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Transition Metal Catalyzed Enantioselective C(sp^2)−H Bond Functionalization

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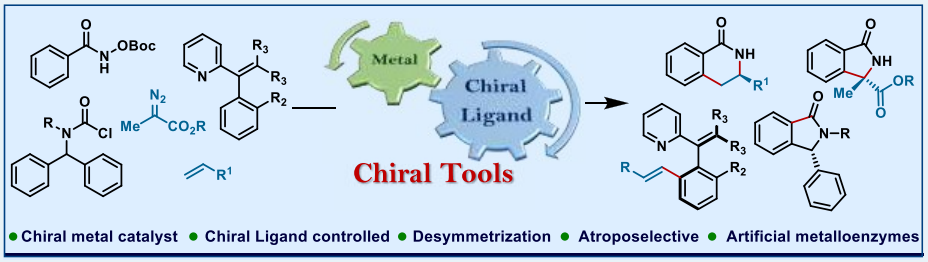

ABSTRACT: Direct catalytic transformation of C−H bonds to new functionalities has provided a powerful strategy to synthesize complex molecular scaffolds in a straightforward way. Unstinting efforts of the synthetic community have helped to overcome the long-standing major challenge of regioselectivity by introducing the directing group concept. However, the full potential of the strategy cannot be realized unless the activated C−H bonds are stereochemically controlled. The enantioselective C−H bond functionalization could provide an imperative tool for a sustainable way of synthesizing chiral complex molecular scaffolds. Despite the intrinsic challenges in achieving stereocontrol, the synthetic community has developed different tools in order to achieve stereoselective C−H bond functionalization. In this review, we discuss the remarkable recent advances in the emerging area of enantioselective C(sp^2)−H bond functionalization to highlight the challenges and opportunities, emphasizing the different techniques developed so far.

KEYWORDS: *asymmetric catalysis, C−H activation, desymmetrization, axial chirality, artificial metalloenzymes*

1. INTRODUCTION

Transition metal catalyzed direct transformations of inert C−H bonds in organic molecules provides a way upfront to construct complex molecular scaffolds overriding the limitation of synthetic manipulation at specific carbon center without having a distinct functional group.[1] Nonetheless, this is a very attractive approach owing to its intrinsic step-economic and environmentally benign nature. Most importantly, this concept opens up a wider avenue in drug discovery and drug design employing single step C−H bond functionalization to a diverse range of functionalities at previously inaccessible carbon centers.[2] However, inherent similar electronic and steric properties of multiple C−H bonds in a molecule provide a fundamental challenge to afford a site-selective C−H bond functionalized product.[3] With determined efforts, the synthetic community has been able to overcome the selectivity issues by regioselective C−H bond metalation with the assistance of electronic biases or directing effects of different functional groups (termed directing groups, DGs).[4] This approach enjoys stupendous development to reach out the distal C−H bonds from the proximal one selectively over time.[4c,5c] Direct C−H bond functionalization strategies have been elegantly applied in the synthesis of several natural products, pharmaceutically relevant molecules, agrochemicals, and several complex molecules.[2a,f,6] However, the widespread applicability of C−H bond activation in organic chemistry cannot be realized unless the modified C−H bonds are stereochemically controlled. An efficient way to introduce chirality in an organic molecule is a prime goal of the synthetic community as often pharmaceuticals and agrochemicals entail chiral components (and that cannot be achieved without direct enantioselective C−H bond functionalization in general).[7] Direct enantioselective C−H bond functionalization would make it possible by precise synthetic manipulation of the C−H bond in a stereocontrolled fashion. Successful execution of stereocontrolled C−H bond functionalization strategies would provide synthetic chemists with the ability to grasp control over the introduction of a stereocenter in a reaction sequence.

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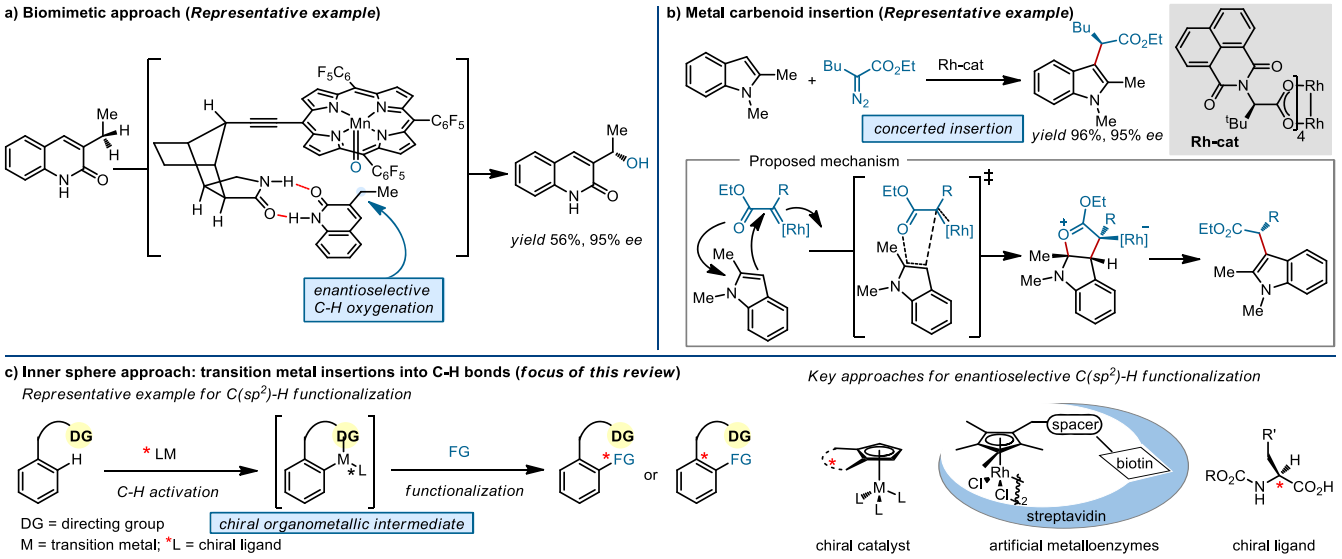

Figure 1. General mechanistic overview of transition metal-catalyzed enantioselective C−H functionalization.

