved via the asymmetric allylic C−H alkylation of terminal alkenes with 2-acylimidazoles **33** using a similar palladium/chiral BINOL-derived phosphoramidite **L15** catalytic system (Scheme 7b).[49] In 2021, Gong and co-workers achieved the palladium-catalyzed enantioselective intermolecular allylic C−H allylation of *N*-allylimine **38** with α-aryl ketones using chiral BINOL-derived phosphoramidite **L14** as ligand (Scheme 7c).[50] Notably, this reaction was proposed to proceed through a concerted proton and two-electron transfer step in the cleavage of allylic C−H bonds. It should be noted that the nitrogen coordination to the palladium center is key to the synthesis of branched products.

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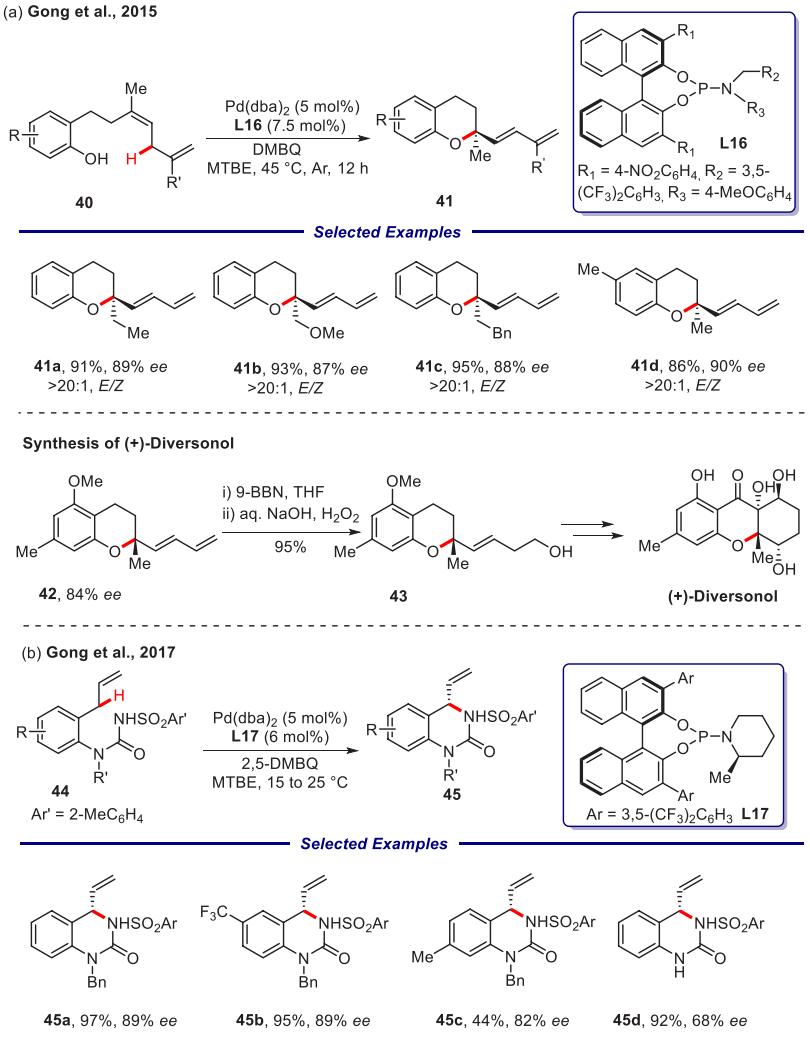
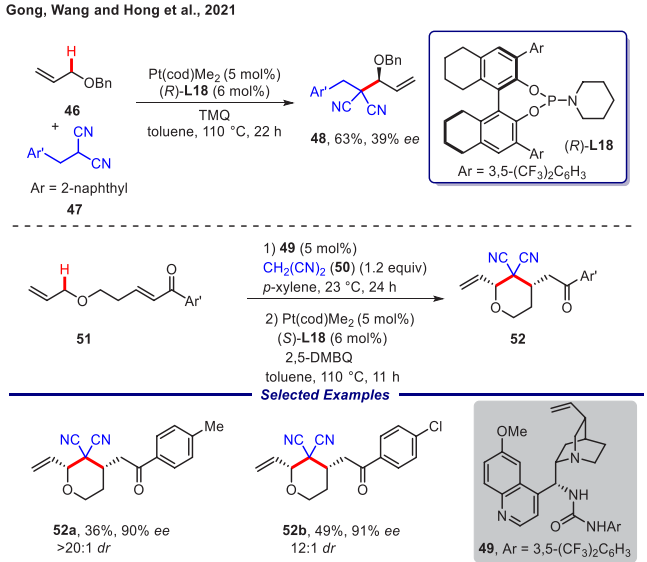
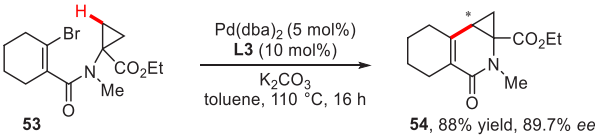
Scheme 8. (a) Palladium-Catalyzed Enantioselective Intramolecular Allylic C−H Oxidation; (b) Palladium-Catalyzed Enantioselective Intramolecular Allylic C−H Amination



Scheme 9. Platinum-Catalyzed Enantioselective Allylic C−H Alkylation of α-Alkenes with Malononitriles



Scheme 10. Palladium-Catalyzed Enantioselective Intramolecular Cyclopropyl C(sp^3)−H Alkenylation to Synthesize Cyclopropyl-Fused Azacycles



In 2015, the Gong group expanded the application of this catalytic system in the enantioselective intramolecular allylic C−H functionalization reaction for the construction of chiral cyclic compounds using chiral BINOL-derived phosphoramidite ligand **L16** (Scheme 8a).[51] Mechanistic studies suggested that the reaction proceeded through a Pd-catalyzed allylic C−H activation and an allylic alkoxylation process instead of the Wacker-type cyclization. More significantly, the resulting chiral cyclic compound **42** could be further converted to the natural product (+)-diversonol. In 2017, an enantioselective intramolecular allylic C−H amination reaction was achieved by the same research group using chiral BINOL-derived phosphoramidite ligand **L17** (Scheme 8b).[52] A wide range of the desired chiral tetrahydroquinazoline scaffolds **45** was obtained in high

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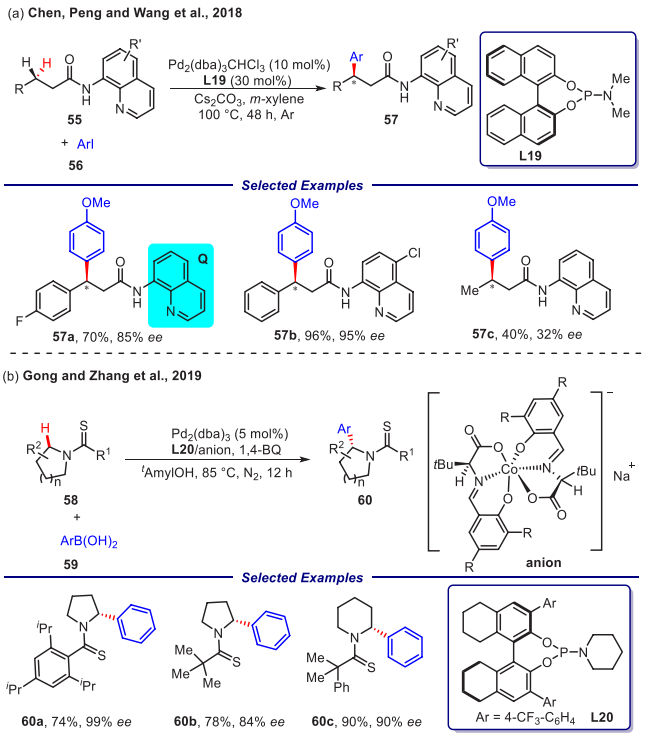
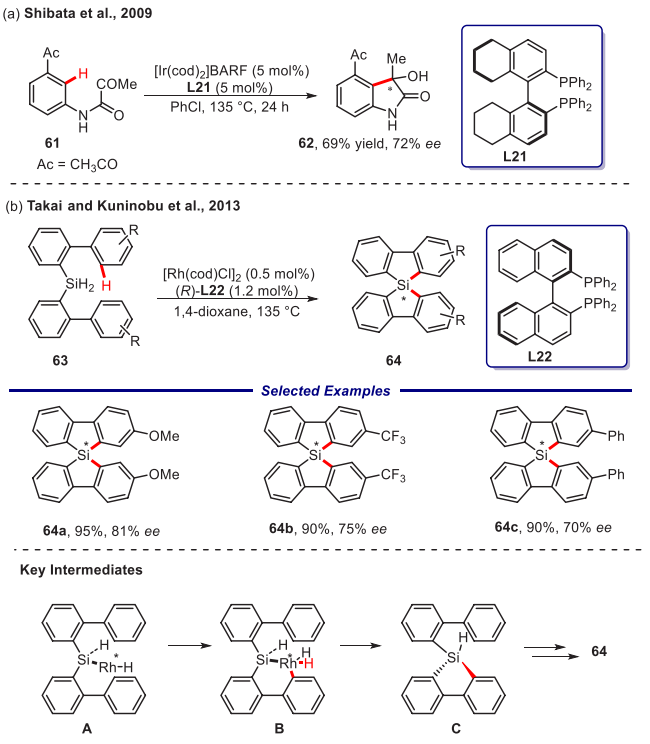
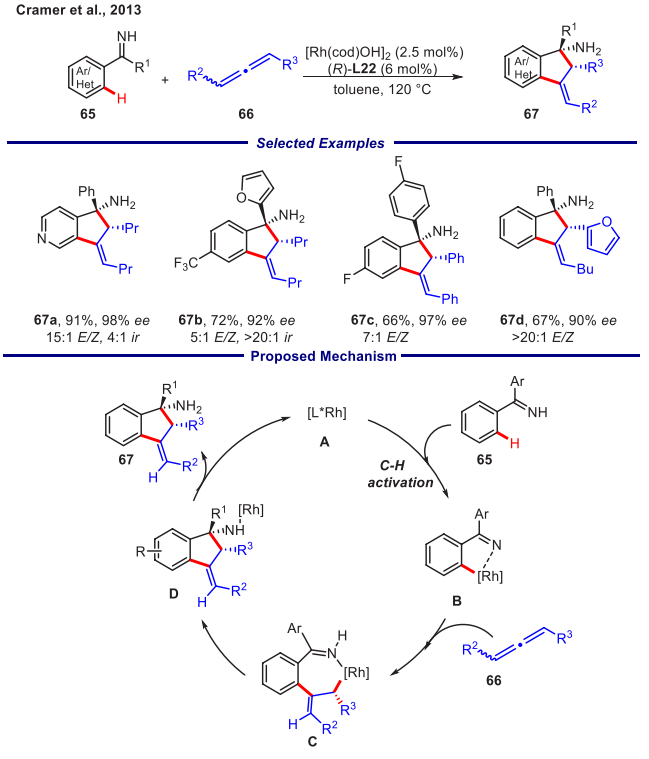
Scheme 11. (a) Palladium-Catalyzed Enantioselective Benzylic C(sp^3)−H Arylation of 3-Arylpropanamides with Aryl Iodides by 8-Aminoquinoline DG; (b) Palladium Catalyst Containing an Anionic Chiral Co^{III} Complex and a Chiral Phosphoramidite Ligand Catalyzed Asymmetric C(sp^3)−H Arylation



Scheme 12. (a) Iridium-Catalyzed Enantioselective Intramolecular C(sp^2)−H Cyclodehydration to Synthesize 4-Acetyloxindole; (b) Rhodium-Catalyzed Enantioselective Intramolecular C(sp^2)−H Double Dehydrogenative Cyclization of Bis(biphenyl)silanes to Synthesize Chiral Spirosilabifluorene Derivatives



Scheme 13. Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Allenes by the [3 + 2] Annulation of Aryl Ketimines



yields and good stereoselectivities. Notably, this method was used as the key step for the enantioselective synthesis of letermovir.

Recently, the same group also achieved the Pt-catalyzed allylic C−H alkylation of α-alkenes using chiral H_8−BINOL-derived phosphoramidite (**L18**) as the ligand and malononitriles **47** as the alkylation reagents (Scheme 9).[53] Notably, chiral tetrahydropyrans **52** could be obtained by a chiral urea-catalyzed Michael addition followed by a Pt-catalyzed allylic C−H alkylation sequence in high enantioselectivities. DFT calculations suggested that the Pt-catalyzed allylic C−H alkylation protocol is mechanistically identical with the Pd-catalyzed process via a concerted proton and two-electron transfer step.

BINOL-derived phosphoramidite ligands were also a type of efficient ligands in asymmetric nonallylic C(sp^3)−H functionalization. In 2016, Ladd and Charette revealed a rare example of palladium-catalyzed enantioselective intramolecular alkenylation of cyclopropyl C(sp^3)−H bonds to synthesize cyclopropyl-fused azacycle using chiral BINOL-derived phosphoramidite **L3** as the chiral ligand (Scheme 10).[54] However, only one single example was reported, and the desired product **54** was obtained in 89.7% *ee*.

Later in 2018, Chen and co-workers reported a palladium-catalyzed enantioselective benzylic C(sp^3)−H arylation of 3-arylpropanamides **55** with aryl iodides **56** assisted by 8-aminoquinoline DG using the chiral BINOL-derived phosphoramidite ligand **L19** (Scheme 11a).[55] A broad range of arylated products were obtained in good to high yields and excellent enantioselectivities (up to 95% *ee*). Mechanistic studies suggested that the reaction process underwent a Pd(0)/Pd(II)

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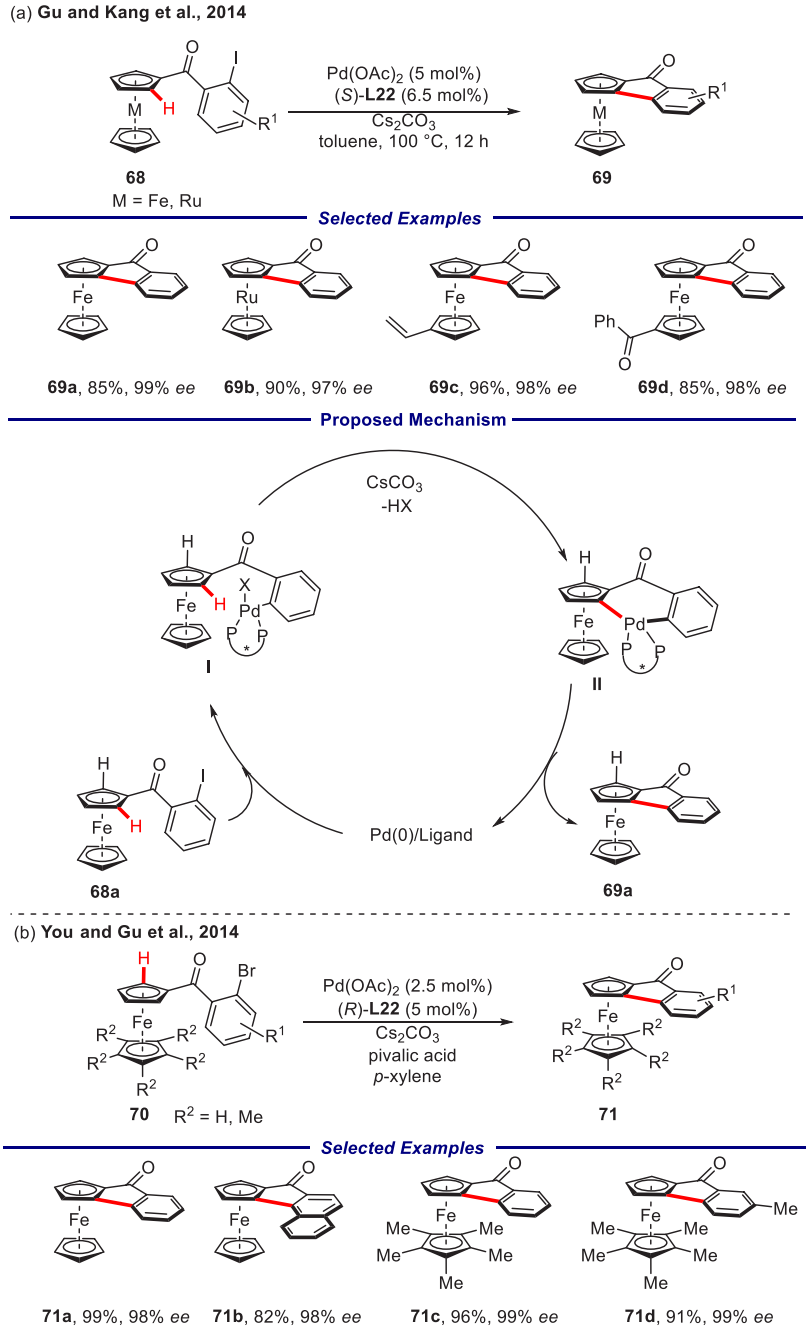
Scheme 14. (a) Palladium-Catalyzed Enantioselective Intramolecular C−H Arylation to Synthesize Planar Chiral Metallocene Compounds; (b) Palladium-Catalyzed Enantioselective Intramolecular C−H Arylation of Ferrocenes



catalytic cycle. DFT calculations suggested that the combination of cesium carbonate base and BINOL-derived phosphoramidite ligand is key to the enantio-determining step. In 2019, Gong and co-workers developed the palladium-catalyzed asymmetric C(sp^3)−H arylation using thioamide DG by combining an anionic chiral Co^{III} complex with a chiral H_8−BINOL-derived phosphoramidite ligand **L20** (Scheme 11b).[56]

3. BINAPHTHYL-BASED PHOSPHINE LIGANDS

BINAP (2,2′-diphenylphosphino-1,1′-binaphthyl), a C2-symmetric bidentate diphosphine ligand, is arguably one of the most widely used phosphine ligands in asymmetric synthesis. BINAP was first used as an efficient chiral ligand in Rh(I)-catalyzed highly enantioselective hydrogenation of α-(acylamino)acrylic acids with esters by the Noyori and Takaya groups in 1980.[57] After this seminal work, BINAP was widely applied in a broad range of metal-catalyzed asymmetric reactions, including the Mannich reaction, Heck reaction, Aldol reaction, etc.[24] Notably, some BINAP analogues and other binaphthyl phosphine derivatives have also been employed as efficient chiral ligands in a variety of transition metal-catalyzed reactions.[58] In this section, we will discuss enantioselective C−H activation taking advantage of BINAP and related binaphthyl-based phosphine ligands as the crucial ligands.