Another major issue is in discriminating the diastereomeric transition state during the asymmetric catalysis under harsh reaction conditions which usually are required to activate and directly functionalize the chemically inert C−H bonds (BDE of C−H bonds are typically 90−110 kcal mol^{-1}). Despite the aforementioned obstacle, several different approaches have been developed for enantioselective C−H bond functionalization.[8] Mainly two different kinds of fundamental mechanisms have been realized in enantioselective functionalization of C−H bonds. In an outer-sphere or coordination mechanism where the C−H bond does not directly interact with the metal center, these include biomimetic approaches[9] operating through H atom abstraction followed by the radical relay[10] or radical rebound mechanism (Figure 1a),[11] metallonitrene and metallocarbene insertions (Figure 1b).[12] In the transition metal-mediated C−H bond activation, the transition metal directly interacts with the C−H bond and provides a well-defined carbon−metal bond (organometallic intermediate) upon C−H bond cleavage (Figure 1c). This is known as the inner-sphere or organometallic approach. In general, the inner sphere approach relies on two fundamental pathways based on the nature of the stereochemistry generating step, such as (i) stereochemistry generating C(sp^2)−H activation and (ii) stereochemistry generating migratory insertion step. Besides these, other several reactions have also been developed whose stereochemistry generation steps are ambiguous.[13] Chemoselective desymmetrization of a prochiral starting material via C−H activation of an enantiotopic C(sp^2)−H bond, followed by either intra- or intermolecular functionalization leading to generate either a central or a planar chiral molecule, is known as the stereochemistry generating C(sp^2)−H activation pathway. In 2008, Yu and co-workers demonstrated an unprecedented Pd-catalyzed enantioselective desymmetric C−H alkylation of prochiral C(sp^2)−H and C(sp^3)−H using alkyl boronic acids as a coupling partner and monoprotected amino acid as chiral ligands (*vide infra*).[14] Contrary to the previous approach, the stereochemistry generating migratory insertion step involves realization of control addition of a coupling partner selectively to one enantiotopic face of the prochiral C−H activated bond with the assistance of a chiral catalyst. This is the majorly explored approach in asymmetric C−H functionalization strategies.

Asymmetric C−H functionalization approaches have been summarized in several reviews, and most of the reviews are very precise directional.[15] Recently, Cramer[15d] and Ackermann[15c] independently summarized the development of Earth-abundant 3d transition-metal catalyzed enantioselective C−H functionalization. Yu's review highlighted the recent advances in transition metal (Pd-, Ir-, and Rh-) catalyzed asymmetric C(sp^3)−H bond functionalization through desymmetrization by using a specific chiral ligand scaffold.[15b] The most recent comprehensive review on asymmetric C−H bond functionalization, mainly on Rh- and Ir-catalyzed asymmetric transformations, was communicated by Cramer at the end of 2016 and thus, did not cover the recent notable advances in the emerging area of transition metal catalyzed enantioselective C−H bond functionalization.[16] Cramer and co-workers organized the literature based on the nature of the stereochemistry-generating step in the different approach on asymmetric C−H functionalization. In this review, we intend to highlight the remarkable advancements in enantioselective C(sp^2)−H bond functionalization, embracing the developed strategies such as (i) enantioselective C(sp^2)−H bond functionalization driven by chiral metal catalysts, (ii) chiral ligand control, (iii) enantioselective C(sp^2)−H point desymmetrization, (iv) atroposelective synthesis, and (v) artificial metalloenzymes. We aim to provide readers with an overview of the state-of-the art methodologies emphasizing mechanistic consideration in those transformations.

2. ASYMMETRIC C−H BOND FUNCTIONALIZATION DRIVEN BY CHIRAL METAL CATALYSTS

Ligand plays a pivotal role in metal-catalyzed functionalization of inert C−H bonds.[17] With the assistance of a suitable ligand, the activation barrier of inert C−H bond becomes achievable by lowering the transition state energy.[5c,18] Metal complexes coordinated by diverse ligands are widely utilized for such C−H functionalization reactions, but their application to asymmetric reactions has been relatively less explored. Chiral metal catalyst, a combination of suitable metal with the judicious choice of chiral ligand, can serve this purpose. In this

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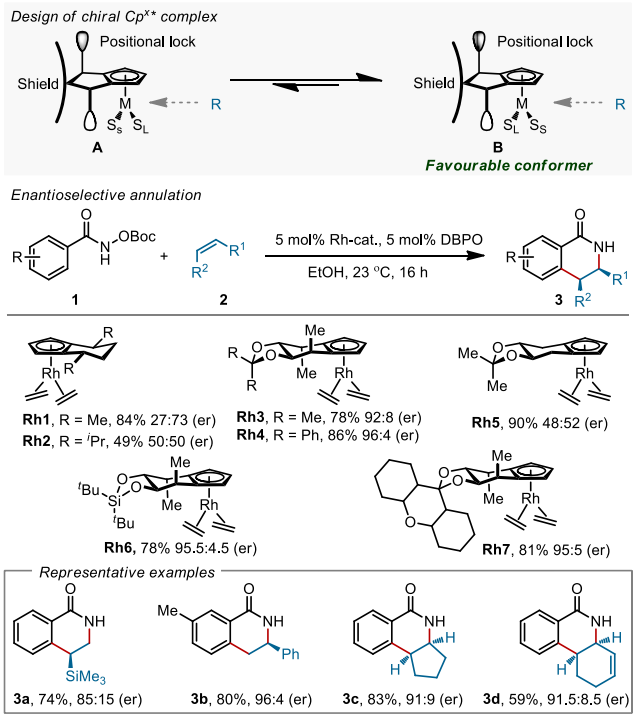
section, we discuss the designing principles of chiral ligands and how the ligands dictate to achieve the maximum attainable stereoselectivity.

2.1. Chiral Rh-Complexes in Enantioselective C−H Functionalization. The cyclopentadienyl (Cp) ligand and its pentamethylsubstituted derivatives (Cp*) are extensively utilized for the synthesis of metal complexes with transition metals, which are efficient catalysts for a number of transformations.[19] However, utilization of Cp ligands in asymmetric synthesis have been largely circumvented, presumably due to the inherent difficulties in the design and synthesis of suitable chiral Cp ligand derivatives. In 2012, the Cramer group strategically developed Cp^x ligand systems.[20] They hypothesized to utilize facial selectivity of the ligand association levied by the chiral space created by the enantiopure Cp congener. They considered three designing principles for an efficient catalyst: (i) utilization of C2-symmetric Cp derivatives just to avoid the confounding influence of diastereomer formation in coordination of the metal to either ligand face; (ii) preferring one of the other in one of two substrate orientations to afford maximum attainable selectivity by curbing the rotation around the Cp ring, and (iii) facilitating one side approach of the reactant to the metal center by steric blocking perpendicular to the Cp ring. Considering all these, they conceived the idea of synthesis of the 1,2-disubstituted Cp ligand which indulges the two orientations of the small and large substrates parallel to the positional locks (structure **A** and **B**, Scheme 1). The bulky backbone dictates the approach of the incoming reactant R from the unsubstituted side. The C2-symmetric chiral space, demonstrated by the positional locks, preferentially orient the three-coordinated intermediate to minimize steric interactions and thus favors the conformer B which further associates with reactant (R) lead to a single diastereomer. To check the feasibility of the hypothesis, they synthesized diverse Rh(I) complexes (**Rh1**−**Rh7**) and utilized them in the well-developed Cp*Rh(III)-catalyzed annulation of hydroxamic acid derivatives with olefins through C−H activation.[21]

Scheme 1. Cp^{x}Rh(III)-Catalyzed Enantioselective Annulation Hydroxamic Acid Derivatives with Olefins through C−H Activation



Complex **Rh1**, bearing steric bulk near the Cp ring, displayed good yield of the annulated product with an enantiomeric ratio (er) of 73:27. Unpredictably, upon replacing of methyl group with a bulkier isopropyl group (**Rh2**), the enantioselectivity dropped sharply. Complex **Rh5** having remote stereochemical substitution delivered very poor selectivity. The more bulky Rh-catalyst **Rh3** led to very good selectivity. Two oxygen atoms of the *trans*-acetal group being in *syn*-relation to both methyl group of cyclohexene forced the moiety into the pseudo axial position, thus enhancing the steric bulk near the metal center and providing excellent selectivity of 92:8 (er). Along with the conformational effect, the bulky acetal group hindered the backside approach of the olefin. The Rh(I)-complex with benzophenone acetal moiety (**Rh4**) turned out to be optimal, providing the desired annulated product in excellent yield and selectivity (86%, 96:4 er), suggesting the importance of the steric effect in stereoselectivity. A variety of olefins were competent reaction partners with aryl hydroxamates. Different steric and electronic variations of coupling partners had very little influence in yield and selectivity (**3a**−**3d**).

The continuous effort of Cramer's group for enantioselective C−H functionalization reaction led them to explore directed C−H allylation of hydroxamates (Scheme 2).[22] They first explored the reaction of methyl hydroxamate and trisubstituted allene with their first generation catalyst, **Rh4**. In the first generation catalyst (Rh1-Rh7), combined effort of the adjusted back wall and the defined side wall helped to transfer the ligand chirality to chirality-at-metal center. The low selectivity with the first generation catalyst stimulated them to develop additional ligand scaffolds. They have come up with tunable chiral Cp ligands having a C2-symmetric atrop-chiral biaryl moiety (**Rh8**−**Rh13**). The lower naphthyl portion turns as the back wall forces the incoming reactant's approach from the unsubstituted face. Substituents at the *ortho*-position strongly influence the selectivity by modulating the chiral pocket, and selectivity increases with the size of the substituents (**Rh8** to **Rh11**). Notably, catalyst **Rh13**, having unsubstituted ortho positions of the ligand, failed to deliver decent results, highlighting the necessity of the suitable *ortho*-substituent. The best selectivity was delivered with **Rh10**, having bulkier OTIPS moieties. However, the introduction of very bulky phenyl moieties at the *ortho*-position (**Rh12**) hindered the catalysis. The selectivity can be further understood with the stereochemical model of cyclometalated intermediates (**7** and **8**). Hydroxamate preferentially binds with the Rh-center oriented in an antiparallel fashion with the ligand backbone, directing away from the bulky OTIPS group. The allene approaches from the unsubstituted side of the ligand and coordinates to the cyclometalated intermediate with the less substituted double bond, while the substituent stays away from the Cp moiety.

In a subsequent study, the Cramer group disclosed synthesis of dihydrobenzofurans containing methyl-substituted quaternary stereocenters by intramolecular cyclization of hydroxamates appended with 1,1-disubstituted olefins at *meta* positions (Scheme 3).[23] The reaction proceeds via Rh-catalyzed directed C−H bond activation and followed by 5-

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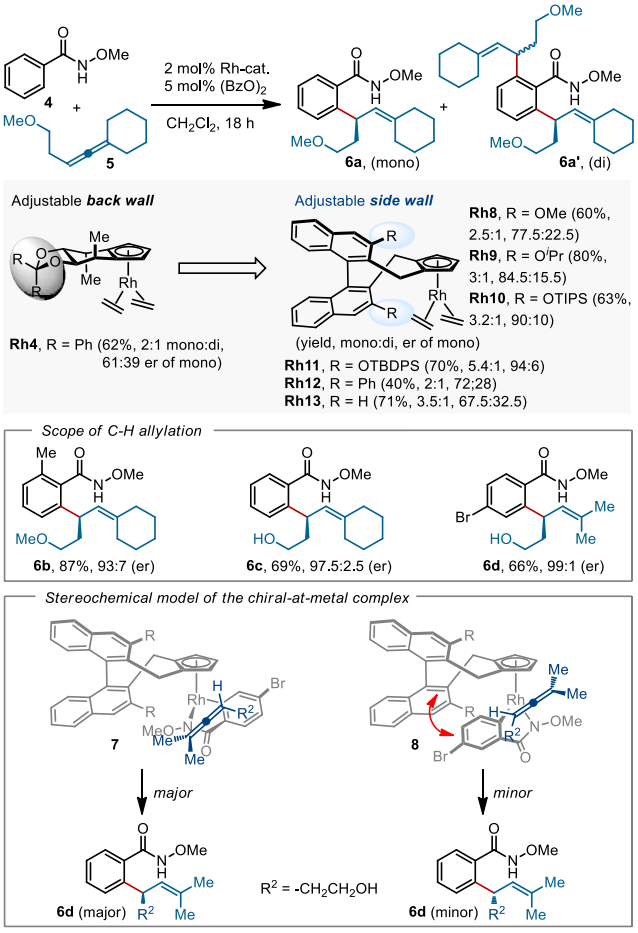
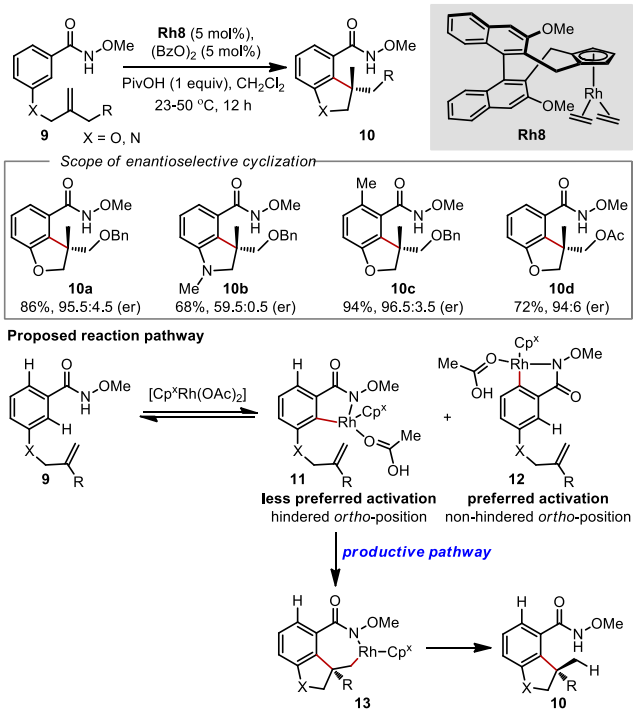
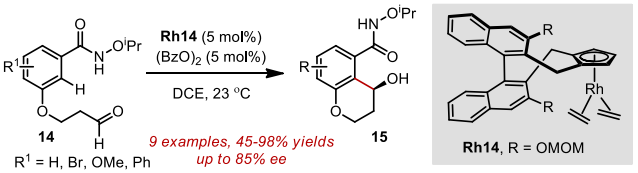
Scheme 2. Cp^{x}Rh(III)-Catalyzed Enantioselective C−H Allylation of Benzamides



Scheme 3. Cp^{x}Rh(III)-Catalyzed Intramolecular Hydroarylative Enantioselective Cyclization



Scheme 4. Cp^{x}Rh(III)-Catalyzed Intramolecular Enantioselective Cyclization



exo-trig cyclization with appended olefin. The reversibility nature of the carboxylate-assisted concerted metalation-deprotonation (CMD) pathway helps to realize the formation of the desired dihydrofuran by activation of the more sterically encumbered *ortho*-C−H bond. Presumably, the presence of an adjacent coupling partner, appended 1,1-disubstituted olefins, further drives the equilibrium for the activation of the sterically encumbered *ortho*-C−H bond over the other one. Notably, dihydrofurans (**10d**) were afforded in 72% yield under reaction conditions with the allylic ester, which in general is very susceptible to undergo ionization to the π-allyl species.