Binaphthyl-based phosphine ligands could be applied in asymmetric C(sp^2)−H functionalization. In 2009, Shibata and co-workers reported the iridium-catalyzed enantioselective intramolecular C(sp^2)−H cyclodehydration to synthesize 4-

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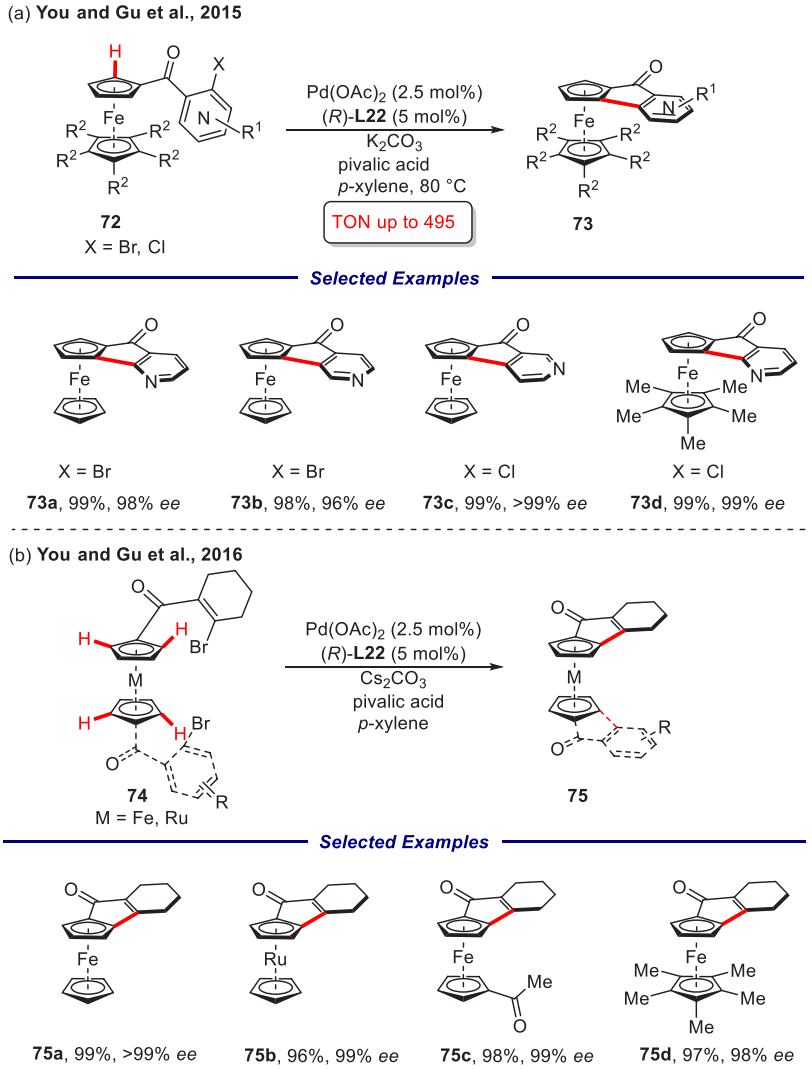
Scheme 15. (a) Palladium-Catalyzed Enantioselective Intramolecular C−H Arylation to Synthesize Planar Chiral Ferrocenyl pyridine Derivatives; (b) Palladium-Catalyzed Enantioselective Intramolecular C−H Alkenylation



substituted benzofurans and indoles using chiral H_8−BINAP **L21** as the chiral ligand (Scheme 12a).[59] The reaction was proposed to proceed via a directed C−H cleavage or electrophilic metalation rather than a Friedel−Crafts-type reaction.

In 2013, Takai and co-workers achieved the rhodium-catalyzed enantioselective intramolecular C(sp^2)−H double dehydrogenative cyclization of bis(biphenyl)silanes to synthesize a silicon stereogenic center using chiral BINAP ligand **L22** (Scheme 12b).[60] The combination of Rh(I)-catalyst, (*R*)-BINAP ligand, and dihydro bis(biphenyl)silanes **63** underwent double dehydrogenative cyclization to obtain the desired chiral spiro scaffolds **64** in high yields and moderate enantioselectivities. Mechanistic studies suggested that the first dehydrogenative cyclization was the enantio-determining step. After determination of the chirality, the second dehydrogenative cyclization occurs between the remaining Si−H bond and the biphenyl group.

In 2013, Tran and Cramer accomplished a rhodium-catalyzed dynamic kinetic asymmetric transformation of allenes by the [3 + 2] annulation of aryl ketimines using chiral BINAP ligand **L22** (Scheme 13).[61] A broad range of allenes **66** and ketimines **65** were tolerated to obtain the corresponding substituted indenylamines in high yields with excellent enantioselectivities. According to the mechanistic studies, this reaction was initiated by the coordination of ketimine **65** with Rh(I) catalyst, followed by the cleavage of *ortho*-C−H bonds to generate cyclometalation intermediate **B**. Subsequently, the coordination and migratory insertion of allene **66** were followed by the isomerization to generate the stable allyl isomer **C** via the $\sigma-\pi-\sigma$ mechanism or β−H elimination/readdition step. Finally, the desired product indanylamine **67** was afforded by the addition of the C−Rh bond across the imine group.

Binaphthyl-based phosphine ligands are also successfully applied to the construction of planar chirality. In 2014, Gu and co-workers achieved the palladium-catalyzed intramolecular arylation to synthesize planar chiral metallocene compounds using chiral BINAP ligand (*S*)-**L22** (Scheme 14a).[62] A series of the corresponding indanone derivatives were obtained in high yields with excellent enantioselectivities. They proposed that the aryl−palladium(II) specie **I** was generated by the oxidative addition of Pd(0) with aryl iodide **68a**, followed by C−H palladation to afford intermediate **II**. The combination of Pd with a chiral BINAP ligand (*S*)-**L22** could distinguish between two *ortho* C−H bonds on the Cp rings to give intermediate **II**. Finally, the cyclization product **69a** was generated by reductive

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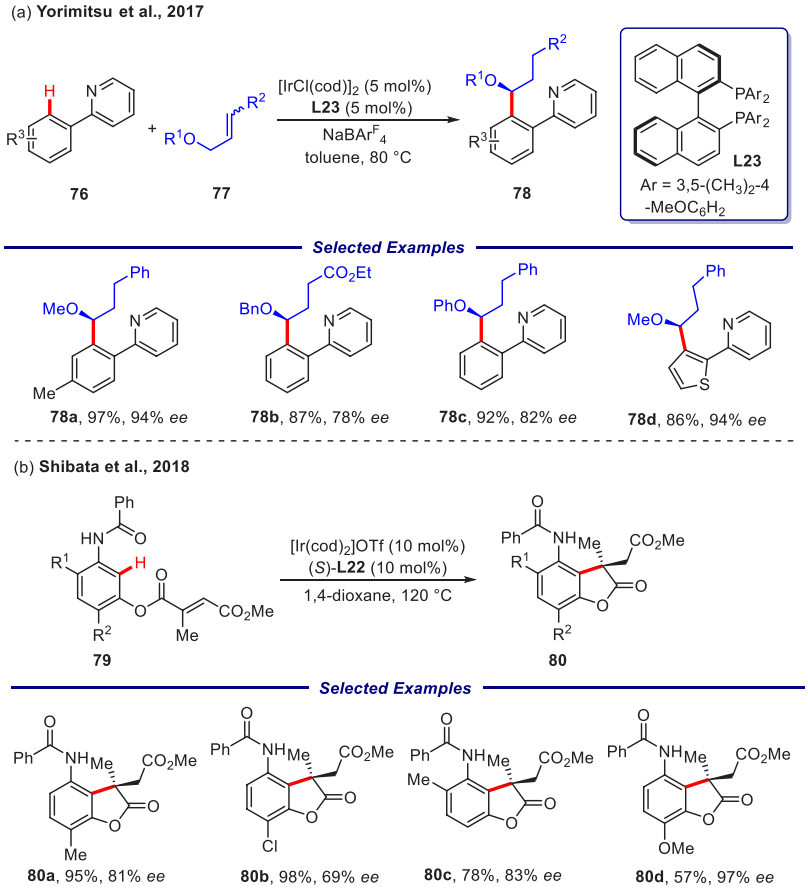
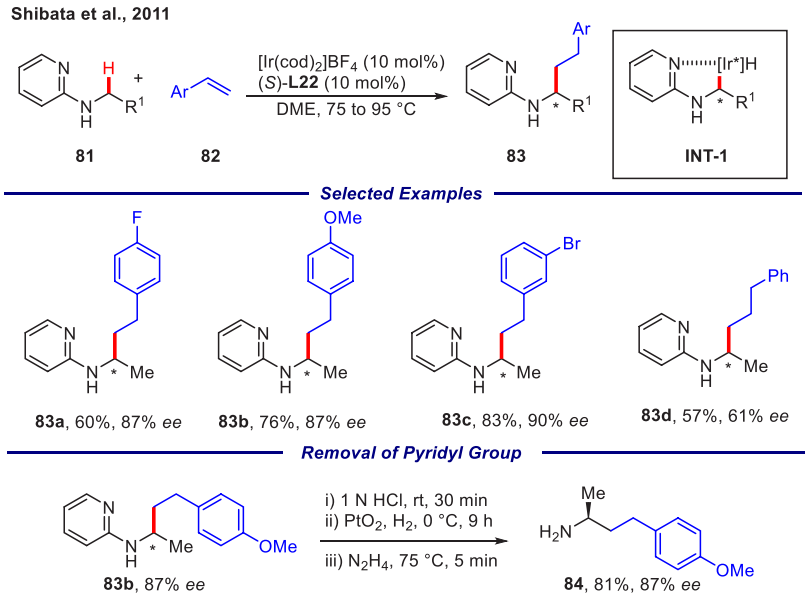
Scheme 16. (a) Iridium-Catalyzed Enantioselective Intermolecular Hydroarylation of Alkenyl Ethers; (b) Iridium-Catalyzed Enantioselective Intramolecular C(sp^2)−H Alkylation of *N*-Arylbenzamides



Scheme 17. Iridium-Catalyzed Enantioselective Two-Fold C(sp^3)−H Alkylation of 2-(Alkylamino)pyridines with Alkenes



elimination. At the same time, You and co-workers independently reported the Pd(0)-catalyzed enantioselective intramolecular C−H arylation using chiral BINAP ligand (*R*)-**L22** (Scheme 14b).[63] It should be noted that the desired products could be easily converted into the planar chiral ferrocene *P*,*N*-ligands.

Shortly after, the You group further expanded the Pd-catalyzed enantioselective intramolecular C−H arylation to synthesize planar chiral ferrocenylpyridine derivatives using chiral BINAP ligand (*R*)-**L22** (Scheme 15a).[64] A range of functional groups were tolerated to afford the corresponding chiral ferrocenylpyridine derivatives in high yields with excellent

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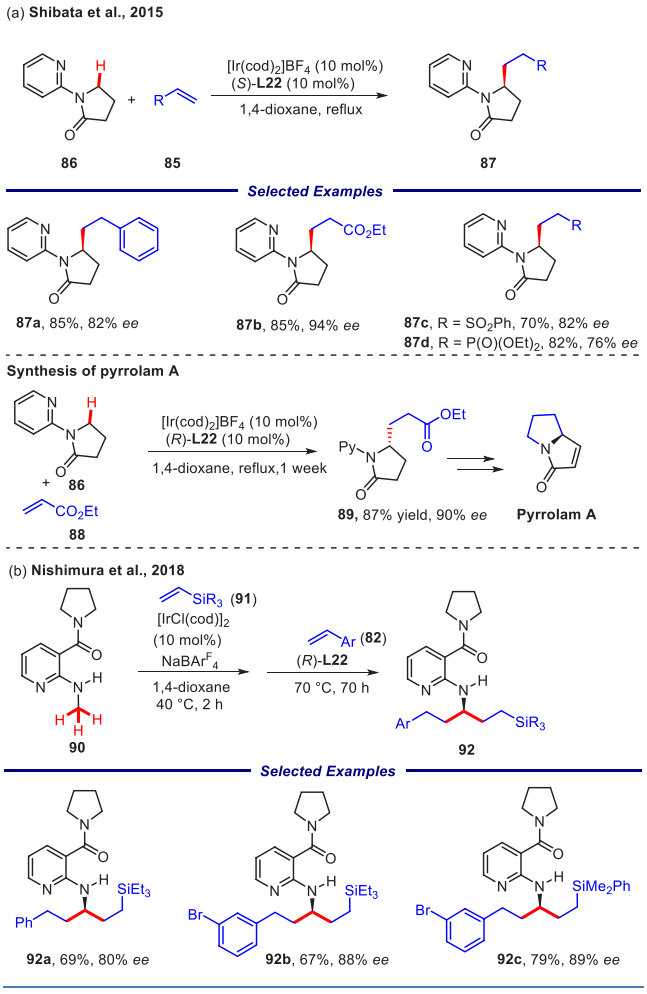
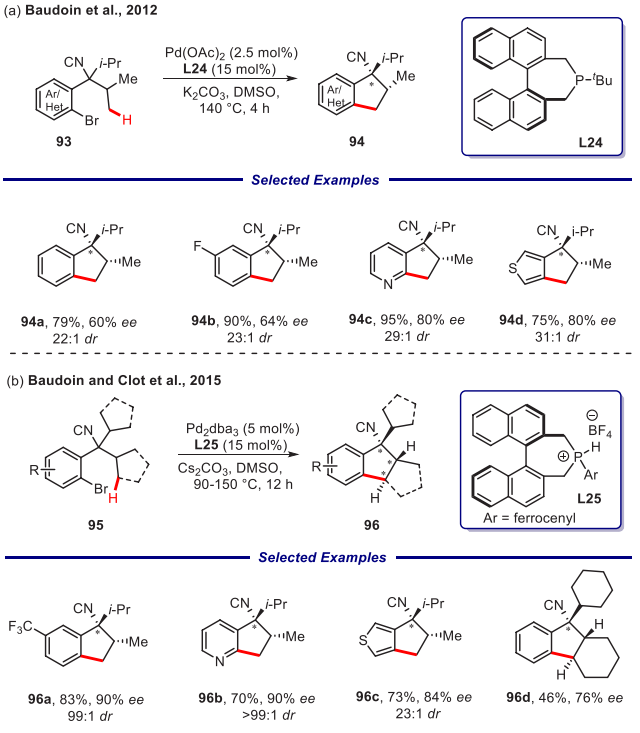
Scheme 18. (a) Iridium-Catalyzed Enantioselective C(sp^3)−H Alkylation of γ-Butyrolactam with Alkenes; (b) Iridium-Catalyzed Sequential *N*-Methyl C(sp^3)−H Alkylation



Scheme 19. (a) Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)−H Arylation for the Synthesis of Fused Cyclopentanes; (b) Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)−H Arylation Using Binepine Ligand



enantioselectivities. Notably, the catalyst loading could be reduced to 0.2 mol % without the erosion of enantioselectivity, which greatly enhanced the practicality of the reaction (TON up to 495). Moreover, the chiral products could be easily converted to the useful pyridine *N*-oxide catalysts. In 2016, a similar strategy was further applied to the asymmetric intramolecular C−H alkenylation using chiral BINAP ligand (*R*)-**L22** (Scheme 15b).[65] The chiral product could be easily transformed into a *N*,*O*-bidentate ligand, which has been successfully applied to the asymmetric alkynylation of 1-naphthaldehyde.

In 2017, Yorimitsu and co-workers achieved the iridium-catalyzed enantioselective intermolecular hydroarylation of alkenyl ethers **77** using chiral BINAP ligand **L23** (Scheme 16a).[66] A broad range of the corresponding addition products were obtained in high yields with excellent enantioselectivities. H/D exchange experiments suggested that the C−H activation and insertion steps are reversible. In 2018, Shibata and co-workers reported the iridium-catalyzed enantioselective intramolecular C(sp^2)−H alkylation of *N*-arylbenzamides **79** with β-substituted α,β-unsaturated esters using chiral BINAP ligand (*S*)-**L22** (Scheme 16b).[67] This protocol could provide chiral γ-lactones bearing a quaternary all-carbon stereogenic center with excellent enantioselectivities.

Binaphthyl-based phosphine ligands could also be applied in asymmetric C(sp^3)−H functionalization. In 2011, Shibata and co-workers reported the Ir-catalyzed enantioselective methylene C(sp^3)−H alkylation of 2-(alkylamino)pyridines **81** with alkenes using chiral BINAP ligand (*S*)-**L22** (Scheme 17).[68] The reaction was proposed to be initiated by the cleavage of the secondary C(sp^3)−H bond adjacent to the nitrogen atom to afford **Int-1** with a carbon stereogenic center. The subsequent alkene inserted into **Int-1**, followed by reductive elimination to give the desired alkylated product. Notably, the pyridyl group of **83b** could be removed to give the desired chiral amine **84** in 81% yield without the erosion of enantiopurity. In the next year, the same group conducted a detailed investigation of this alkylation protocol.[69]

In 2015, a similar strategy was also applied to the Ir-catalyzed enantioselective C(sp^3)−H alkylation of γ-butyrolactam with various alkenes using chiral BINAP ligand (*S*)-**L22** by the Shibata group (Scheme 18a).[70] A broad scope of alkenes were tolerated to provide the alkylated products with excellent enantioselectivities. This asymmetric alkylation protocol could be used in the synthesis of pyrrolam A. Hattori and Nishimura successfully expanded this protocol to Ir-catalyzed sequential C(sp^3)−H alkylation of the *N*-methyl group on 3-carbonyl-2-(methylamino)pyridine **90** with two different alkenes (Scheme 18b).[71] This cascade reaction provided an efficient method to prepare α-substituted chiral amines in good yields with moderate enantioselectivities (80−89% *ee*).

Other binaphthyl-based phosphine ligands have also been successfully applied in asymmetric C−H functionalization. In 2012, Baudoin and co-workers reported the palladium-catalyzed enantioselective intramolecular C(sp^3)−H arylation for the synthesis of fused cyclopentanes using chiral binaphthyl-based phosphine ligand **L24** (Scheme 19a).[72] Particularly, the

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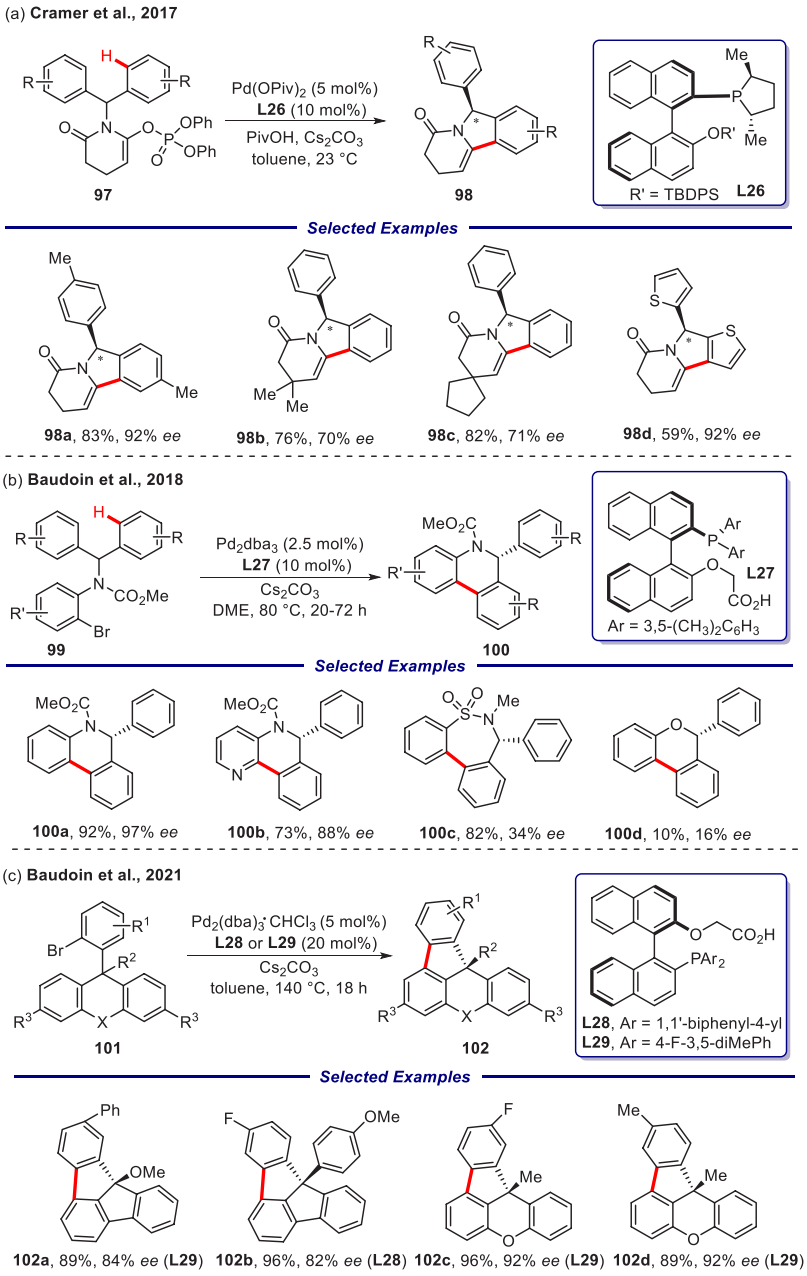
Scheme 20. (a) Palladium-Catalyzed Enantioselective Intramolecular C−H Alkenylation to Synthesize Isoindolines; (b) Palladium-Catalyzed Enantioselective Intramolecular C−H Arylation to Synthesize 5,6-Dihydrophenanthridines; (c) Palladium-Catalyzed Enantioselective Intramolecular C−H Arylation to Synthesize the Chiral Warped Molecules



enantioselective syntheses of chiral fused cyclopentanes were successful in good yields, albeit with moderate enantioselectivities (up to 80% *ee*). In 2015, the same group further achieved palladium-catalyzed enantioselective intramolecular C(sp^3)−H arylation using a modular binepine ligand **L25** (Scheme 19b).[73] The observation of a linear correlation between the product *ee* and ligand *ee* suggested that the enantio-determining step could involve a monoligated Pd complex.