In a similar approach, the Cramer group in 2015 expanded the scope of suitable π-bond coupling partners. Instead of 1,1-disubstituted olefins, an aldehyde was used as the π-bond coupling partner attached with the carboxamate moiety through phenolic oxygen (Scheme 4).[24] The reaction proceeds in a similar fashion, Rh-catalyzed directed C−H bond activation and subsequent cyclization with the aldehyde intramolecularly, demonstrating the nucleophilic character of cyclometalated intermediates. Second generation catalyst **Rh14** appeared to be suitable for the synthesis of hydroxychromanes.

In 2014, the Cramer group reported the utilization of diazo derivatives as one-carbon components in chiral Rh(III)-catalyzed enantioselective C−H bond functionalization. They showed a straightforward way to access enantiomerically enriched isoindolones from hydroxamates and diazo derivatives utilizing geometrical and conformational constraints of the catalyst and substrates (Scheme 5).[25] The C−H activated five-membered rhodacyclic intermediate (**17**) exposes a single face to the formation of tetrahedral chiral-at-metal intermediate, while additionally suitable substituents at diazo components is highly desirable to afford highly enantioselective isoindolones. Increasing the size of substituents of diazo esters (**18a**−**18c**) gradually decreases the reaction selectivity, and presumably a similar size of both the substituents hinders the discrimination of the two enantiotopic faces by the catalyst. With the smallest substituent, methyl substituted diazo ester (**18d**−**18h**) disclosed the opposite trend. An increase in the size of substituents provided steadily improved selectivities. Both the families of Rh-catalysts were effective for catalysis, although second generation catalysts **Rh10** showed a better potential for asymmetric inductions. Varieties of aryl hydroxamates were explored under optimal reaction conditions, indicating the independency of the reaction from the arene substitution pattern (**19a**−**19d**). A range of diazo esters also compatible in the reaction system (**19e**−**19h**). Stereochemical models for isoindolone formation shed some light to rationalize the origin of enantioselectivity. The hydroxamate group stays away from the bulky OTIPS moiety favoring the preferred intermediate for approach of the carbene unit (**20**), and additionally unfavorable interaction of the hydroxamate with large ester substituent of diazo ester can be avoided. On

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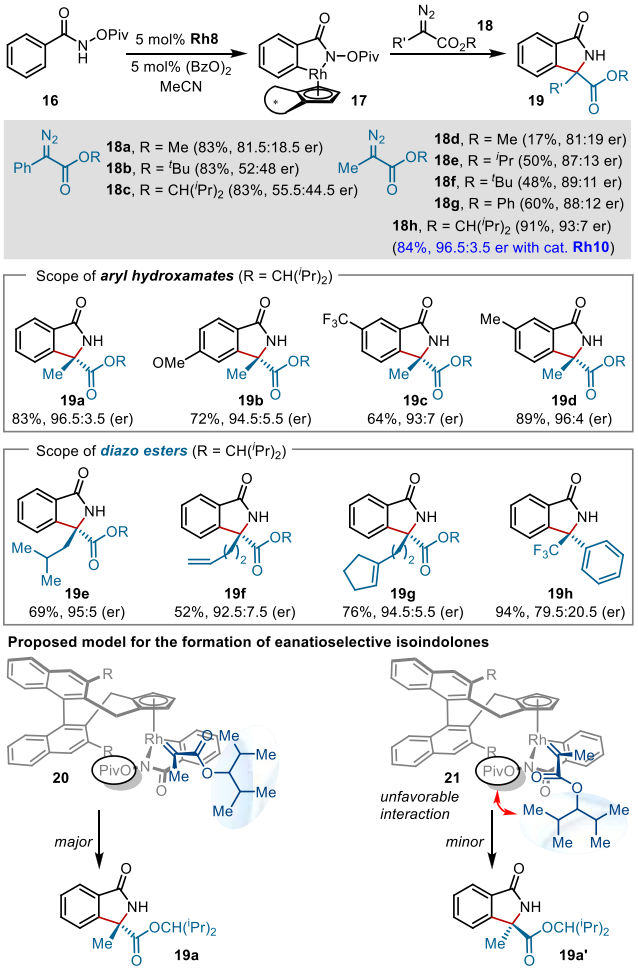
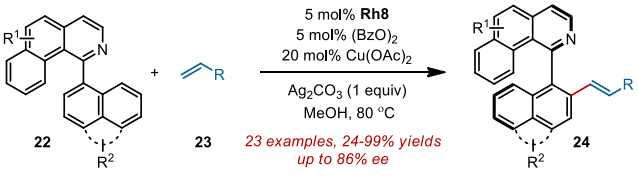
Scheme 5. Chiral Cp^{x}Rh(III)-Catalyzed Enantioselective Isoindolone Synthesis



the other hand, large unfavorable interactions in the stereochemical model (**21**) lead to the minor isomer.

Later, You group employed Cramer's second generation Rh(III)-catalyst for construction of axially chiral biaryls by C−H alkenylation (Scheme 6).[26] Employing C_2-symmetric Rh-

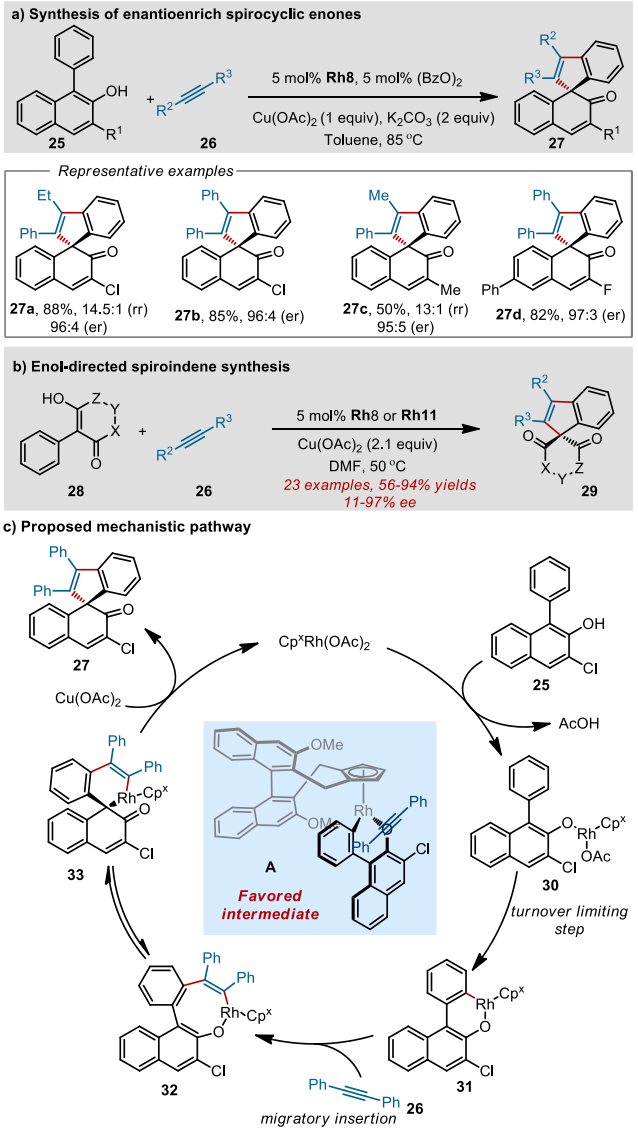
Scheme 6. Cp^{x}Rh(III)-Catalyzed Induction of Axial Chirality through *ortho*-C−H Alkenylation