In 2017, Grosheva and Cramer reported a Pd-catalyzed enantioselective intramolecular C−H alkenylation to synthesize isoindolines **98** using chiral binaphthyl-based phosphine ligand **L26** (Scheme 20a).[74] Notably, the monodentate electron-rich binaphthyl-based phosphine ligand was highly efficient, which was proposed to accelerate the oxidative addition of alkenyl phosphates to Pd(0) species. Moreover, some ketene aminal phosphate substrates were successfully applied in parallel kinetic resolutions. In 2018, Baudoin and co-workers achieved the palladium-catalyzed enantioselective intramolecular C−H arylation to synthesize 5,6-dihydrophenanthridines **100** using chiral binaphthyl-based phosphine ligand **L27** (Scheme 20b).[75] This catalytic system was suitable for a series of substituted dihydrophenanthridines substrates. It should be noted that binaphthyl scaffold phosphine ligands without a carboxylic acid moiety were applied with additional carboxylic acids, displaying very low enantioselectivities in the transformation. Recently, the same group further achieved the Pd-catalyzed enantioselective intramolecular C(sp^2)−H arylation to synthesize the chiral warped molecules **102** using chiral binaphthyl-based phosphine ligand **L28** or **L29** (Scheme 20c).[76]

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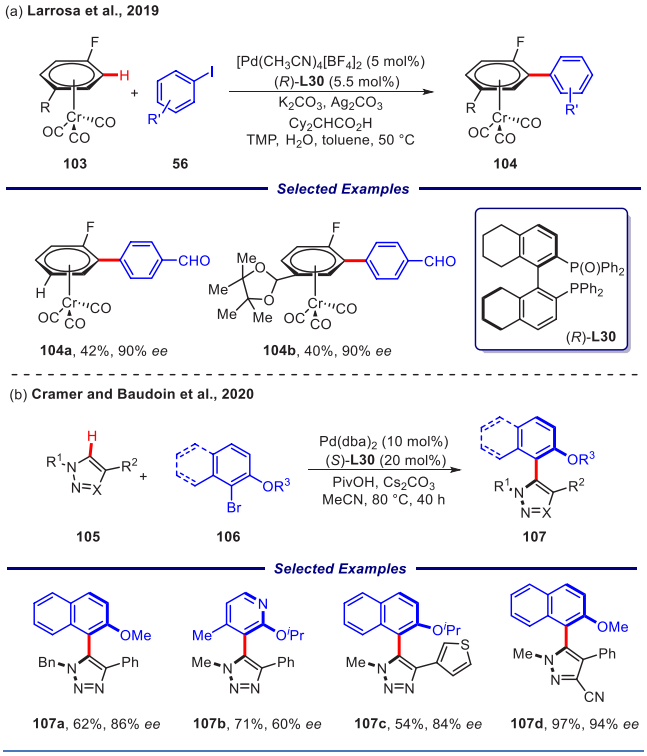
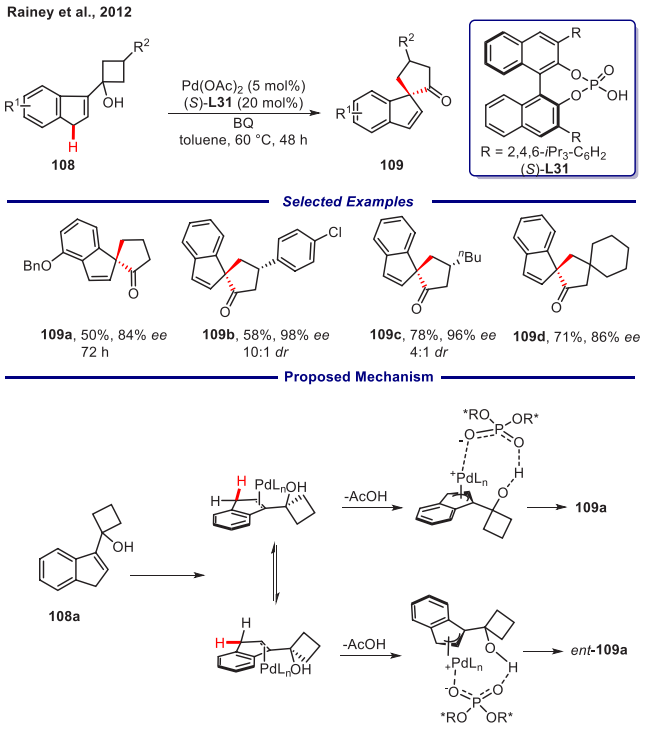
Scheme 21. (a) Palladium-Catalyzed Enantioselective Intermolecular C−H Arylation of (η^6-Arene)chromium Complexes; (b) Palladium-Catalyzed Atropo-Enantioselective Intermolecular C−H Arylation of Heteroarenes



Scheme 22. Palladium-Catalyzed Enantioselective Intramolecular Allylic C−H Activation to Synthesize Chiral Spirocyclic Indenes



Notably, hydrogenated chiral H_8−BINAPO was also an effective ligand in the asymmetric C−H activation. In 2019, Larrosa and co-workers accomplished a palladium-catalyzed enantioselective intermolecular arylation of (η^6-arene)chromium complexes **103** using chiral H_8−BINAPO **L30** as the chiral ligand (Scheme 21a).[77] Mechanistic studies suggested that a Pd/Ag bimetallic catalytic system was involved in this reaction, while the sliver salts could promote the C−H activation step. Recently, Cramer and co-workers reported a palladium-catalyzed atropo-enantioselective intermolecular C−H arylation of heteroarenes to synthesize axially chiral compounds using chiral H_8−BINAPO **L30** as the chiral ligand (Scheme 21b).[78] A wide range of arylated products were obtained in good yields and excellent enantioselectivities. Especially, this method could also be used in the construction of axial chiral biaryls containing two stereogenic axes via an atropo-enantioselective double arylation reaction. Mechanistic studies suggested that the C−H activation step was the rate-determining step and the reductive elimination was the enantio-determining step.

4. BINOL-DERIVED PHOSPHORIC ACID LIGANDS

Chiral phosphoric acid (CPA) is a class of important chiral Bronsted acid catalysts and ligands and has been employed in many asymmetric transformations.[79] The pioneer reports from the Akiyama and Terada groups demonstrated that BINOL-derived phosphoric acids could be used as a new class of chiral Bronsted acid catalyst in asymmetric synthesis.[80,81] Since then, chiral BINOL-derived phosphoric acids have been extensively investigated as ligands and catalysts in various enantioselective reactions.[82,83] BINOL-derived phosphoric acid ligands also received considerable attention as chiral ligands in transition metal-catalyzed asymmetric C−H functionalization.[23]

In 2012, Chai and Rainey reported the first enantioselective semipinacol rearrangement through palladium-catalyzed allylic C−H activation (Scheme 22).[84] BINOL-derived phosphoric acid **L31** was found to be the best ligand, delivering the chiral spirocyclic indenes **109** with high enantioselectivity. They proposed that the combination of $Pd(OAc)_2$ and CPA **L31** produced an active Pd(II) species by ligand exchange, which coordinated with substrate **108a** to generate a diastereomeric mixture of equilibrating alkene complexes. A rate-limiting C−H cleavage that possibly proceeded through proton abstraction by an acetate ligand would lead to the formation of diastereomeric π-allylpalladium intermediates. Finally, semipinacol ring expansion gave the corresponding product **109a** and a Pd(0) species, which was reoxidized to Pd(II) catalyst by BQ to close the catalytic cycle.

In 2014, Gong and co-workers[85] reported the first palladium-catalyzed enantioselective allylation of aldehydes with terminal alkenes by the combination of asymmetric counteranion catalysis and Pd-catalyzed allylic C−H activation (Scheme 23).[42] BINOL-derived phosphoric acid (*R*)-**L31** and cumylamine **B1** were identified to be the best choice. They proposed that, in the presence of Pd(0) catalyst, a chiral BINOL-derived phosphoric acid, and an oxidant, olefins containing allylic C−H bonds could be oxidized to form the π-allyl palladium phosphate complex **I**, which was a key intermediate for the subsequent asymmetric allylic alkylation. Complex **I** reacted with enamine **II**, possibly via **TS-4**, to give the allylated chiral product **111**.

In 2016, the Gong group achieved a palladium-catalyzed enantioselective allylic C−H alkylation reaction of terminal alkenes **18** with pyrazol-5-ones **21** (Scheme 24a).[86] The combination of (*R*)-H_8−BINOL-based phosphoric acid (*R*)-**L32** and (*S*)-H_8−BINOL-derived phosphoramidite **L18** could

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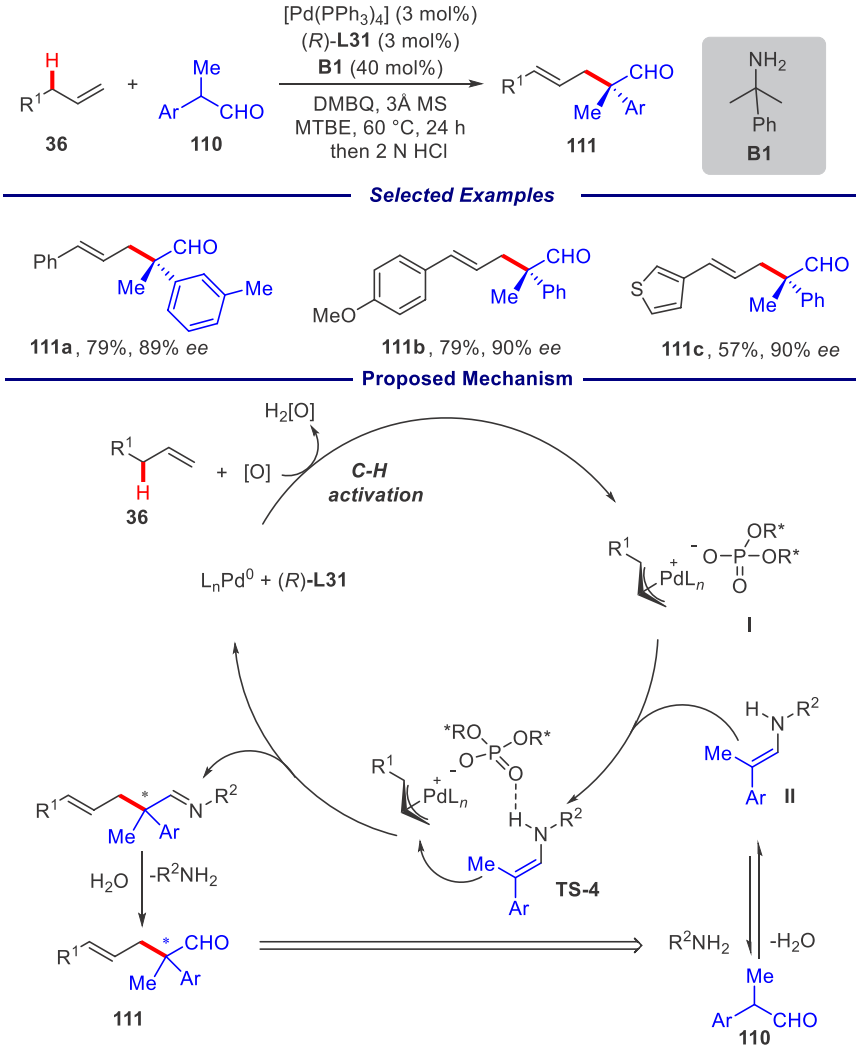
Scheme 23. Palladium-Catalyzed Enantioselective Intermolecular Allylic C−H Allylation of Aldehydes with Terminal Alkenes



enable the transformations with high yields and enantioselectivities. As shown in the proposed transition state **TS-5**, the stereochemistry was controlled by the combination of chiral phosphoramidite ligand and chiral phosphoric acid. The authors have also established an asymmetric allylation of aldehydes **110** with 1,4-dienes **20** using chiral BINOL-derived phosphoric acid (*R*)-**L31** (Scheme 24b).[87] $Pd(dba)_2$ and $P(4\text{-}MeOC_6H_4)_3$ are the most efficient catalytic systems enabling *in situ* generation of a palladium complex, which allowed a series of substituted 1,4-dienes to react with aldehydes, furnishing the desired products in excellent regio-, *E*/*Z*-, and stereoselectivities.

In 2019, Gong and co-workers reported a palladium-catalyzed enantioselective allylic C−H alkylation of terminal alkenes (Scheme 25a).[88] In this transformation, chiral (*S*)-H_8−BINOL-derived phosphoramidite **L18** and chiral H_8−BINOL-derived phosphoric acid **L33** were used as cocatalysts. A series of terminal alkenes and carbon nucleophiles are tolerated, affording the corresponding chiral products in moderate to high enantioselectivities. Very recently, Gong and co-workers achieved a cascade allylic C−H borylation of allyl ethers and carbonyl allylation of aldehydes under the relay catalysis of palladium and BINOL-derived phosphoric acid (*R*)-**L31** (Scheme 25b).[89] The chiral homoallylic vicinal antidiols were synthesized in synthetic useful yields with excellent stereoselectivity. The application of this protocol has been demonstrated by the total synthesis of aigialomycin D in 7 linear steps with high overall yield.

The use of chiral BINOL-derived phosphoric acids to control stereochemistry in asymmetric $C(sp^2)$−H functionalization was also disclosed. In 2016, Duan and co-workers reported the Pd(0)-catalyzed enantioselective intramolecular $C(sp^2)$−H arylation to synthesize planar chiral ferrocenes using chiral BINOL-derived phosphoric acid **L34** (Scheme 26).[90] A plausible Pd(0)/Pd(II) catalytic cycle is shown in Scheme 26. First, the oxidative addition of Pd(0) with **70a** gave the palladium(II) species **I**, which underwent C−H palladation to afford intermediate **II**. Reductive elimination of intermediate **II** afforded the cyclization product **119a**.

Subsequently, Duan and co-workers disclosed the Pd-catalyzed asymmetric $C(sp^2)$−H arylation of phosphine oxides **120** to construct P-stereogenic dibenzophospholes **121** using chiral BINOL-derived phosphoric acid ligand (*S*)-**L34** and chiral BINOL-derived phosphoric amide ligand **L35** as cocatalyst (Scheme 27).[91] Particularly, the combination of $Pd(PCy_3)_2$ and (*S*)-**L34** ligand as a catalytic system could obtain the corresponding product in 85% yield and 76% *ee*. It should be noted that using chiral BINOL-derived phosphoric acid (*S*)-**L34**/chiral binaphthyl-based phosphoric amide **L35** as the ligand system is effective for this reaction.

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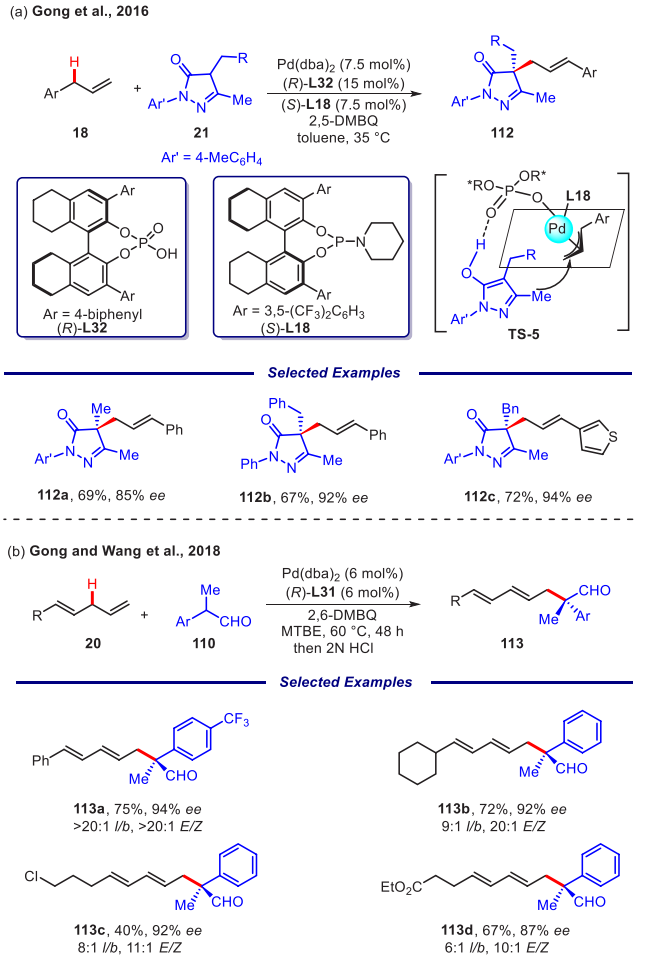
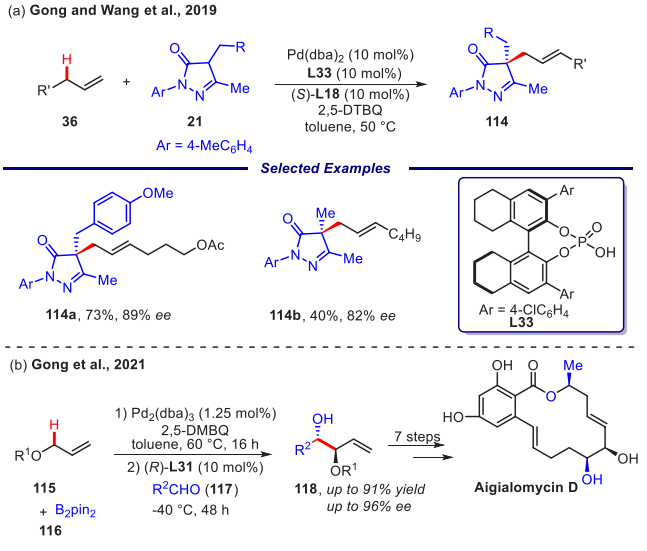
Scheme 24. (a) Palladium-Catalyzed Enantioselective Intramolecular Allylic C−H Alkylation of Terminal Alkenes with Pyrazol-5-ones; (b) Palladium-Catalyzed Enantioselective Allylation of Aldehydes with 1,4-Dienes



Scheme 25. (a) Palladium-Catalyzed Enantioselective Intermolecular Allylic C−H Alkylation of Terminal Alkenes with Pyrazol-5-ones; (b) Palladium-Catalyzed Sequential Allylic C−H Borylation and Asymmetric Carbonyl Allylation



Chiral BINOL-derived phosphoric acid ligands could also be applied in asymmetric C(sp^2)−H activation to synthesize axially chiral biaryl compounds. In 2022, Shi and co-workers reported palladium-catalyzed enantioselective C(sp^2)−H allylation by a combination of DFT calculations and experiments using chiral BINOL-derived phosphoric acid ligand **L36** (Scheme 28).[92] Asymmetric C−H allylation was successfully developed, leading to a series of axially chiral biaryl thioether products **124** in high yields with excellent enantioselectivities. In contrast to ether and selenoether directing groups, the experimental results suggested that the thioether group is the optimal directing group in reactivity and enantiocontrol via a Pd(II)/chiral BINOL-derived phosphoric acid catalytic system.

In 2015, Duan and co-workers developed a palladium-catalyzed enantioselective intermolecular C(sp^3)−H arylation of 8-aminoquinoline amides **55** using chiral binaphthyl-based phosphoric amide (*R*)-**L35** (Scheme 29).[93] Chiral phosphoric amides and acids were found to have a significant influence on the enantioselectivity and the reaction rate. In general, this protocol gave moderate to good enantiocontrol for the arylation of benzylic C(sp^3)−H bonds (48−82% *ee*). However, both the reactivity and enantioselectivity were significantly reduced for the arylation of unbiased methylene C(sp^3)−H bonds (**125d**, 68%, 26% *ee*; **125e**, 20%, 28% *ee*). As shown in Scheme 29, the reaction was proposed to be initiated by the ligand exchange of $PdCl_2(CH_3CN)_2$ with substrate **55** in the presence of Cs_2CO_3 and chiral binaphthyl-based phosphoric amide ligand (*R*)-**L35** to give Pd(II) intermediate **A**. Enantio-determining cleavage of methylene C(sp^3)−H bonds would give chiral intermediate **B**, which underwent oxidative addition with aryl iodide to afford Pd(IV) intermediate **C**. Subsequent reductive elimination of intermediate **C** led to the formation of intermediate **D**. Finally, the corresponding product **125** was generated after a ligand exchange with substrate **55**.

In 2016, Chen and co-workers reported the example of palladium-catalyzed intermolecular arylation of enantioselective benzylic C(sp^3)−H activation using chiral BINOL-derived phosphoric acid ligand (*R*)-**L34** via a Pd(II)/Pd(IV) catalytic cycle (Scheme 30).[94] Notably, this reaction achieved the rare example of enantioselective γ-C(sp^3)−H arylation of the picolinamide directing group. It should be noted that a chiral BINOL-derived phosphoric acid ligand (*R*)-**L34** combined with a Cs_2CO_3 base under solvent-free conditions is crucial to provide high enantioselectivity. Mechanistic studies suggested that the stereodetermining C−H palladation step could involve multiple chiral BINOL-derived phosphoric acid ligands. The authors proposed two different models. Unlike the monomeric (*R*)-**L34** ligand coordinated with the substrate in model **A**, one (*R*)-**L34** of the Cs complex was coordinated with the Pd(II) intermediate while the other one was involved as an internal base in model **B**.

In 2017, Yu and co-workers accomplished a palladium-catalyzed highly enantioselective C−H arylation of thioamides **128** with aryl boronic acids using chiral BINOL-derived phosphoric acid **L37** through a Pd(II)/Pd(0) catalytic cycle (Scheme 31a).[95] Various amines, including ethyl amines, pyrrolidines, azetidines, azepanes, piperidines, indolines, and tetrahydroisoquinolines, were well tolerated. In the same year, palladium-catalyzed enantioselective desymmetric methyl C-(sp^3)−H amination to synthesize chiral aziridines **131** using anionic chiral BINOL-derived phosphoric acid (*R*)-**L31** was developed by the Gaunt group (Scheme 31b).[96] A range of aliphatic amines were tolerated with the desymmetric C−H

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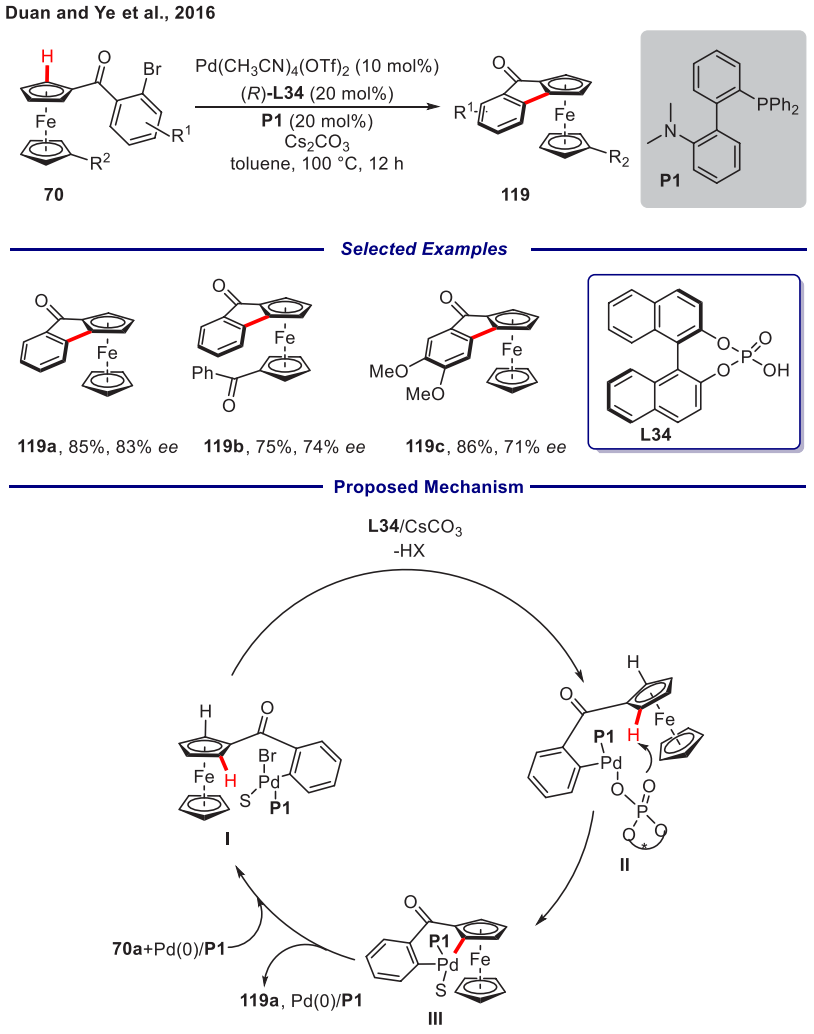
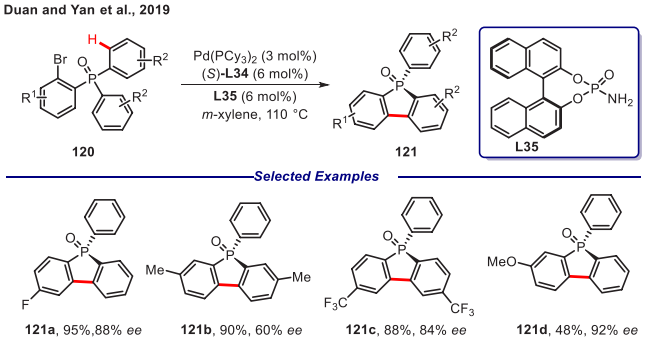
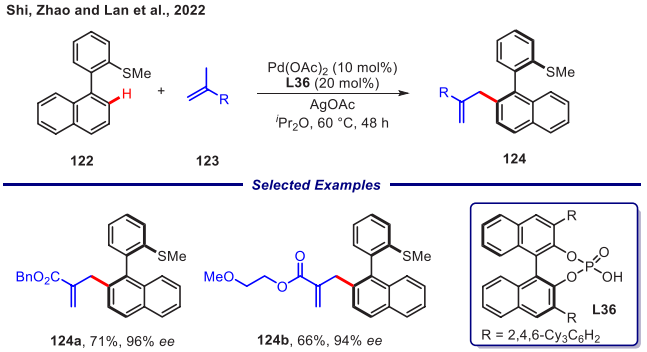
Scheme 26. Palladium-Catalyzed Enantioselective Intramolecular C(sp²)−H Arylation



Scheme 27. Palladium-Catalyzed Asymmetric C(sp²)−H Arylation of Phosphine Oxides



Scheme 28. Palladium-Catalyzed Enantioselective Intermolecular C(sp²)−H Allylation



activation process. Two different modes of enantiocontrol were proposed. In the first mode, a hydrogen bond interaction between the N−H and the chiral phosphate ligand might be involved to create a rigid transition structure for the enantio-determining C−H cleavage by a concerted metalation−deprotonation pathway using the acetate group (**TS-6**). An alternative pathway might involve a hydrogen bonding reaction between an acetate group and amine, and the enantio-determining C−H cleavage was assisted by the chiral phosphate ligand (**TS-7**).

Particularly, non-C2-symmetric chiral BINOL-derived phosphoric acid ligand was also effective in asymmetric C(sp³)−H activation. In 2018, Shi and co-workers reported the first palladium-catalyzed enantioselective arylation of unbiased methylene C(sp³)−H bonds directed by the strongly coordinating bidentate DG (Scheme 32a).[97] The synergistic effect between 2-pyridinylisopropyl (PIP) DG and a non-C_2-symmetric chiral BINOL-derived phosphoric acid ligand **L38** is crucial for the high enantiocontrol.[98,99] They proposed that the steric communication between the binaphthyl backbone of

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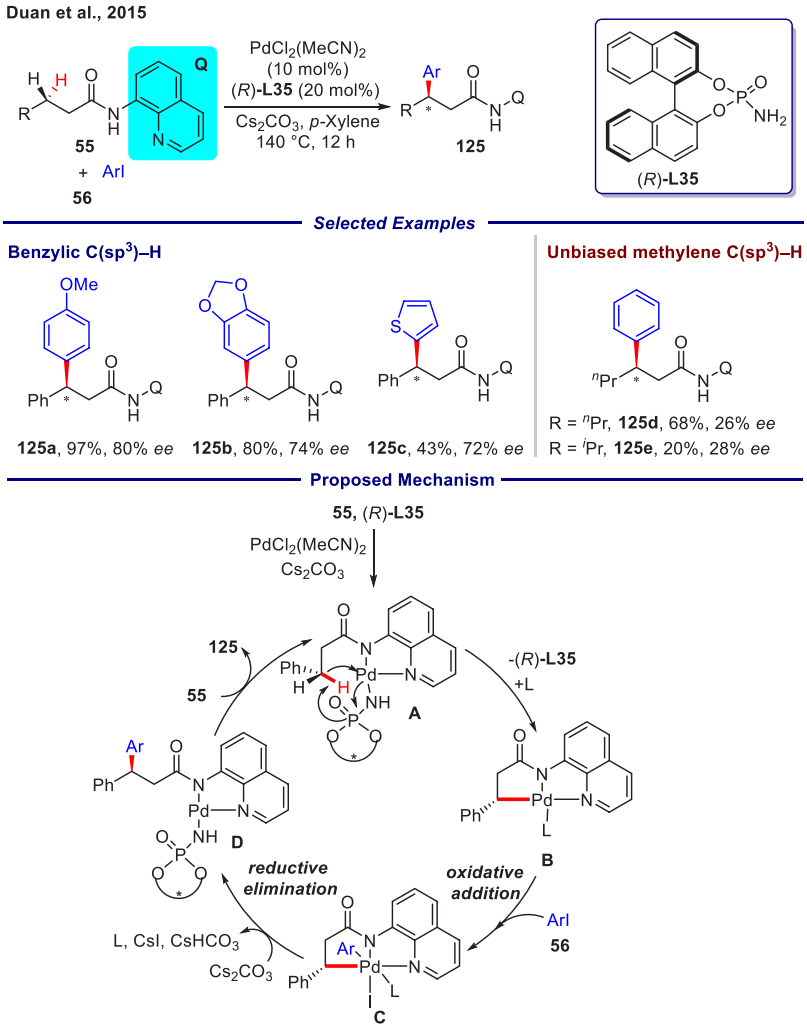
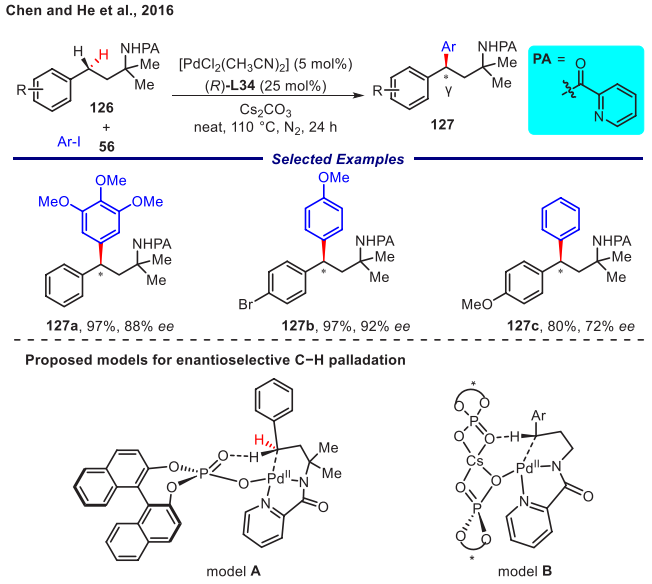
Scheme 29. Palladium-Catalyzed Enantioselective Intermolecular C(sp^3)–H Arylation of 8-Aminoquinoline Amides



Scheme 30. Palladium-Catalyzed Enantioselective Benzylic C(sp^3)–H Arylation



the ligand and the *gem*-dimethyl group of the PIP DG can inhibit the rotation in the transition state (**TS-8**) and create a rigid chiral environment for the enantio-determining C–H cleavage. A series of aliphatic carboxylic acids and aryl bromides were tolerated, delivering the arylated products in high yields with good enantioselectivities. Shortly after, an intramolecular version was developed by the same group using a non-C_2-symmetric chiral BINOL-derived phosphoric acid **L39** as the chiral ligand (Scheme 32b).[100] A range of chiral benzo-ring compounds were prepared in good enantioselectivities. Notably, the PIP amine DG could be easily removed by the treatment of nitrosyl tetrafluoroborate and subsequent protection to afford the phenyl amide product **136** with the retention of chirality.

In 2020, Gong and co-workers achieved a palladium-catalyzed thioamide directed enantioselective C(sp^3)–H arylation using chiral BINOL-derived phosphoric acid **L37** via a Pd(II)/Pd(0) catalytic cycle (Scheme 33).[101] Notably, the chiral product **138a** methylated and subsequently reduced to provide an aldehyde, which was further reduced with $NaBH_4$ to afford the chiral alcohol **139**. The chiral alcohol **139** can be easily transformed to a bioactive **S1P agonist**. The DFT analysis suggested the bulky chiral BINOL-derived phosphoric acid combined with the thioamide substrate to define a robust chiral cavity, which achieved a high enantioselectivity.

In 2017, Baudoin and co-workers reported the palladium-catalyzed enantioselective intramolecular C(sp^3)–H arylation via a Pd(0)/Pd(II) catalytic cycle (Scheme 34).[102] The authors

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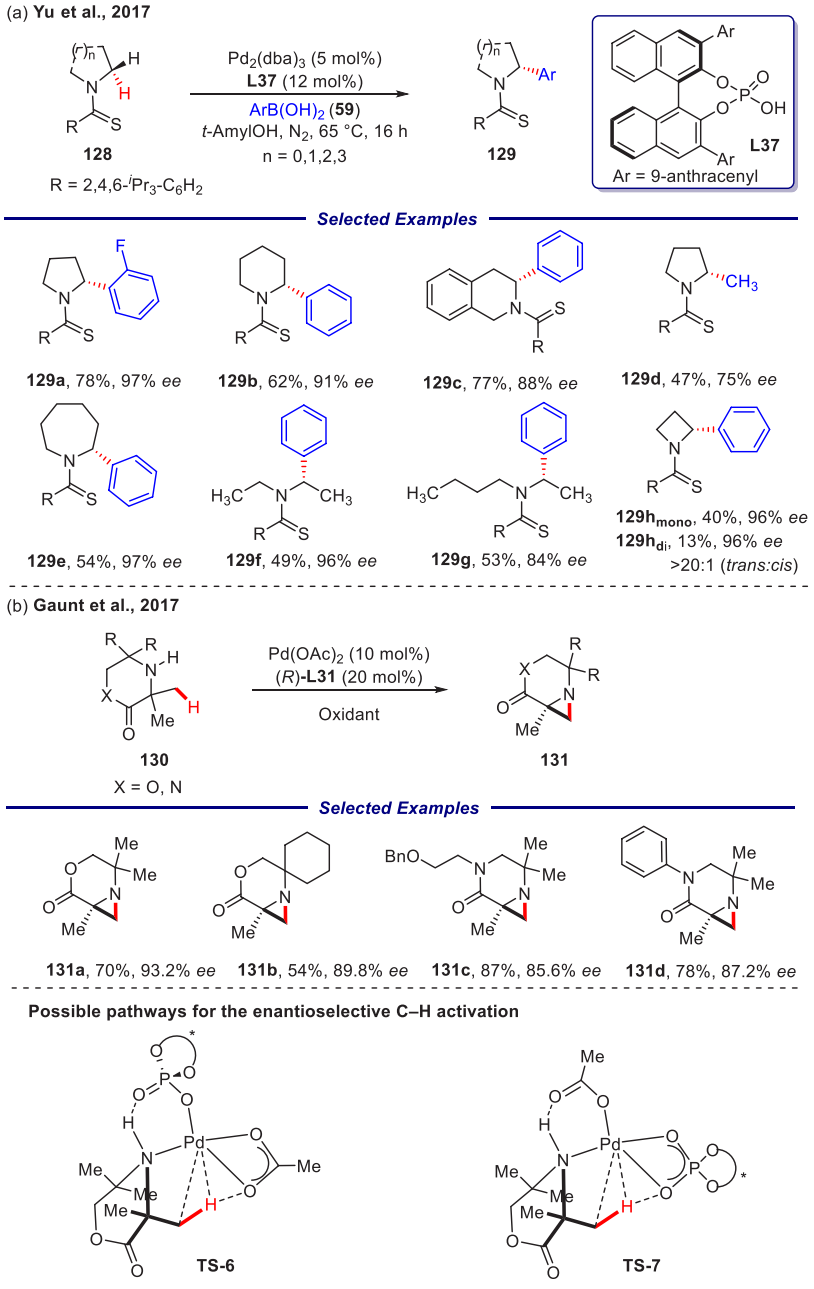
Scheme 31. (a) Palladium-Catalyzed Asymmetric Intermolecular C(sp^3)−H Arylation of Thioamides; (b) Palladium-Catalyzed Enantioselective Intramolecular Methyl C(sp^3)−H Amination



discovered that a variety of indoline products **141** were obtained in high enantioselectivities related to a fine-tuning of the chiral BINOL-derived phosphoric acid ligand **L40** and the reaction solvent.