catalyst **Rh8**, energetically unfavorable coplanarity of two sterically hindered arenes was accessed by formation of five-membered cyclometalated species through C−H activation. We have highlighted the recent developments of atroposelective transformations in Section 5.

In 2015, the You group demonstrated an intermolecular enantioselective [3 + 2] spiroannulation reaction. Enantioenriched spirocyclic enones bearing an all carbon quaternary stereogenic center were synthesized from 1-aryl-2-naphthols and internal alkynes using Cramer's second generation catalyst (Scheme 7a).[27] Various enantio-enriched spirocyclic enones were afforded in good to excellent yields and selectivities with

Scheme 7. Cp^{x}Rh(III)-Catalyzed Enantioselective Intramolecular Spiroannulation Reactions



the catalyst, **Rh8** along with oxidants of $Cu(OAc)_2$ and air (oxygen). The reactions proceeded as usual like the metal-catalyzed directing group assisted C−H functionalization chemistry. The hydroxyl group of naphthol acts as a directing group, likely by deprotonation by the Rh catalyst, leading to intermediate **30** which subsequently provides rhodacycle **31** by C−H activation. Here the catalyst plays a crucial role for enantiselective spirocyclic enone synthesis. The back and side walls of the biaryl complex (**Rh8**) influence to organize the formation of the tetrahedral complex with the 1-aryl-2-naphthols minimizing the steric interaction (Scheme 7, **A**). Coordination of alkyne to the Rh followed by migratory insertion provides a strained eight-membered rhodacycle (**32**), which is likely to be in equilibrium with six-membered isomers (**33**). Catalyst utilizing its inherent steric nature dictates the rotation of rhodacycle (**33**) in conversion toward reductive elimination to afford the desired product. The activated

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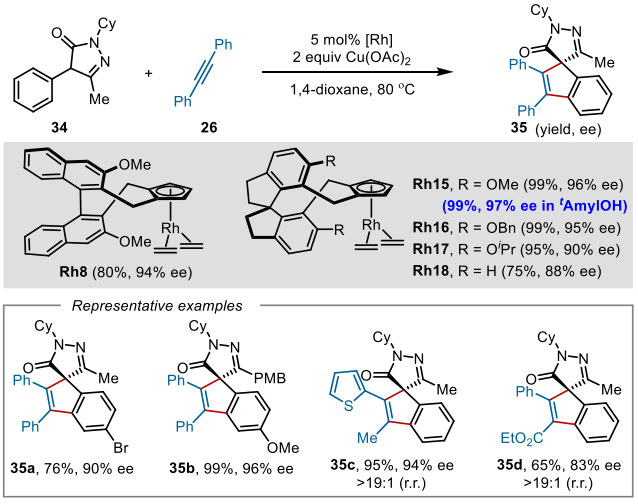
Rh(III) catalyst is generated by concomitant oxidation of released Rh(I) species by $Cu(OAc)_2$ and oxygen.

At the same time, Lam and co-workers reported a straightforward strategy for enantioselective spiroindene synthesis from oxidative annulation reaction of aryl cyclic 1,3-dicarbonyl compounds with internal alkyne (Scheme 7b).[28] Enantioselective enol-directed C(sp^2)−H activation was recognized employing the chiral cyclopentadienyl rhodium complex, **Rh8** and **Rh11** (Cramer catalyst), and subsequently annulation with alkyne provided spiroindenes containing all-carbon quaternary stereocenters.

You and co-workers demonstrated another important annulation strategy for the synthesis of enantioenriched five-membered-ring 4-spiro-5-pyrazolones (Scheme 8).[29] This very

Scheme 8. Cp^{x}Rh(III)-Catalyzed Enantioselective 4-Spiro-5-pyrazolones Synthesis through C−H Activation

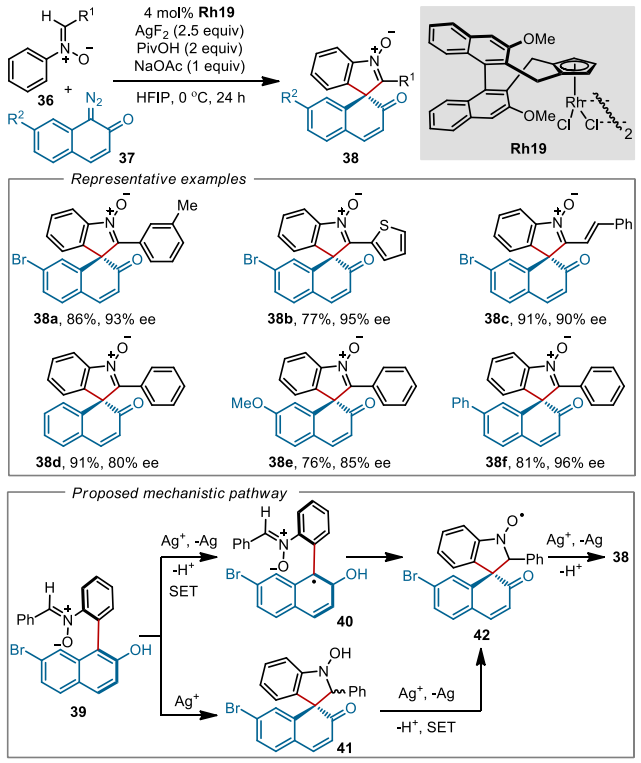


important pharmaceutically relevant scaffold was achieved by chiral CpRh(III)-catalyzed C−H activation of 4-aryl-5-pyrazolones and subsequent [3 + 2] annulation reaction with alkynes. Cramer's catalyst **Rh8** efficiently catalyzed the reaction with modest yield and excellent enantioselectivity of the desired five-membered-ring 4-spiro-5-pyrazolone. However, another class of chiral CpRh-catalysts (**Rh15−18**) was identified as superior in terms of both yield and selectivity. Catalyst **Rh15** provided the desired product in quantitative yield with excellent enantioselectivity. The generality of the methodology was further supported by the compatibility of various pyrazole-5-ones and alkynes under the reaction conditions, leading to the desired spiro compounds (**35a−35d**).