5. BINAPHTHYL-BASED CHIRAL CARBOXYLIC ACID LIGANDS

Binaphthyl-based chiral carboxylic acid (CCA) was synthesized by the Miyano group in 1981.[103] Afterward, binaphthyl-based chiral carboxylic acid as a new type of chiral Brønsted acid catalyst was first used in the asymmetric Mannich reaction of arylaldehyde *N*-Boc imines with diazo compounds by Hashimoto and Maruoka in 2007.[104] In recent years, binaphthyl-based chiral carboxylic acids were increasingly used as the efficient chiral catalysts in many asymmetric catalysis reactions.[105,106] In this context, binaphthyl-based chiral carboxylic acids as ligands could also be applied in asymmetric C−H functionalization.[10]

In 2018, Matsunaga and co-workers reported the $Cp^xRh(III)$-catalyzed asymmetric intermolecular C(sp^2)−H alkylation of diarylmethanamines **142** with diazomalonate **143** and the subsequent cyclization and decarboxylation to synthesize 1,4-dihydroisoquinolin-3(2*H*)-one **144** in good enantioselectivity (Scheme 35).[107] The reaction was initiated by chloride abstraction with Ag_2CO_3 and ligand exchange of $[Cp^xRhCl_2]_2$ with CCA **L41** to generate dicarboxylate **I** and cationic monocarboxylate **II** in equilibrium. The amino group of **142** coordinated with **II**, followed by enantioselective C−H bond cleavage via the chiral carboxylate-assisted concerted metalation−deprotonation process (transition state **A**) to afford chiral rhodacycle intermediate **B**. The subsequent addition to

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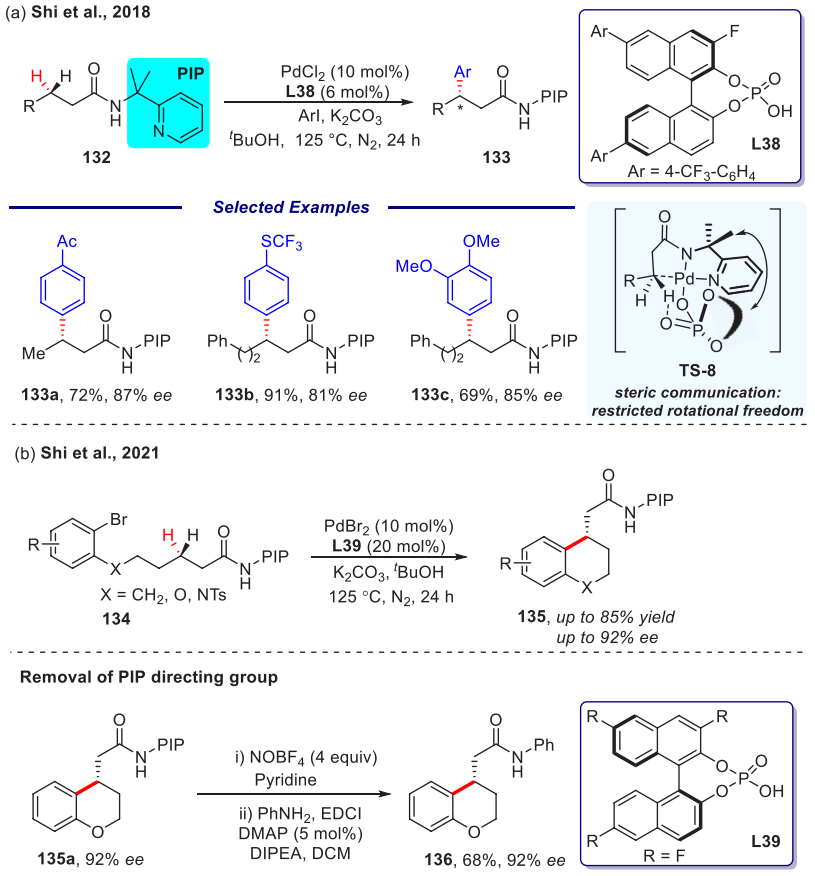
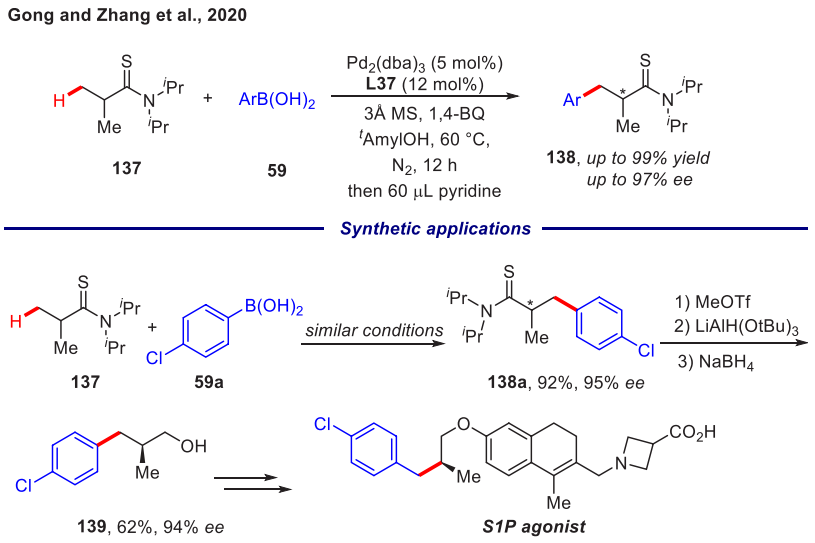
Scheme 32. (a) Pd-Catalyzed Enantioselective Arylation of Unbiased Methylene C(sp^3)−H Bonds: (a) Intermolecular; (b) Intramolecular



Scheme 33. Palladium-Catalyzed Asymmetric C(sp^3)−H Arylation of Thioamides



diazomalonate **143** afforded intermediate **C**. Aryl migration with the release of N_2 led to the formation of intermediate **D**. Finally, protonation of intermediate **D** and lactam formation would obtain intermediate **E** and regenerate active catalyst **II**. Intermediate **E** underwent decarboxylation to provide **144** in the presence of LiCl.

In the same year, the same group disclosed a $Cp^xRh(III)$-chiral disulfonate hybrid catalysis for enantioselective C−H functionalization (Scheme 36).[108] A preformed hybrid catalyst, $[Cp^xRhL_N][(S)\text{-BINSate}]$, was proposed to be the active catalyst. The chiral organic anion (*S*)-BINSate can efficiently control the enantioselectivity of this transformation in the absence of a chiral Cp^x ligand.

Subsequently, the same group achieved a $Cp^xCo(III)$/chiral carboxylic acid-catalyzed 1,4-addition reaction of indoles **148** with maleimides **149** via asymmetric C−H activation (Scheme 37a).[109] A binaphthyl-based chiral carboxylic acid ligand **L42** was used as the chiral source in this transformation. Binaphthyl-

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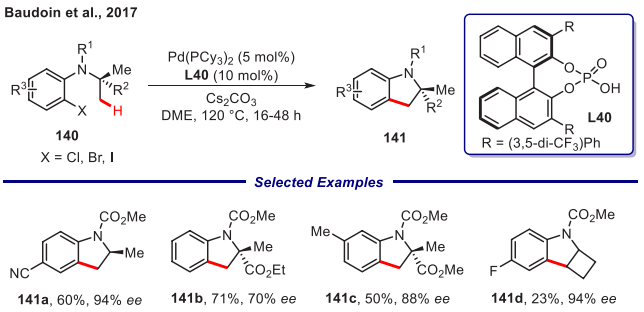
Scheme 34. Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)−H Arylation

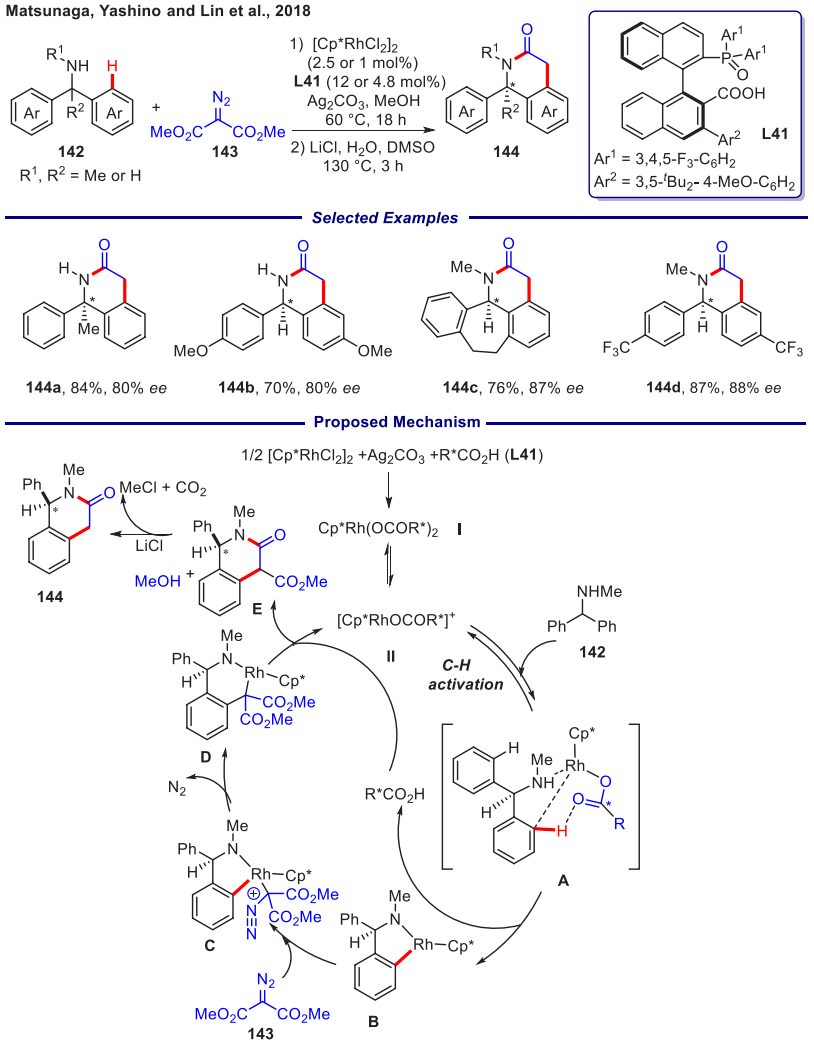


based chiral carboxylic acid ligands were also successfully applied to construct chiral compounds with planar chirality. In 2021, Matsunaga and co-workers accomplished the Cp^{x}Ir(III)/chiral carboxylic acid-catalyzed enantioselective C−H alkylation of ferrocene carboxamides **151** with diazomalonates **143** (Scheme 37b).[110] The achiral Cp^{x}Ir(III) complex combined with a binaphthyl-based chiral carboxylic acid ligand **L43** was demonstrated to be a highly efficient catalytic system to obtain planar chiral alkylated ferrocenes **152** in good yields with moderate to good enantioselectivities.

Recently, Shi and co-workers accomplished a Ru(II)-catalyzed enantioselective C−H activation/annulation of sulfoximines **153** with α-carbonyl sulfoxonium ylides **154** using binaphthyl-based chiral carboxylic acid ligand **L44** (Scheme 38a).[111] This catalytic system was compatible with desymmetrization, kinetic resolution, and parallel kinetic resolution reactions. A series of chiral sulfoximines **155** were obtained in high yields with excellent stereocontrol (up to 99% yield and 99% *ee*). The resolution products can be easily converted into chiral sulfoxides as crucial intermediates for the synthesis of kinase inhibitors. Matsunaga and co-workers independently reported a similar ruthenium(II)/binaphthyl-based CCA catalyzed enantioselective C−H functionalization of sulfoximines (Scheme 38b).[112] A pseudo-C_2-symmetric binaphthyl-based CCA **L45** was found to be the appropriate chiral source.

Apart from asymmetric C(sp^2)−H functionalization reactions, binaphthyl-based chiral carboxylic acid ligands could also be successfully applied in asymmetric C(sp^3)−H functionalization. In 2019, Matsunaga and co-workers reported the example of a Cp^{x}Rh(III)/binaphthyl-based CCA catalyzed asymmetric

Scheme 35. Cp^{x}Rh(III)-Catalyzed Asymmetric Intermolecular C(sp^2)−H Alkylation of Diarylmethanamines with a Diazomalonate



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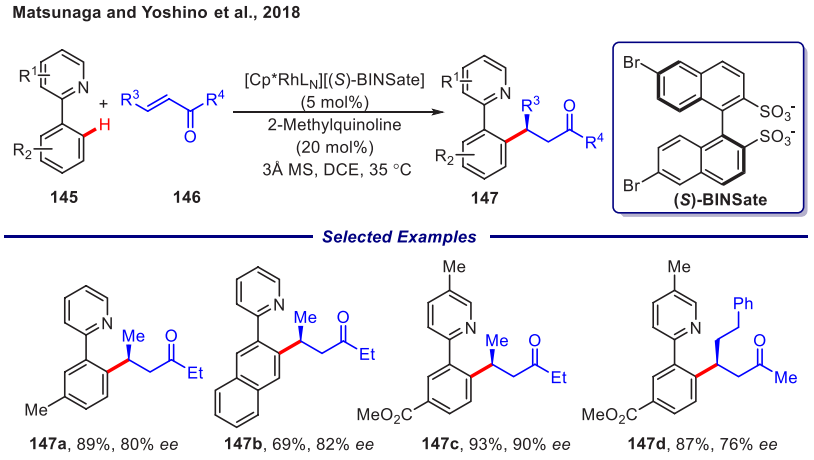
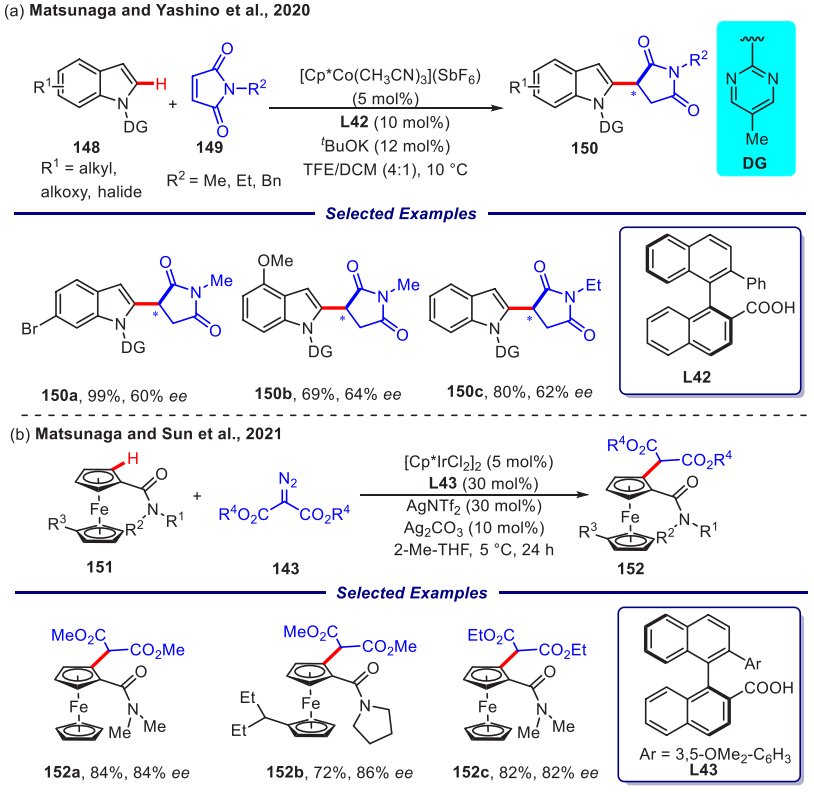
Scheme 36. Cp^{x}Rh(III)-Chiral Disulfonate Hybrid Catalysis for Enantioselective C−H Functionalization



Scheme 37. (a) Cp^{x}Co(III)/CCA-Catalyzed 1,4-Addition Reaction of Indoles and Maleimides by Asymmetric C−H Activation; (b) Cp^{x}Ir(III)/CCA-Catalyzed Enantioselective C−H Alkylation of Ferrocene Carboxamides with Diazomalonates



methylene C(sp^3)−H amidation of 8-alkylquinolines **157** (Scheme 39a).[113] A binaphthyl-based CCA **L46** served as an efficient ligand to distinguish the methylene C−H bonds, which promoted high chiral introduction in the C−N bond formation process. H/D exchange experiments suggested that the C−H activation step is almost irreversible and the binaphthyl-based CCA ligand **L46** would participate in a carboxylate assisted C−H activation process. Shortly after, the same group further achieved Cp^{x}Rh(III)-catalyzed enantioselective C(sp^3)−H alkylation of 8-ethylquinolines **157a** with α,β-unsaturated carbonyl compounds **160** using the same CCA ligand **L46** (Scheme 39b).[114]

Recently, Matsunaga and co-workers accomplished Cp^{x}Rh-(III)-catalyzed enantioselective C(sp^3)−H amidation reactions of 2-alkylpyridines **162** with heteroaromatic substrates **158** (Scheme 40).[115] The combination of binaphthyl-based CAA **L45** with a sterically hindered rhodium catalyst was the optimal catalysis, giving the desired products in good enantioselectivity (up to 92% *ee*).

6. 3,3′-DISUBSTITUTED BINOL LIGANDS

BINOL and modified BINOLs, such as the 3,3′-disubstituted or 6,6′-disubstituted BNOLs, are widely used in a series of asymmetric catalytic transformations.[25,26] In this part, we have discussed the advances of enantioselective C−H activation using 3,3′-disubstituted BINOL as a chiral ligand.

The applications of modified chiral BINOL ligands were generally achieved in asymmetric C(sp^3)−H functionalization.

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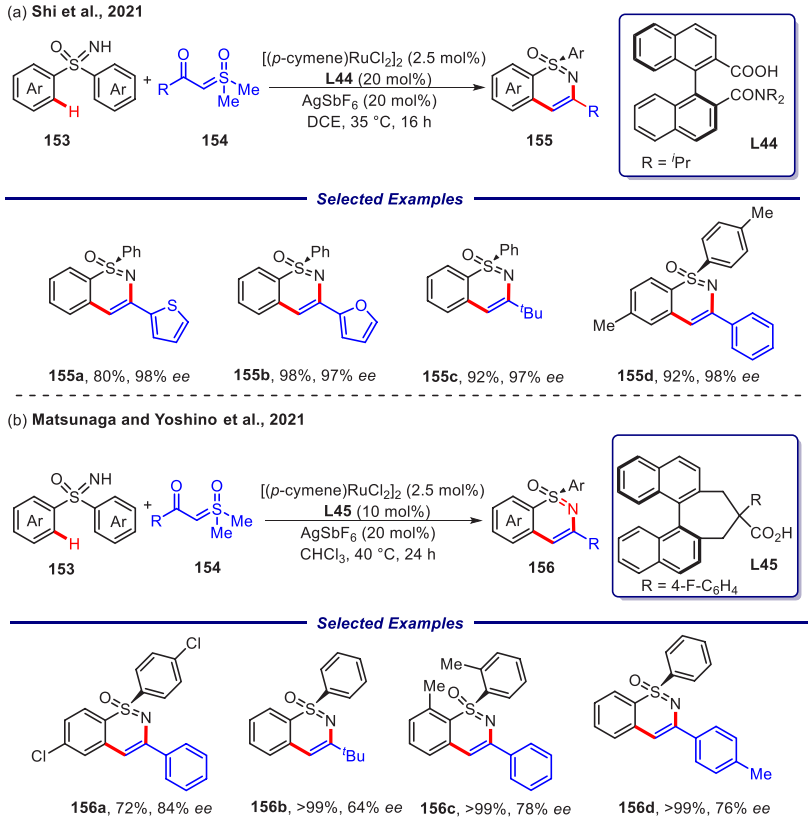
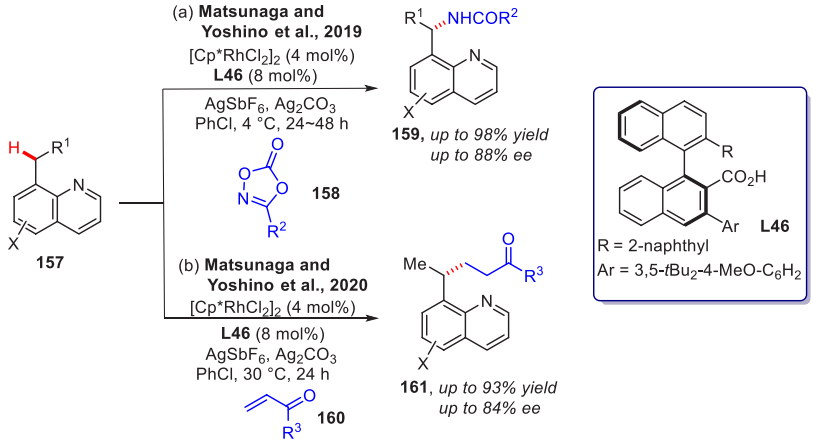
Scheme 38. (a) Ru(II)-Catalyzed Enantioselective C−H Activation/Annulation of Sulfoximines with α-Carbonyl Sulfoxonium Ylides; (b) Ru(II)/CCA-Catalyzed Enantioselective C−H Activation/Annulation of Sulfoximines



Scheme 39. $Cp^xRh(III)$-Catalyzed Asymmetric Intermolecular Methylene C(sp^3)−H Amidation and C(sp^3)−H Alkylation of 8-Alkylquinolines



In 2019, Shi and co-workers disclosed the first example of palladium-catalyzed enantioselective intermolecular C(sp^3)−H alkynylation of unbiased methylene using 3,3′-difluorous-BINOL ligand (Scheme 41).[116] PIP auxiliary was used as an efficient directing group. A broad range of aliphatic carboxamides were well compatible with high enantioselectivities (up to 96% *ee*). Notably, a significant nonlinear effect between the *ee* values of the 3,3′-difluorous-BINOL ligand **L47** and the products was observed. As a comparison, the alkynylated product **165a−AQ** was obtained in only 36% yield with 48% *ee* when using 8-aminoquinoline (AQ) as the directing group.