Recently, Li and co-workers developed an axial-to-central chirality transfer strategy for the synthesis of enantio-enriched spirocycles using a chiral Cp^{x}Rh(III) catalyst (Scheme 9).[30] The reaction can be realized by first formation of atropomerically metastable biaryl from *N*-aryl nitrone via directed C−H arylation with *ortho*-quinone diazide and subsequent intramolecular dearomative trapping under oxidative conditions. The judicious choice of the nitrone directing group plays a pivotal role in chirality transfer, which provides first enantioselective biaryl without racemization as well as does not resist chirality transfer, whereas overall bulky DG does.

Catalyst **Rh19** was found to be effective for enantioenriched spirocycles (**38a−38f**) synthesis. Substitution at the C-7

Scheme 9. Cp^{x}Rh(III)-Catalyzed Enantioselective Synthesis of Spirocycles through Axial-to-Central Chiral Transfer Strategy



position of quinone diazides is very important to access highly enantioselective products (e.g., **38d**, 80% ee; for **38e** to **38f**, size of OMe < Ph, 85% < 96% ee) indicating steric influence from C-7 substituents on enantioselectivity. Cyclization of metastable biaryls can be realized by electrochemical oxidation in the presence of AgF_2. Intermediate **39** may undergo either SET oxidation followed by radical cyclization with the nitrone to give a stable nitroxide radical **42** or first cyclization with the nitrone and subsequent SET oxidation to radical **42**, which further experiences SET oxidation to furnish the spirocyclic nitrone.

Considering the biologically relevant and versatile functional group in organic synthesis, Cramer and co-workers employed oxime ethers as a directing group in asymmetric C−H functionalization reactions. The reaction between aryl ketoxime ethers and diazabicycle olefins provided enantio-enriched cyclopentenylamines, imperative motifs of various natural products, and pharmaceutically relevant compounds, using chiral precatalyst **Rh20** and benzoyl peroxide as an oxidant (Scheme 10).[31] We have discussed that in previous transformations with hydroxamates the **Rh8** precatalyst turned out the best. In contrast, the precatalyst **Rh20** bearing a cyclooctadiene (cod) unit instead of two ethylene groups (e.g., **Rh8**) delivered the best yield and enantioselectivity for this particular transformation. Clearly indicating the role of olefin is not just an innocent bystander unit; it has a large influence on both the reactivity and selectivity. Such an effect of olefins on metal-catalyzed cross-coupling reactions has been exemplified in a number of articles.[32] The authors do not explain the role of olefin, and it is certainly a matter of further studies for explicit understanding. The generality of the methodology was demonstrated with various aryl/alkyl ketoxime ethers and

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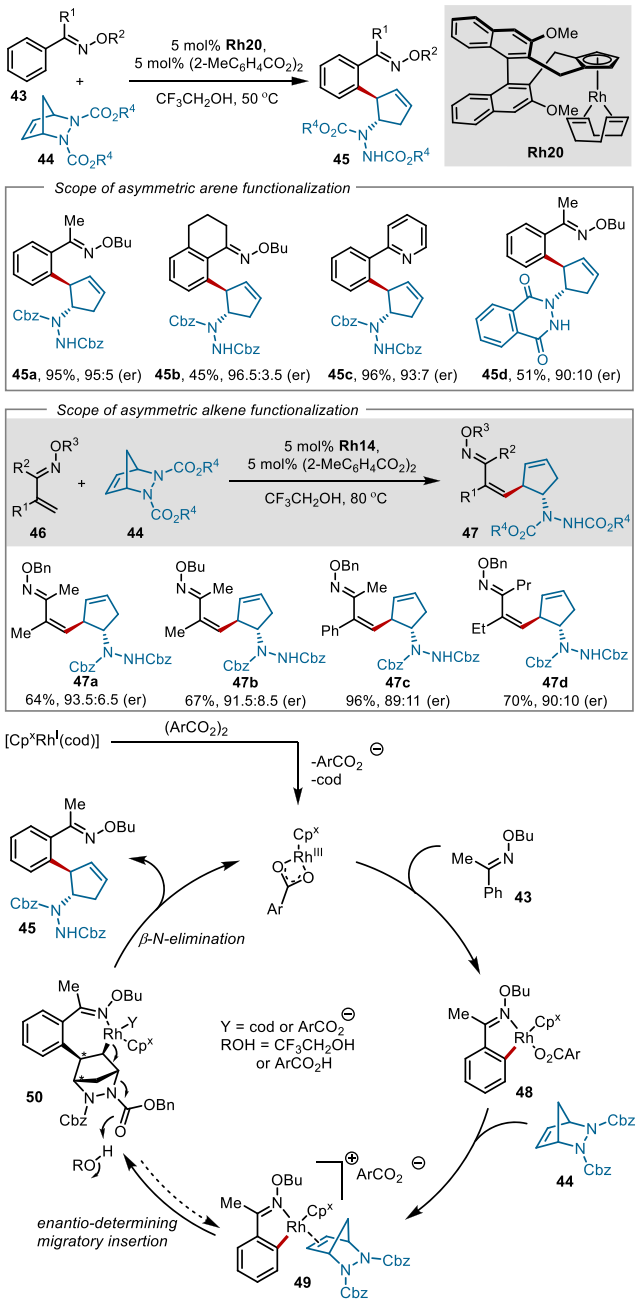
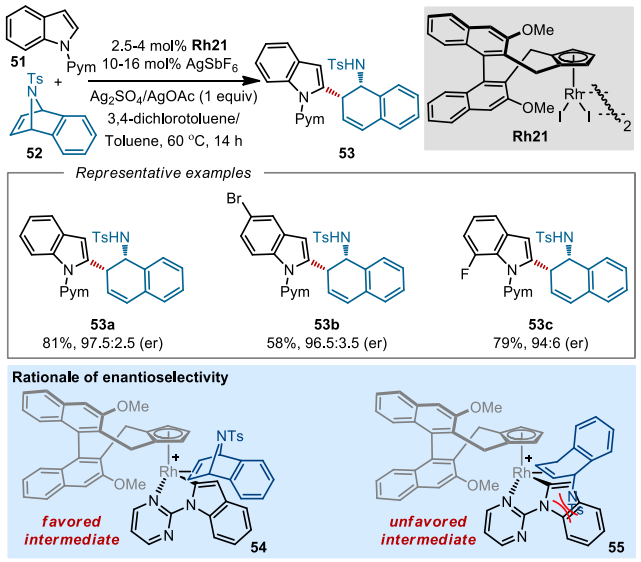
Scheme 10. Cp^{x}Rh(III)-Catalyzed Synthesis of Enantio-Enriched Cyclopentenylamines through C−H Functionalization/Ring-Opening Route



diazabicycle derivatives (**45a−d**, **47a−d**). In the presence of benzoyl peroxide derivative, precatalyst Cp^{x}Rh(I)-complex oxidized to active catalyst Cp^{x}Rh(III), which activates the *ortho*-C−H bond of oxime ethers via the CMD pathway. Coordination of the diazabicycle olefins to the Rh-center gives intermediate **49**. Exploiting the chiral environment of the Cp-ligand, the double bond of olefins undergoes enantio-determining exoselective migratory insertion to alkyl rhodium intermediate **50**. Subsequent anti-*β*-nitrogen elimination leads to the desired densely functionalized chiral cyclopentenyl-amines selectively.