In 2020, Pd(II)-catalyzed tandem enantioselective unbiased methylene C(sp^3)−H alkenylation/cyclization assisted by PIP DG was accomplished by the same group (Scheme 42a).[117] Two chiral 3,3′-disubstituted BINOLs **L47** and **L48** are key for the high reactivity and enantioselectivity, and they proposed a possible reaction mechanism. A Pd(II)-catalyzed enantioselective C(sp^3)−H alkenylation proceeded first to give the alkenylated product **II**, which underwent a *syn*-aminopalladation to give **III**. Subsequent *β*-hydride elimination generated the aza-Wacker cyclized product **167**. Later in 2021, palladium-catalyzed enantioselective intermolecular arylation of unbiased methylene C(sp^3)−H bonds using 3,3′-F_2−BINOL ligand **L47** was also reported by the same group (Scheme 42b).[118]

The Shi group also achieved the palladium-catalyzed intermolecular arylation of unbiased methylene C(sp^3)−H

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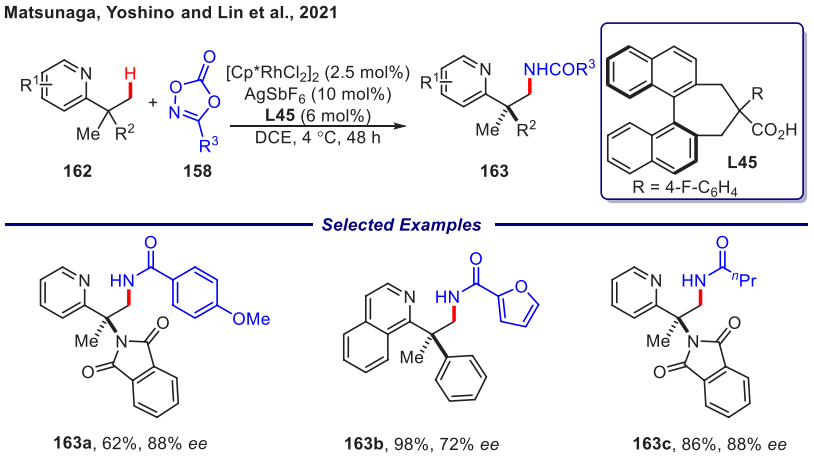
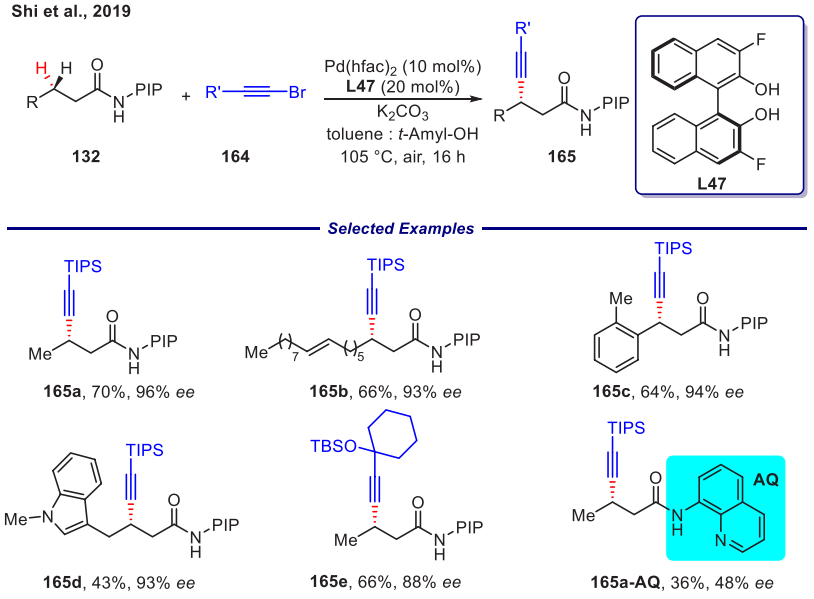
Scheme 40. Cp^{x}Rh(III)-Catalyzed Enantioselective C(sp^3)−H Amidation Reactions of 2-Alkylpyridines



Scheme 41. Palladium-Catalyzed Enantioselective Intermolecular C(sp^3)−H Alkynylation



bonds of aliphatic amides in a highly enantio-, chemo-, and diastereoselective manner (Scheme 43a).[119] It should be noted that the four chemically identical β-methylene C(sp^3)−H bonds could be distinguished by employing the Pd(II)/3,3′-F$_2$−BINOL catalytic system. A series of aliphatic amides and aryl iodides were well tolerated, affording the arylated products **169** in good yields with high chemo-, diastereo-, and enantioselectivities (up to >99% *ee* and >20:1 dr). In 2021, γ-lactams containing α,β-contiguous stereogenic centers were also synthesized by a similar catalytic system via Pd(II)-catalyzed tandem methylene C(sp^3)−H alkenylation/aza-Wacker cyclization of α-*gem*-dialkyl aliphatic amides **168** using 3,3′-F$_2$−BINOL ligand **L47** (Scheme 43b).[120] Notably, the directing group could be easily removed by treatment with hydrazine hydrate, and the corresponding six-membered cyclic acyl hydrazone **171** was obtained in 80% yield with the same enantioselectivity (93% *ee*) and diastereoselective rate (>20:1). **171** was easily reduced under excessive LiAlH$_4$, giving the corresponding chiral tetrahydropyridazine **172** in 52% yield without the loss of enantioselectivity.

Apart from using 3,3′-disubstituted BINOL ligands to achieve asymmetric C−C bond formation reactions, these chiral ligands could also be applied in asymmetric C−X formation reactions. In 2020, the Shi group reported the Pd(II)-catalyzed enantioselective intramolecular amidation of both benzylic and unbiased methylene C(sp^3)−H bonds using PIP DG and 3,3′-disubstituted BINOL **L49** or H$_8$−BINOL **L50** as chiral ligands (Scheme 44a).[121] A range of chiral β-lactams were synthesized with high enantioselectivities. Notably, aryl iodide **I-1** was used as the oxidant to promote the C−N reductive elimination process. Chen and co-workers independently achieved a palladium-catalyzed enantioselective intramolecular C(sp^3)−H amidation by the use of 8-aminoquinoline as the DG and 3,3′-F$_2$−BINOL **L47** as the chiral ligand (Scheme 44b).[122] 2-Methoxy-5-chlorophenyl iodide was identified to be the choice oxidant to achieve the desired C−N reductive elimination. Compared to the protocol of Shi's group,[121] only benzylic methylene C(sp^3)−H amidation could be achieved in this reaction.

In 2021, asymmetric intramolecular methylene C(sp^3)−H arylation of iodoaryl-derived amides **134** was also achieved using 3,3′-F$_2$−BINOL **L47** as the ligand and Pd(hfac)$_2$ as the catalyst (Scheme 45).[123] A variety of chiral chromane and tetrahydroquinoline derivatives were formed in good yields with high

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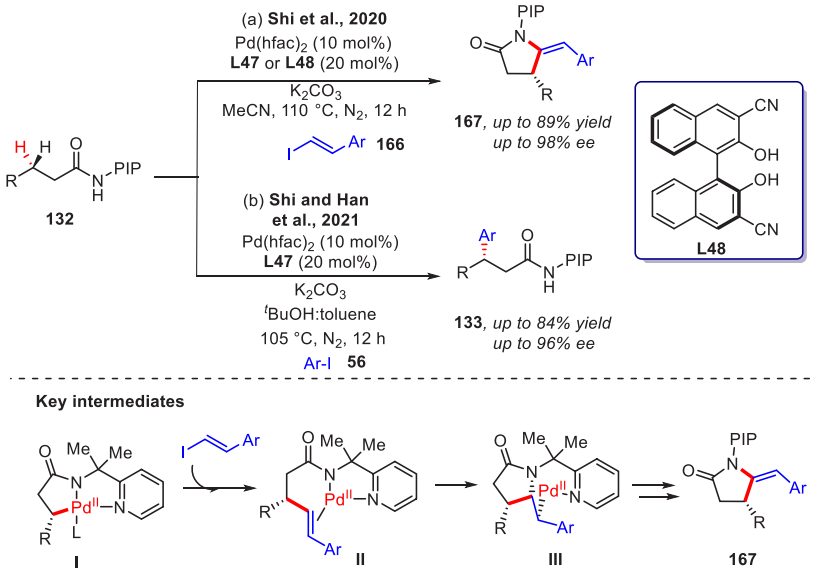
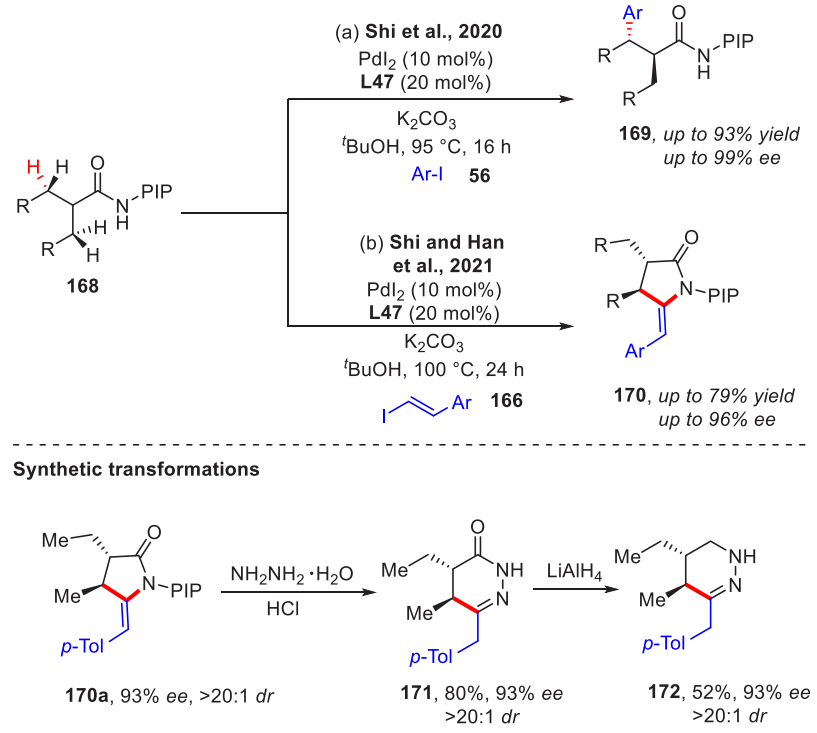
Scheme 42. Palladium-Catalyzed Enantioselective Intermolecular C(sp^3)−H Alkenylation/aza-Wacker Cyclization and C(sp^3)−H Arylation



Scheme 43. Palladium-Catalyzed Enantioselective Intermolecular C(sp^3)−H Arylation and C(sp^3)−H Alkenylation/aza-Wacker Cyclization



enantioselectivities. Cleavage of the PIP directing group afforded the corresponding methyl ester **175** without significant erosion of enantiomeric excess.

7. BINAPHTHYL-DERIVED CHIRAL CYCLOPENTADIENYL LIGANDS

Metal complexes ligated with a cyclopentadienyl (Cp) ligand are generally regarded as useful catalysts.[124−127] However, the application of these metal catalysts in asymmetric reactions has been limited because of the difficulty to modify the Cp ring.[128,129] Pioneered by Ye and Cramer[130] and Rovis and co-workers,[131] chiral Cp^x ligands have emerged as powerful ligands in enantioselective C−H activation reactions. In 2012, Ye and Cramer developed a C_2-symmetric mannitol-linked chiral Cp ligand, which could be successfully applied in rhodium(III)-catalyzed enantioselective C−H functionalization with high levels of efficiency and enantiocontrol.[130] Rovis and co-workers independently reported a biotinylated rhodium(III)-catalyzed asymmetric C−H activation reaction for the synthesis of enantioenriched dihydroisoquinolones. A macromolecular streptavidinenzyme-linked chiral Cp ligand was disclosed, and moderate enantioselectivities were achieved in the coupling of

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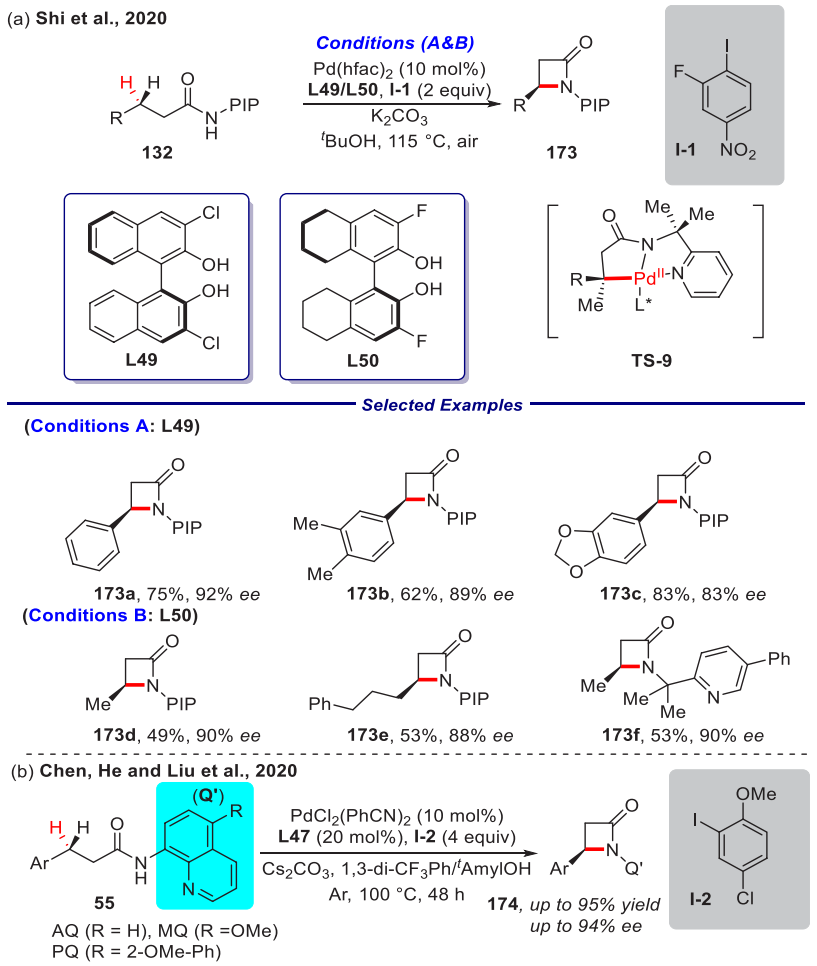
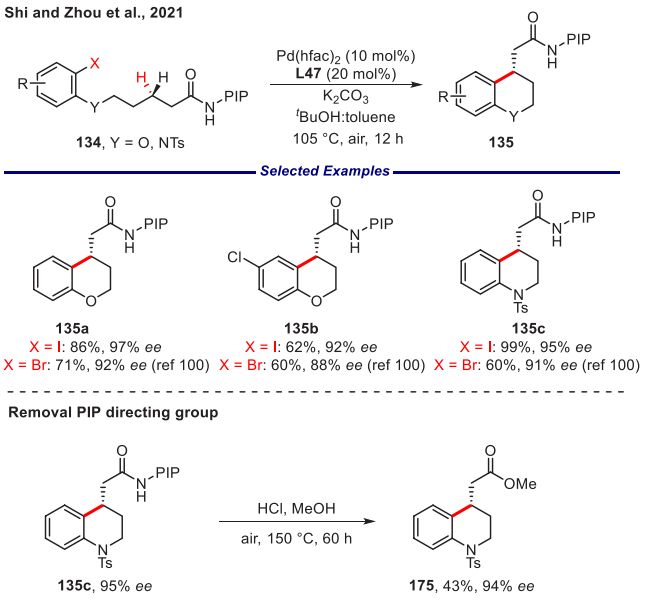
Scheme 44. Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)−H Amidation Using Chiral 3,3′-Disubstituted BINOLs



Scheme 45. Palladium-Catalyzed Enantioselective Intramolecular C(sp^3)−H Arylation



benzamides and alkenes.[131] Soon after, the Cramer group further developed sterically and electronically modifiable C2-symmetric binaphthyl scaffold chiral Cp ligands, which could be widely applied in rhodium catalyzed asymmetric reactions.[27−29] In this section, the application of metal complexes coordinated by binaphthyl-derived chiral Cp ligands in enantioselective C−H activation reactions are discussed.

Ye and Cramer introduced a novel C2-symmetric chiral Cp ligand in 2012,[130] and they further improved this type of ligand with a binaphthyl scaffold. In 2013, they reported an enantioselective C−H allylation of benzamides **176** with allenes **177** using the Rh(I) complexes with sterically adjustable binaphthyl backbones (Scheme 46a).[132] Notably, the fine turning of binaphthyl-derived chiral Cp could not only adjust the electronic and steric parameters of Rh complexes but also create a chiral pocket to adjust their reactivity and selectivity. Binaphthyl-derived chiral Cp **Rh1** with 3,3′-disubstituted bulky OTIPS was demonstrated to be the optimal catalyst, providing excellent yields and high enantioselectivities for the corresponding allylated products. In 2014, the same group further disclosed an asymmetric intramolecular hydroarylation of internal alkenes **179** using the **Rh2** catalyst containing a binaphthyl-derived chiral Cp ligand (Scheme 46b).[133] A broad range of dihydrobenzofurans bearing methyl-substituted quaternary stereocenters was obtained in high yields with good enantioselectivities. Besides the aryl hydroxamates, a substrate bearing a nitrogen atom (**179d**) could react smoothly for the cyclization and deliver the corresponding product **180d** in good

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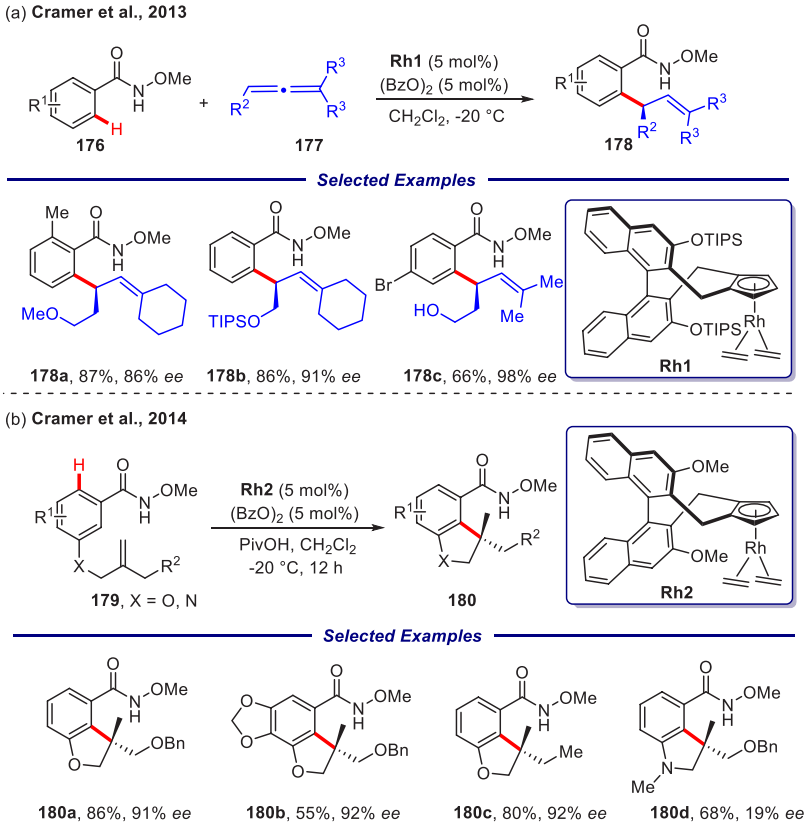
Scheme 46. Cp^{x}Rh(III)-Catalyzed Enantioselective C(sp^2)−H Functionalization of *N*-Methoxybenzamides with Allenes and Internal Alkenes



yield but with poor enantioselectivity. In this transformation, silver salts show a significant role toward the selectivity of the cyclization process. The same group also expanded the rhodium(III)-catalyzed enantioselective intramolecular cyclization reaction to access hydroxychromane and phthalide backbones bearing chiral secondary alcohol motifs.[134] In 2020, Wang and co-workers realized a Grignard-type addition of the inert C(sp^2)−H bond to aldehydes using the catalyst **Rh2**, providing the chiral 3-phthalides in good yields with high enantioselectivities.[135]

In 2017, Ellman and co-workers achieved an asymmetric aryl C−H bond conjugate addition to nitroalkenes **182** using binaphthyl-derived chiral complex **Rh3** (Scheme 47a).[136] However, only four addition products were obtained with moderate enantioselectivity. In 2019, the same group further demonstrated that the chiral complex **Rh3** could be employed in an asymmetric third component reaction, enabling the synthesis of *α*-methyl branched amines in the presence of arenes bearing pyrazole or oxime functional groups, ethylene gas, and dioxazolones as coupling partners (Scheme 47b).[137] In 2020, Duchemin and Cramer revealed a Cp^{x}Rh(III)-catalyzed intermolecular enantioselective carboamination of *N*-enoxysuccinimides with acrylates,[138] and the sterically hindered trisubstituted chiral Cp ligand was proven to be crucial for the reaction reactivity. Various unnatural *a*-amino esters were obtained with high enantiomeric ratios. In the same year, a similar Cp^{x}Rh(III) catalyst was also used in the diastereo- and enantioselective C−H cyclopropylation reaction of cyclopropenyl alcohols with *N*-phenoxytosylamides, furnishing the *trans*-cyclopropanes under mild conditions.[139]

Heterobicyclic olefins could also be used as coupling partners in asymmetric C−H functionalization reactions by binaphthyl-derived chiral Cp^{x}Rh^{III} catalyst systems. In 2019, Wang and Cramer achieved the enantioselective C−H activation/ring-opening sequence to synthesize chiral cyclopentenyl amines **189** with the aid of binaphthyl-derived chiral Cp**Rh4** as the catalyst and aroyl peroxide as the additive (Scheme 48a).[140] A wide range of aryl ketoxime ethers **187** were tolerated and gave access to the desired products in high yields and good enantioselectivities. It should be noted that this method could also be compatible for *α,β*-unsaturated oxime ethers at the higher reaction temperature. In the same year, Li and co-workers developed a Cp^{x}Rh(III)-catalyzed enantioselective coupling of indoles **190** and 7-azabenzonorbornadienes **191** by a desymmetrization strategy (Scheme 48b).[141] Notably, the additive $AgSbF_6$ displayed pronounced effects on increasing the reaction efficiency by suppressing the C3−H activation of the indoles. Subsequently, the Li group further disclosed a Cp^{x}Rh(III)-catalyzed oxidative annulation reaction of arenes with azabenzonorbornadienes via enantioselective 2-fold C−H activation.[142]

Notably, this binaphthyl-derived chiral Cp^{x}Rh catalyst system also demonstrated potential in the construction of quaternary carbon stereocenters. One of the typical strategies is [4 + 1] annulation of aryl hydroxamates with carbon electrophilic partners to construct the tetrasubstituted carbon stereocenters. In 2014, Ye and Cramer reported the enantioselective C−H functionalization with aryl hydroxamates **194** to synthesize chiral isoindolinones **195** using binaphthyl-derived chiral Cp**Rh1** as the catalyst (Scheme 49a).[143] In 2017, Song and co-workers further accomplished the enantioselective C−H

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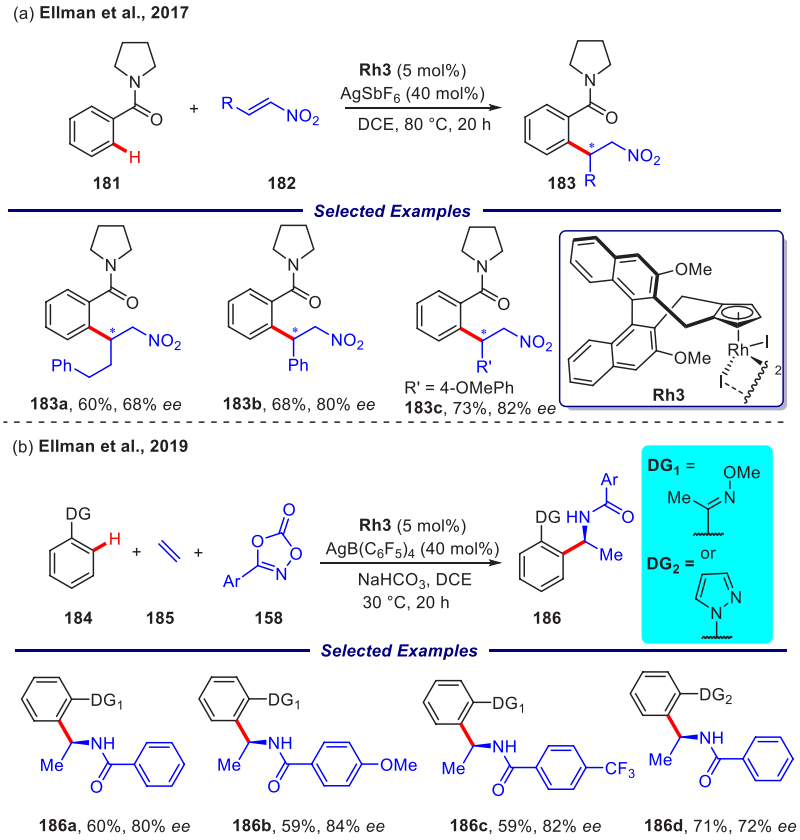
Scheme 47. (a) Cp^{x}Rh(III)-Catalyzed Enantioselective Benzamide C−H Addition with Michael Acceptors; (b) Cp^{x}Rh(III)-Catalyzed 1,1-Addition of C−H Bonds and Aminating Agents to Terminal Alkenes



annulation of indolyl hydroxamates **196** with diazo ester **193** using a chiral binaphthyl-derived Cp**Rh3** as a catalyst (Scheme 49b).[144] Particularly, the [4 + 1] annulation reaction could also be achieved through asymmetric alkenyl C−H functionalization with alkenes to access the enantioenriched α,β-unsaturated-γ-lactams containing a chiral quaternary stereocenter.[145] Afterward, You and co-workers accomplished the [4 + 1] annulation reaction of benzamides with styrenes to construct chiral isoindolinones.[146] Notably, Li and co-workers further disclosed the [4 + 1] spiroannulation reaction between *N*-aryl nitrones and quinone diazides through an enantioselective C−H activation and axial-to-central chirality transfer process to access spirocycles bearing quaternary carbon stereocenters.[147]

Alternatively, the [3 + 2] spiroannulation of alkynes with different coupling partners was also an effective way to construct the tetrasubstituted carbon stereocenters. In 2015, You and co-workers established the enantioselective dearomatization of β-naphthols **199** with internal alkynes **198** via the asymmetric C−H functionalization/annulation reaction using a chiral binaphthyl-derived Cp**Rh2** as a catalyst (Scheme 50a).[148] A series of simple naphthol derivatives were tolerated to obtain chiral spirocyclic β-naphthalenones **202** in moderate to good yields and excellent enantioselectivities. Simultaneously, Lam and co-workers developed an enantioselective C−H functionalization/spiroannulation with alkynes **198** to synthesize spiroindenes **203** using **Rh5** as a catalyst (Scheme 50b).[149] It should be noted that $Cu(OAc)_2$ as an oxidant is crucial to regenerate activated rhodium catalyst. In 2016, Cramer and co-workers reported *N*-sulfonyl ketimines **201** as nucleophilic coupling partners in the synthesis of spirocyclic sultams **204** by enantioselective annulation of alkynes (Scheme 50c).[150] Notably, catalyst **Rh2** plays a key role in the enantio-induction process, and the chiral carboxylic acid additive **A1** has no influence on the enantiocontrol.

Axially chiral biaryl compounds widely exist in natural products and biologically active molecules.[151−153] Binaphthyl-derived chiral Cp ligands could be successfully applied in the synthesis of these unique compounds. In 2014, Zheng and You reported the asymmetric dehydrogenative coupling of biaryls **205** with alkenes **85** to construct axially chiral molecules using **Rh2** as a catalyst (Scheme 51a).[154] It should be noted that the axially chiral biaryl product **206c** could be employed as a useful ligand in the rhodium-catalyzed conjugate addition reaction. In 2019, Li and co-workers achieved the asymmetric synthesis of axially chiral biindolyls **209** via the C−H activation and alkyne cyclization process (Scheme 51b).[155] The authors have successfully isolated a chiral rhodacyclic intermediate with 50% yield, which provides a direct mechanistic support that originally revealed a stereochemical model by Ye and Cramer.[130] In 2020, the same group further accomplished an enantioselective synthesis of biaryls by C−H activation and intermolecular coupling with alkynes **211** using binaphthyl-derived chiral complex **Rh6** or **Rh7** (Scheme 51c).[156] Both benzamides and heteroaryl carboxamides were tolerated, forming the desired products in excellent yields and good enantioselectivities. More recently, Li and co-workers developed a Cp^{x}Rh(III)-catalyzed asymmetric [3 + 2] annulation of *N*-benzylnitrones and alkynes to construct the axially and centrally chiral indenes.[157] In addition, Li and co-workers demonstrated a diastereo- and enantioselective Cp^{x}Rh(III)-catalyzed 1:2 coupling of diary-

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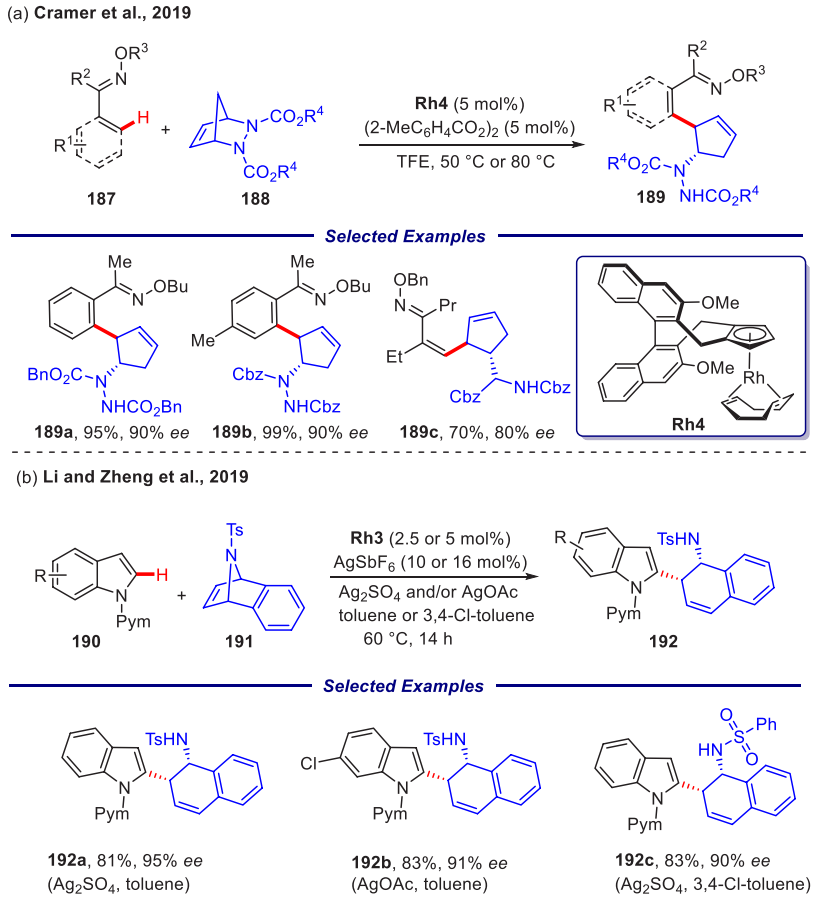
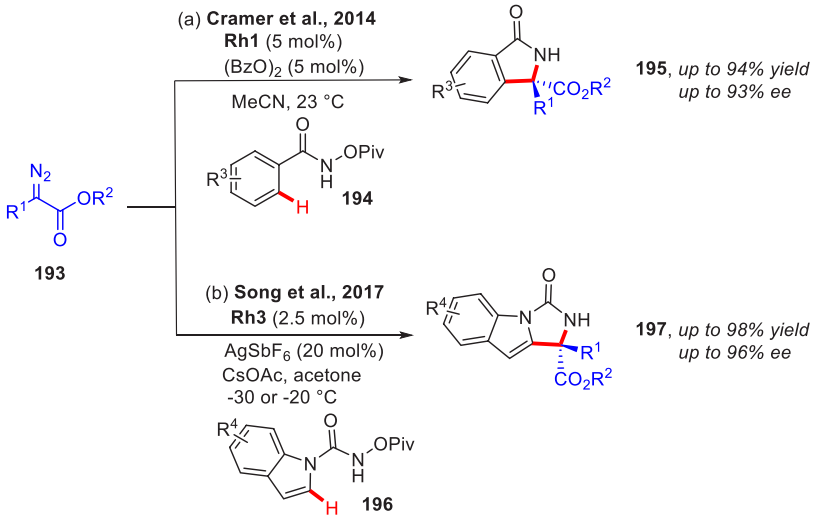
Scheme 48. Cp^{x}Rh(III)-Catalyzed Enantioselective C−H Functionalization with Heterobicyclic Olefins



Scheme 49. Cp^{x}Rh(III)-Catalyzed [4 + 1] Annulation to Synthesize Chiral Isoindolinones with Diazo Compounds



lphosphinic amides and diarylacetylenes to synthesize the biaryls with both a P stereogenic center and chiral axis through 2-fold C−H activation.[158]

Binaphthyl-derived chiral Cp is also an effective ligand for the construction of planar chirality. In 2016, You and co-workers reported a Rh(III)-catalyzed racemic annulation reaction with internal alkynes **214** for the synthesis of ferrocene-based pyridinones **215** (Scheme 52).[159] Unfortunately, only one asymmetric example was given in the presence of a binaphthyl-derived chiral Cp**Rh2** catalyst, albeit with moderate enantioselectivity (46% *ee*).

In 2017, Sun and Cramer expanded the application of such ligands in the formation of heteroatom stereogenic centers. Using **Rh2** as a catalyst realized the enantioselective C−H activation of diaryl phosphinamides **216** with internal alkynes **198** to construct P stereogenic center heterocycles by the desymmetrization strategy (Scheme 53a).[160] Deuteration experiments suggested that K_2CO_3 is the key to decrease the

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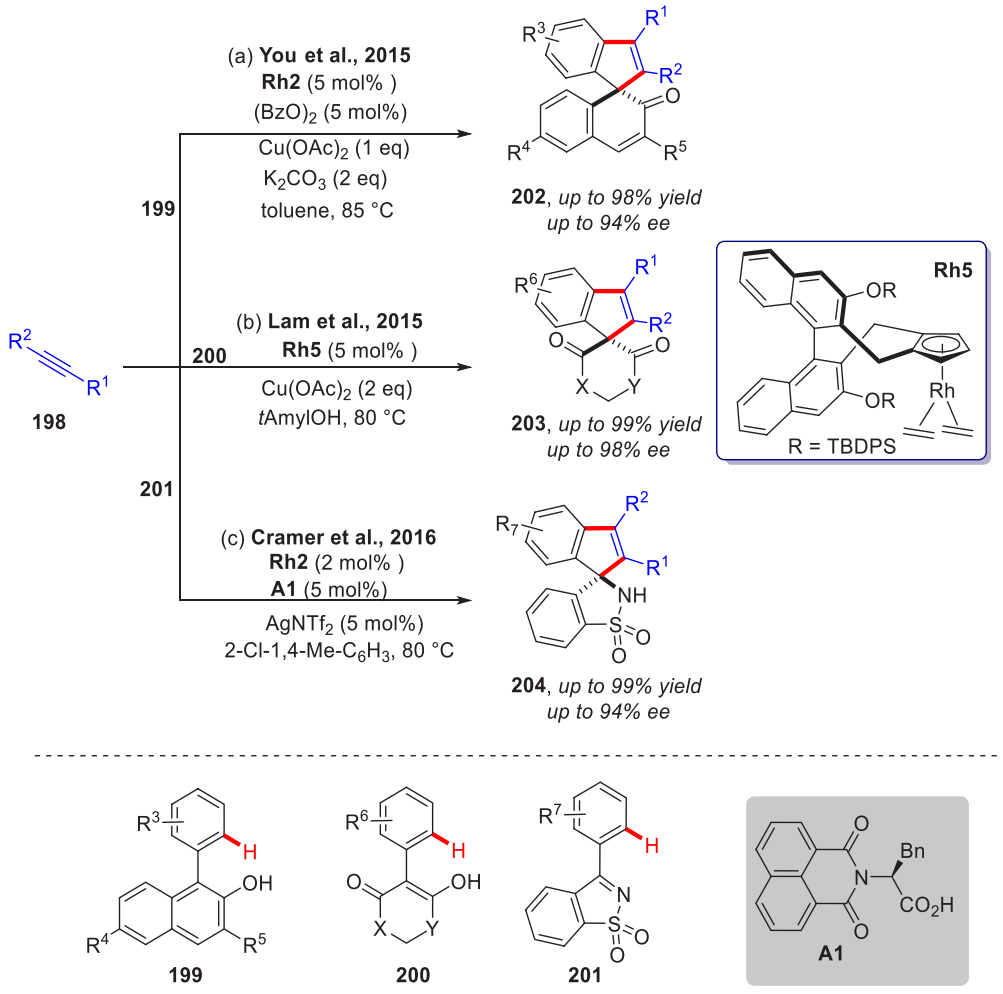
Scheme 50. Cp^{x}Rh(III)-Catalyzed [3 + 2] Spiroannulation to Construct Quaternary Carbon Stereocenters with Alkynes as Coupling Partners



reversibility of the enantio-determining C−H activation step. Notably, the desired chiral phosphorus(V) product **217a** could be readily reduced to the synthetically useful P(III)-chiral compounds **220** without a significant loss of the chirality. Subsequently, the same group developed a kinetic resolution strategy to synthesize stereogenic phosphorus(V) heterocycles using a catalyst **Rh8** (Scheme 53b).[161] It should be noted that the introduction of a bulky *tert*-butyl group on the Cp ring could significantly increase the selectivity of the kinetic resolution process and moderate s factors were obtained in this catalytic system (up to 50).

In 2018, Sun and Cramer established a Cp^{x}Rh catalyzed desymmetrizing [4 + 2] annulation of diaryl sulfoximines **153** and α-ketodiazo compounds **221** to synthesize stereogenic sulfur heterocycles (Scheme 54a).[162] Importantly, the combination of catalyst **Rh9** and a matching chiral carboxylic acid **A2** could significantly improve the reaction efficiency and asymmetric induction. In the same year, Li and co-workers achieved a similar catalytic system to construct S stereogenic centers using chiral **Rh3** as a catalyst (Scheme 54b).[163] Interestingly, in the presence of 2-methoxybenzoic acid **A3** as additive and MeOH as solvent, the desired product was obtained as *R* enantiomer. However, when 2,6-dimethoxybenzoic acid **A4** was used as additive with tetrachloroethane as solvent, the corresponding product was switched to an *S* enantiomer. Subsequently, Brauns and Cramer disclosed a kinetic resolution methodology to synthesize stereogenic sulfur heterocycles with the assistance of a chiral **Rh10** complex (Scheme 54c).[164] It should be noted that the corresponding products could be easily converted into two useful kinase inhibitors through a formal synthesis.