Prior to Cramer's report, Li and co-workers demonstrated the utilization of 7-azabenzonorbornadienes as coupling partners for enantioselective C_2−H activation of *N*-pyrimidyl-indoles (Scheme 11).[33] A combination of Cramer's catalyst Cp^{x}Rh(I) and $AgSbF_6$ efficiently catalyzed the reactions and

Scheme 11. Cp^{x}Rh(III)-Catalyzed Enantioselective C−H Functionalization



provided enantioselective C−C coupled products in excellent yields and selectivities. From the typical features of norbornadienes, subsequent C_3−H activation of *N*-pyrimidyl-indoles was expected. However, the pleasant finding of $AgSbF_6$ in optimal conditions helps to suppress the C_3−H activation of the indoles. The C−H activation is realized to follow a carboxylate assisted CMD-type pathway. The second C−H activation at the C_3-position of indoles has been inhibited by the Lewis acidic $AgSbF_6$, which abstracts the OAc ligand from the metal center of the intermediate like **50** (Scheme 10), preferring *β*-nitrogen elimination in the same process. The preferential enantioselectivity can be realized from the stereochemical model of the intermediate **54** and **55**. The steric bias of the catalyst and substrates concomitantly helps to organize in an energetically favorable conformation for coordination and subsequent migratory insertion of azabenzo-norbornadienes.

The observation of 2-fold C−H activation with azabenzo-norbornadienes led the authors to the development of asymmetric [3 + 2] transannulation of arenes with 7-azabenzonorbornadienes (Scheme 12).[34] In the previous study, a low tendency of dechelation from the pyrimidine directing group hinders the second C−H activation by the active Rh(III) species (Scheme 11). The judicious choice of a flexible directing group amides facilitates the first C−H activation at the *ortho* position while accommodating the second C−H activation at the *meta* position of arenes with the help of azabenzonorbornadienes by dechelation (**61**), provid-ing enantioenriched [3 + 2] annulated products.

In 2017, Ellman and co-workers developed directing group assisted catalytic enantioselective addition of nitroalkenes to aryl C(sp^2)−H bonds employing Cramer's elegantly designed chiral catalyst **Rh21** (Scheme 13a).[35] The developed method-ology provides a general approach to afford enantiomeric nitroalkanes (**64**) which are versatile chemotype intermediates, such as amines, carbonyl compounds, etc.[36]

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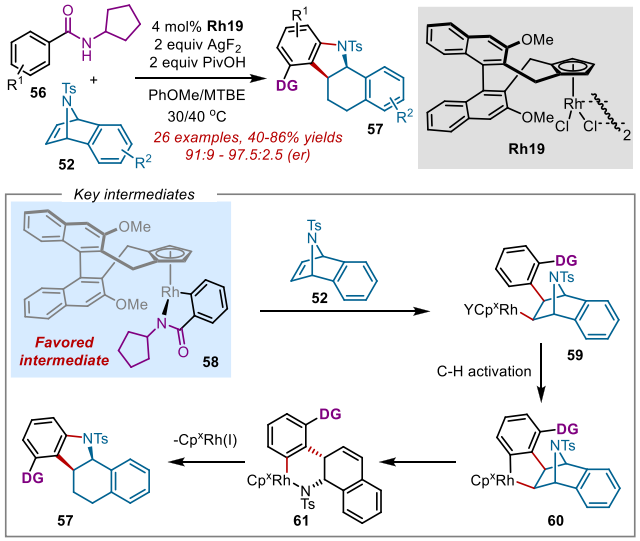
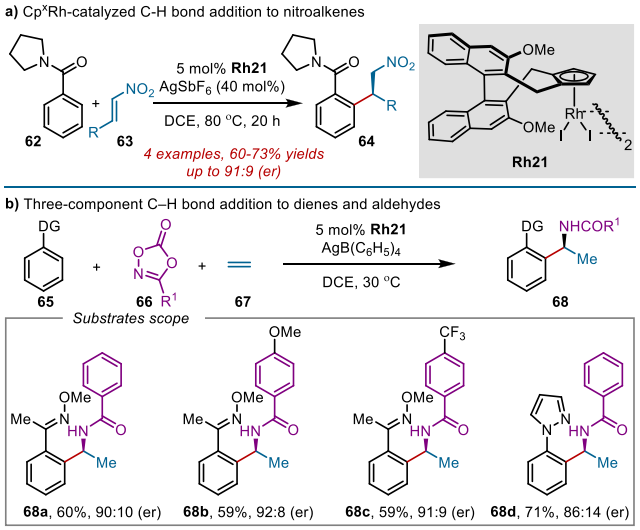
Scheme 12. Cp^{x}Rh(III)-Catalyzed Enantioselective [3 + 2] Transannulation of Arenes with 7-Azabenzonorbornadienes



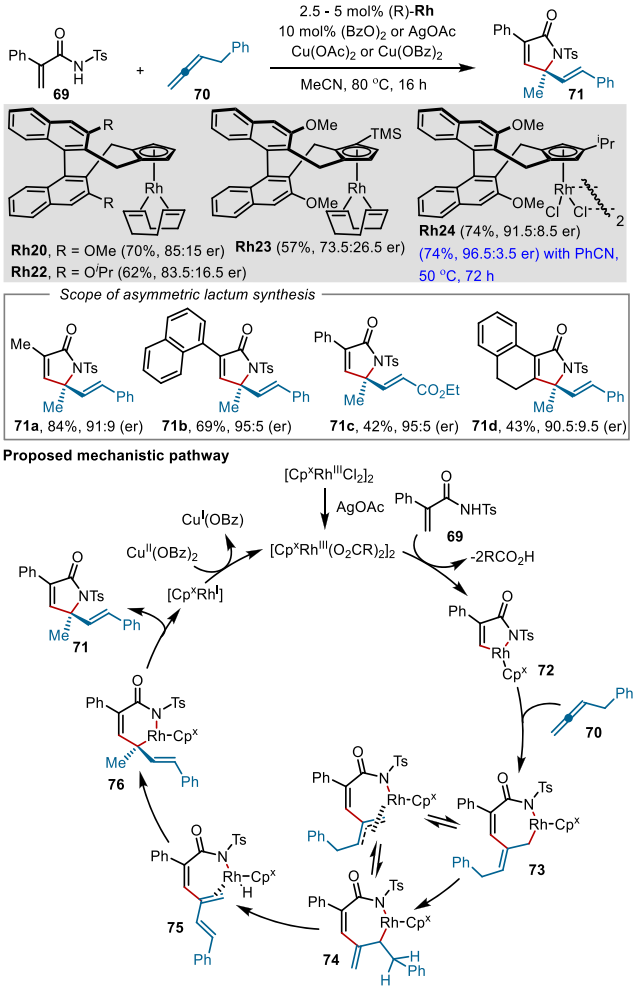
Scheme 13. Cp^{x}Rh(III)-Catalyzed Enantioselective Synthesis of Nitroalkanes and α-Branched Amines



Recently, the same research group has demonstrated a convergent synthesis of α-branched amines, from three readily available precursors: arenes, terminal alkenes, and aminating agent. The synthetically important motifs, α-branched amines, were achieved by Cp*Rh(III)-catalyzed intermolecular 1,1-addition of arene C−H bonds and aminating agents to the terminal alkenes.[37] Mostly, they focused on the development of the concept with an achiral catalyst. Upon successful execution of the methodology, they have shown asymmetric synthesis of α-methyl branched amines employing Cramer's chiral catalyst, **Rh21** (Scheme 13b).[37] The preliminary findings were very promising, and α-methyl branched amines **68** were obtained in very good yields and enantioselectivities.