On the basis of the literature research, binaphthyl-derived chiral Cp combined with Rh as catalyst has been widely used in asymmetric C−H activation reactions, but there are relatively few reports that employ chiral Cp^{x}Ir(III) as a catalyst. In 2017, Cramer and co-workers accomplished a Cp^{x}Ir(III)-catalyzed enantioselective C(sp^2)−H amidation of aryl phosphine oxides **225** enabled by a desymmetrization strategy (Scheme 55a).[165] The authors discovered that the combination of binaphthyl-derived chiral Cp **Ir1** with the phthaloyl *tert*-leucine chiral carboxylic acid **A6** was crucial for the achievement of high reactivity and enantioselectivity. Poor enantio-induction was observed in the presence of chiral acid **A6** with achiral Cp*Ir(III) catalyst. Importantly, a match/mismatch effect was found toward the enantiomer of **Ir1** and **A6** in this reaction. In 2018, the authors extended a similar catalytic system to the biaryl backbone and P-chiral biaryl phosphine oxides using binaphthyl-derived chiral **Ir1** and phthaloyl *tert*-leucine **A6** as cocatalyst (Scheme 55b).[166] Moreover, the resulted products could readily be reduced to the chiral P(III) compounds, which may find a potential application in asymmetric catalysis. In 2021, Woźniak and Cramer also achieved an enantioselective C−H

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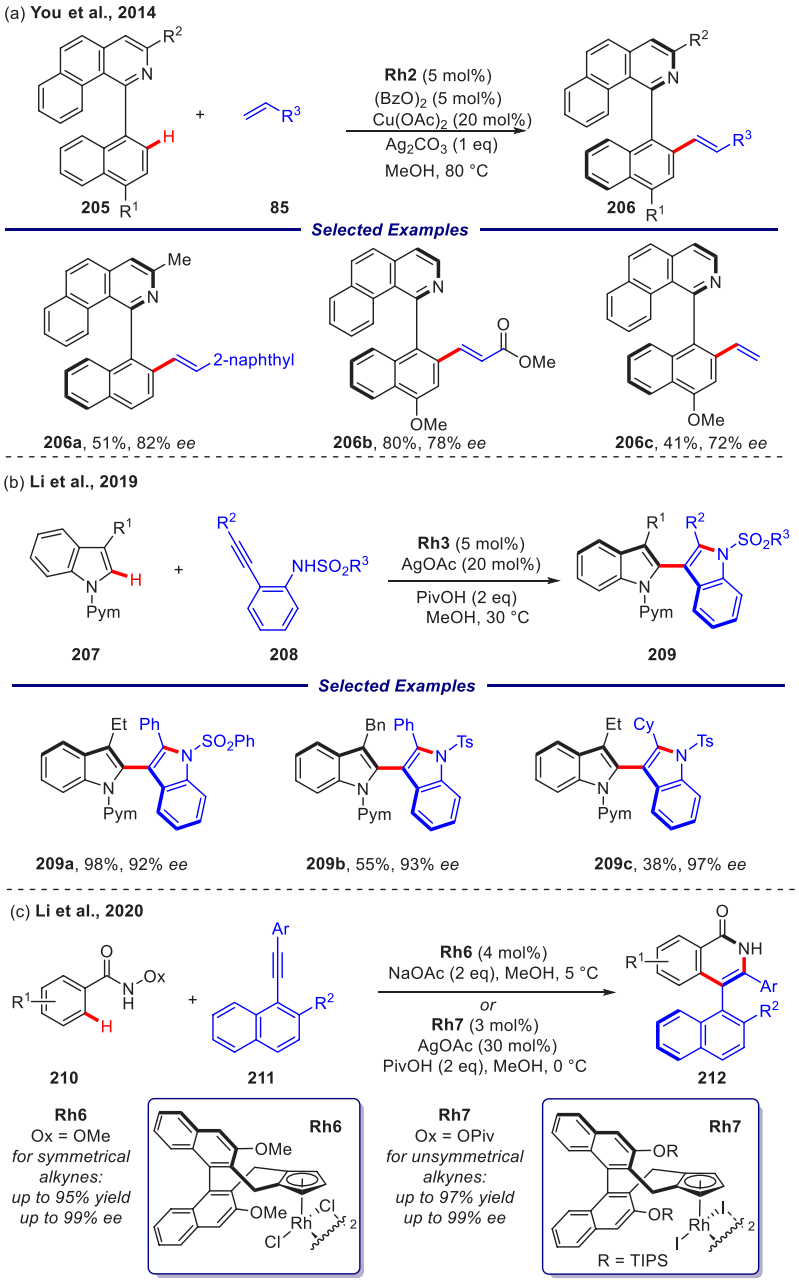
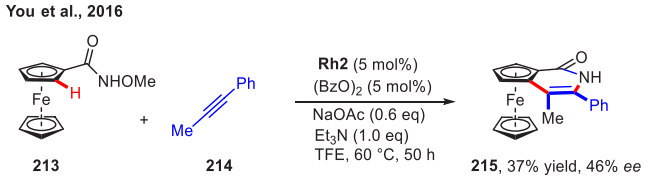
Scheme 51. Cp^{x}Rh(III)-Catalyzed Atroposelective C−H Functionalization to Synthesize Axially Chiral Biaryls with Alkene and Alkyne Acceptors



Scheme 52. Cp^{x}Rh(III)-Catalyzed Ferrocenyl C−H Functionalization to Synthesize Planar Chirality with Alkyne



arylation of tetralone derivatives with aryl boronic esters using a similar chiral Cp^{x}Ir(III) complex.[167]

Compared to the precious metal catalysts, enantioselective C−H functionalizations using catalysts based on abundant 3d metals remain a challenging field.[7,168] Early reports from Matsunaga and co-workers have proven that the combination of achiral Cp^{x}Co^{III} with chiral acids could provide an effective approach for asymmetric C−H bond activation.[10,169] In this context, binaphthyl-based chiral Cp^{x}Co catalyst could be used as an alternative catalyst system toward cobalt-catalyzed enantioselective C−H transformations. In 2019, Cramer and co-workers disclosed a [4 + 2] annulation reaction of *N*-chlorobenzamides **231** with alkenes **232** to synthesize dihydroisoquinolones **233** using binaphthyl-derived trisubstituted chiral Cp complex **Co1** (Scheme 56).[170] This methodology is compatible with a series of alkenes, furnishing the desired products in high yields and excellent enantioselectivities.

A rare-earth metal catalyst bearing a binaphthyl-derived chiral Cp ligand was developed by the Hou group. In 2014, Hou and co-workers achieved a pyridyl-directed enantioselective C-(sp^2)−H alkylation of pyridines **234** with alkenes **85** to

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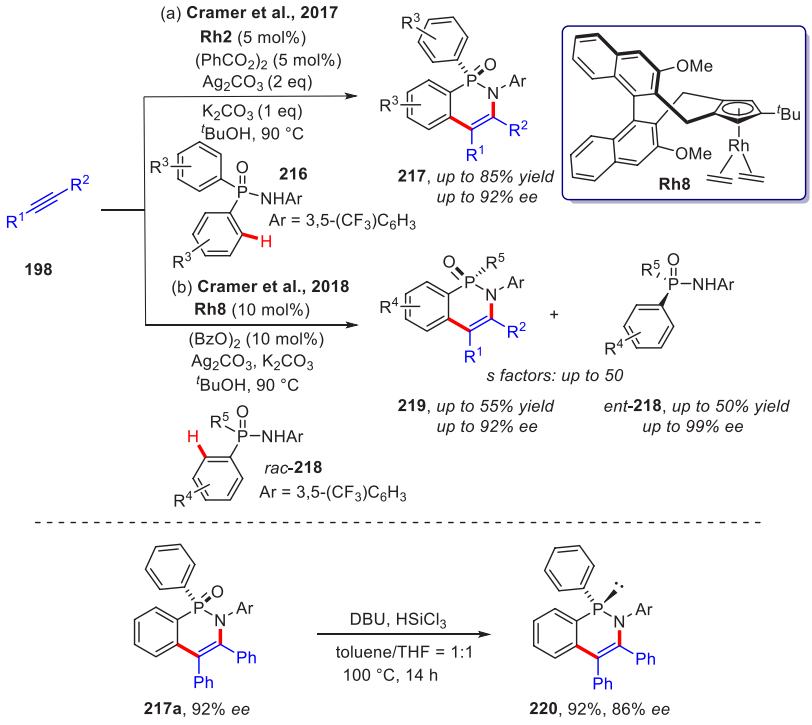
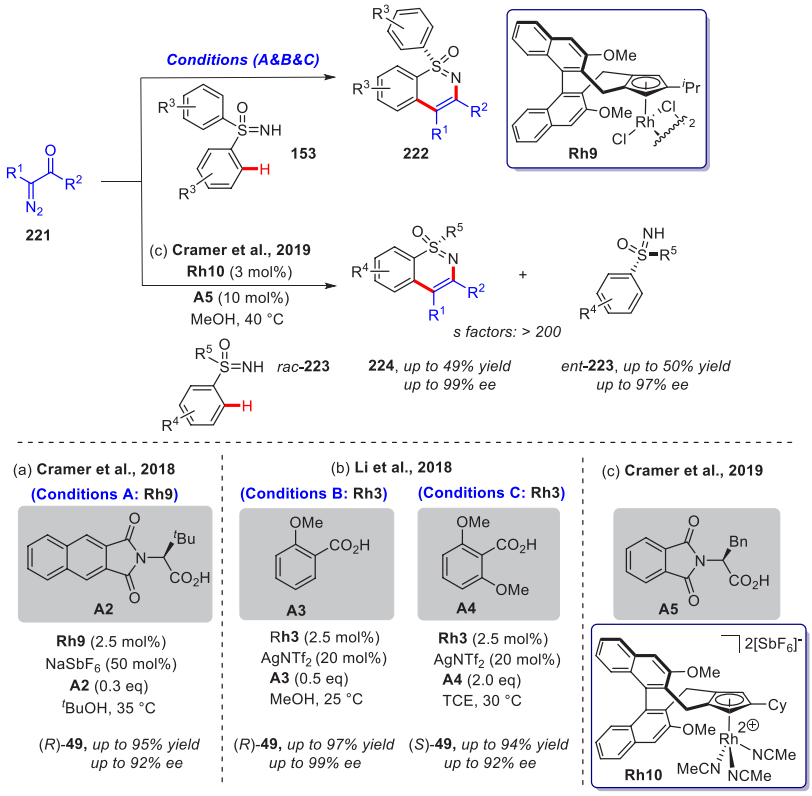
Scheme 53. Cp^{x}Rh(III)-Catalyzed the Construction of P Stereogenic Center Heterocycles with Alkynes



Scheme 54. Cp^{x}Rh(III)-Catalyzed the Construction of S Stereogenic Center Heterocycles with Diazo Compounds



synthesize alkylated pyridine derivatives **235** using binaphthyl-derived chiral complex **Sc1** as a catalyst (Scheme 57a).[171] A wide range of terminal alkenes were tolerated to obtain the branched products in high yields and excellent enantioselectivities. In 2020, the authors extended a similar catalytic system to construct all-carbon quaternary stereocenters through an asymmetric intramolecular C(sp^2)−H alkylation of imidazoles **236** with 1,1-disubstituted alkenes using **Sc2** as the chiral catalyst (Scheme 57b).[172] In 2021, the same group further disclosed the enantioselective C(sp^2)−H alkenylation of ferrocenes **238** with internal alkynes **198** to access planar chiral ferrocene scaffolds **239** employing **Sc3** bearing the Cp^x ligand as

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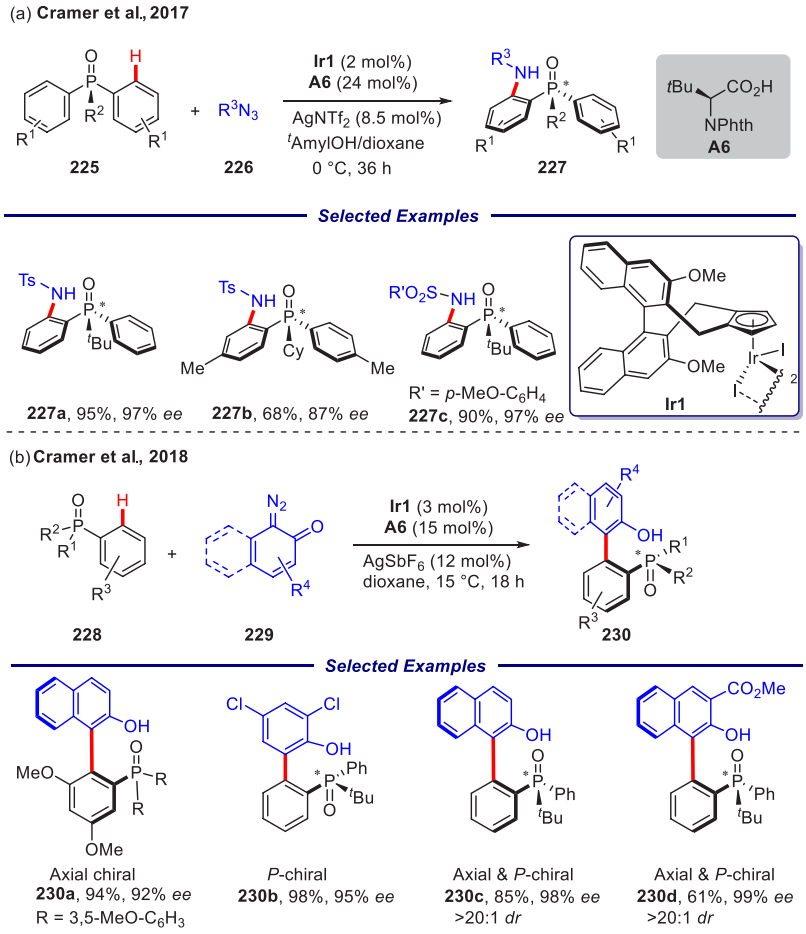
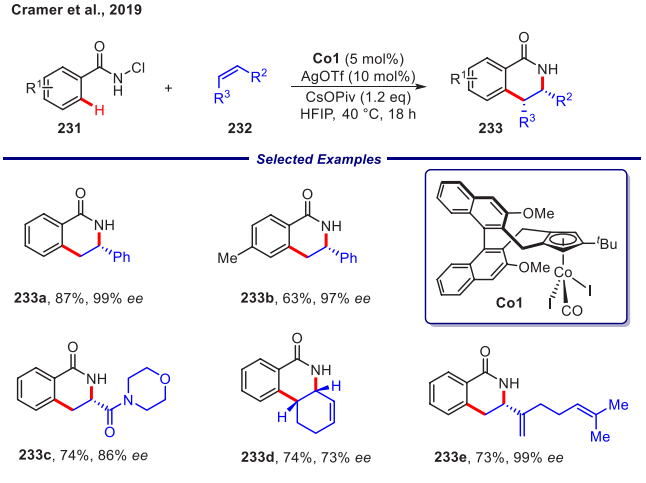
Scheme 55. Cp^{x}Ir(III)-Catalyzed the Synthesis of Axial and/or P-Chiral Biaryl Phosphine Oxides by C(sp^2)−H Functionalization



Scheme 56. Cp^{x}Co(III)-Catalyzed [4 + 2] Annulation Reaction of *N*-Chlorobenzamides with Alkenes to Synthesize Dihydroisoquinolones



a catalyst (Scheme 57c).[173] It should be noted that the desired **239a** product could serve as a useful chiral ligand in Rh-catalyzed asymmetric 1,4-addition of an aryl boronic acid to α,β-unsaturated ketone to form the corresponding product in high yield and high enantioselectivity. Moreover, the authors developed a similar catalytic system for the yttrium-catalyzed enantioselective pyridine benzylic C(sp^3)−H addition reaction using a chiral complex **Y** as the catalyst.[174]

8. SUMMARY AND OUTLOOK

In this Review, we summarized the advance of binaphthyl-based chiral ligands in transition metal-catalyzed enantioselective C−H functionalization. Several classes of binaphthyl-based chiral ligands such as BINOL-derived phosphoramidites, phosphines, phosphoric acids, and carboxylic acids as well as 3,3′-disubstituted BINOLs were discussed in detail. Divergent enantioenriched molecules bearing point, axial, and planar chirality were synthesized using different transition metal catalysts (Pd, Rh, Ir, Ru, etc.). The advances of chiral metal complexes ligated with binaphthyl-based chiral cyclopentadienyl ligands in asymmetric C−H activation reactions are also provided.

Despite the above-mentioned success of the metal/binaphthyl-based chiral ligand catalytic system, the transition metal catalysts used for the asymmetric C−H functionalization reaction were generally limited to noble metal catalysts. In sharp contrast, catalysis based on inexpensive and sustainable 3d transition metals is relatively underdeveloped. In addition, most of these transformations are C−C bond formation reactions, thus making the construction of C-heteroatom bonds highly desirable.[175] Another issue for the metal/binaphthyl-based chiral ligand catalytic systems is their limitation in enantioselective C(sp^3)−H functionalization. Since the binaphthyl-based chiral scaffolds can be modified to influence the steric and electronic environment around the metal center, the broad opportunity to access the new ligand/catalyst catalytic system may expand their accessibility in the asymmetric C(sp^3)−H

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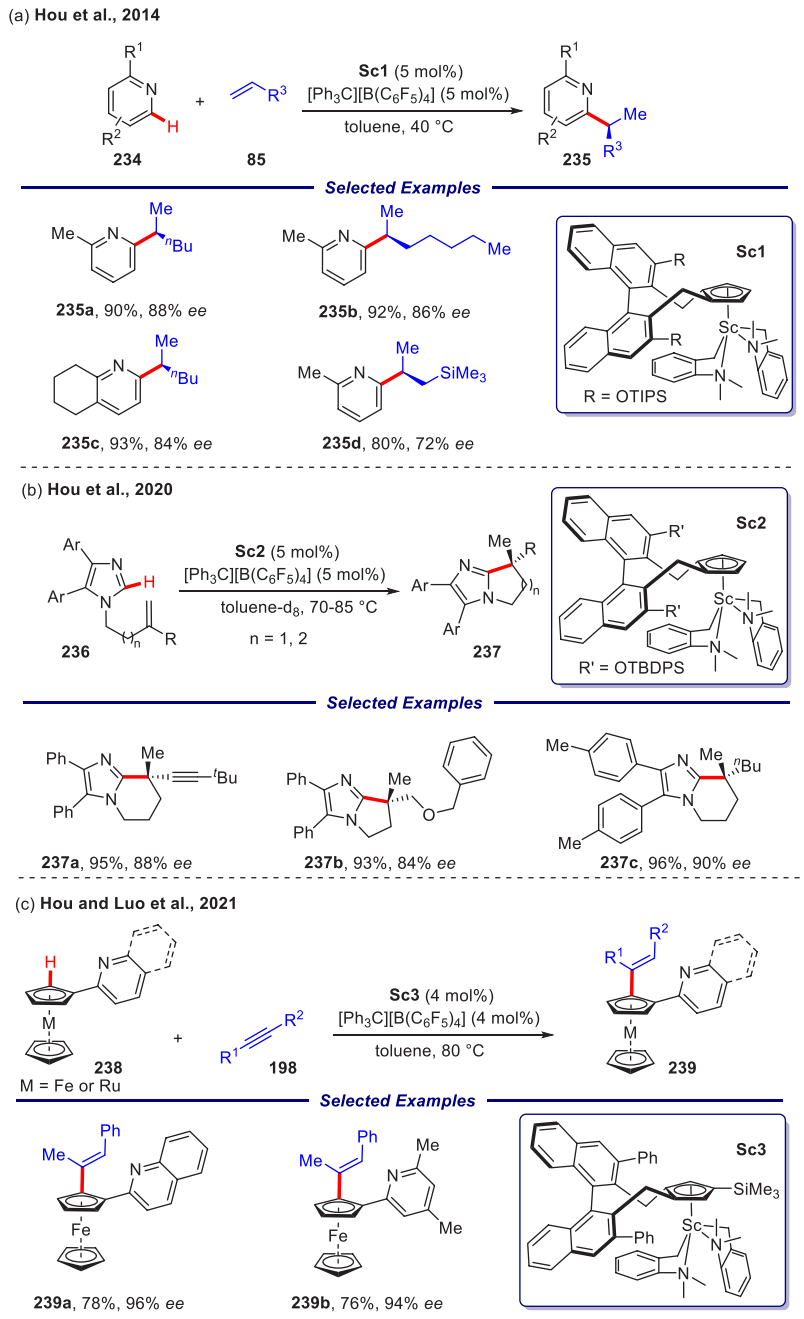
Scheme 57. $Cp^xSc(III)$-Catalyzed Enantioselective $C(sp^2)-H$ Functionalization



functionalization reaction. The design and development of electronically and sterically tunable binaphthyl-based Cp^x ligands also represent an alternative option to access chiral molecules with high enantioselectivity.

In summary, the development of a new family of binaphthyl-based chiral ligands may lead to improved ligands, thereby providing opportunities for the discovery of new reactions. A further investigation toward the reaction mechanism and substrate scope may extend their practical applications. We hope that this Review will provide some insights and inspiration to the exciting area of asymmetric C−H functionalization.

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Notes

The authors declare no competing financial interest.

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This paper was published ASAP on July 18, 2022, with an incorrect graphic for Scheme 23. The corrected version was reposted on July 19, 2022.

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