In particular, asymmetric functionalization of alkenyl C−H bonds are relatively unattainable compared to aryl C−H bonds, remaining as an enduring challenge. However, in 2019, the Cramer group demonstrated asymmetric C−H functionalization of acrylamides using their very established precatalyst Cp^{x}Rh(I)-complex (Scheme 14).[38] In the presence of a suitable oxidant, converted active Cp^{x}Rh(III)-catalyst provided

Scheme 14. Cp^{x}Rh(III)-Catalyzed Synthesis of Enantioenriched 2*H*-Pyrrole-2-one Derivatives



straightforward access to enantio-enriched 2H-pyrrole-2-one derivatives from acrylamides and allenes through C−H bond activation. Importantly, allene participates as a one-carbon unit in the [4 + 1] annulation reactions, providing five-membered heterocycles. Trisubstituted Cp^{x}Rh(III)-complex (**Rh24**) showed better reaction performance over the disubstituted Cp^{x}Rh(III)-complex (**Rh20** and **Rh22**). The bulkiness and position of the third substituents on Cp ring play a crucial role in both the catalysis and the selectivity. The trisubstituted Cp^{x}Rh(III)-complex bearing ^{i}Pr group (**Rh24**) provided the optimal yield and selectivity compared to the relatively bulky TMS group (**Rh23**). A wide range of acrylamides and various allenes were evaluated to check the feasibility of the methodology for the synthesis of α,β-unsaturated-γ-lactums bearing a quaternary stereocenter (**71a−d**). The reaction was assumed to follow amide-directed and carboxylate-mediated CMD-type C−H bond activation, leading to intermediate rhodacycle **72.** Coordination and followed migratory insertion of allene provide three different interconvertable allyl-rhodium species, which subsequently undergo β-H elimination to generate diene **75**. The rhodium delivers hydride enantioselectively to the double bond to give rhodacycle **76**. Further

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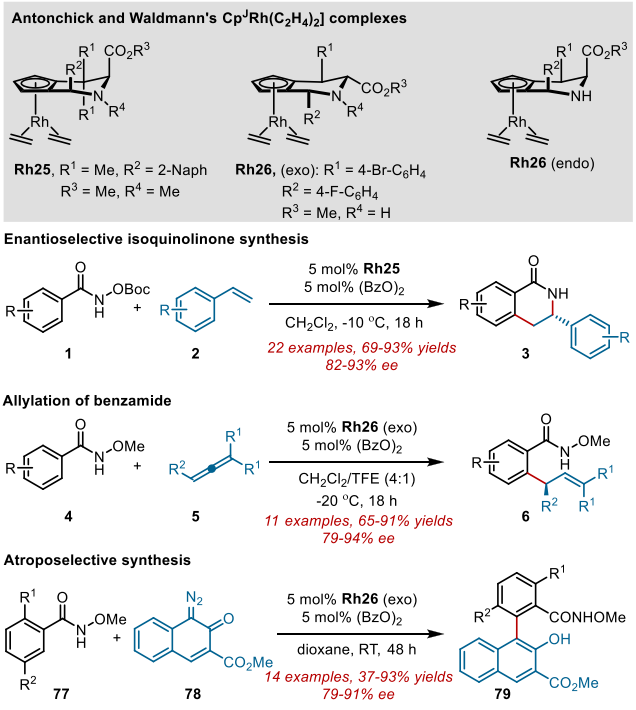
reductive elimination leads to lactum and precatalyst Cp^{x}Rh-(I)-species.

So far, the transition metal catalyzed asymmetric C(sp^2)−H functionalization reaction was mostly limited with Cramer's catalysts. Therefore, to broaden the scope of the chemistry, conceptual developments of various chiral catalysts are arguably high priorities along with the discovery of new enantioselective transformations. In 2017, Antonchick, Waldmann, and co-workers demonstrated an approach to access a library of novel rhodium complexes with chiral cyclopentadienyl ligands. Importantly, these chiral ligands were synthesized by enantioselective cycloadditions of imino esters to fulvenes, providing an opportunity to rapidly vary and tune their structures. They categorized their developed [Cp^{J}Rh-(C$_2$H$_4$)$_2$] complexes into two classes based on mono- and disubstitutions with R^1 (**Rh25** and **Rh26** (Scheme 15).[39] We

Scheme 15. Cp^{J}Rh(III)-Catalyzed Enantioselective Transformation through C−H Activation

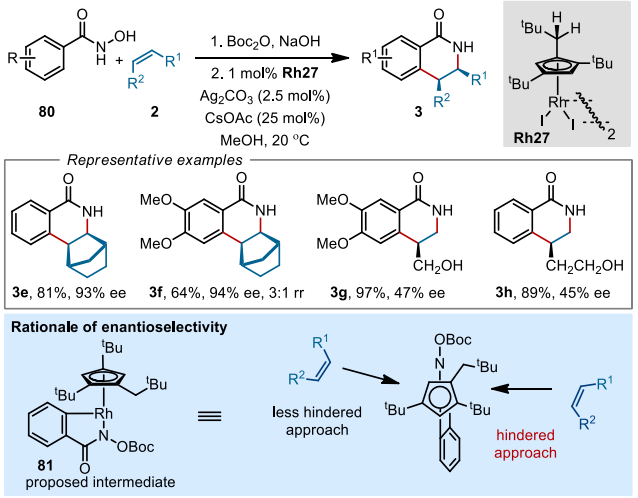


have shown in this review two different catalysts from both the classes as representative examples. To explore the potential of the catalysts, three different types of enantioselective C−H bond functionalization reactions were performed. Initially, they screened the catalyst's performance in an annulation reaction with hydroxamates and olefins, initially developed by the group of Glorius,[21a] Fagnou,[21b] Ward, Rovis,[40] and Cramer.[20] The highly functionalized ligand **Rh25** was identified to be optimal. The pattern and bulkiness of the substituents of the ligand provide a chiral pocket to the Rh center, which accommodates the hydroxamates in a less sterically encumbered fashion locating the Boc protecting group on the less hindered side. Olefins coordinate to the rhodacycle intermediate from the open face with the bulky substituents of olefins pointing away from the ligand like earlier studies (Scheme 2) to avoid unfavorable steric interactions.

In their second attempt, they investigated the enantioselective C−H allylation of benzamides with allenes that had been previously established by the Cramer group,[22] to the check the generality and applicability of the ligand systems. However, their developed catalyst system efficiently provided enantio-enriched isoquinolones, but failed to provide promising results. Amusingly, another class of exo Cp^{J}Rh(I)-complexes were identified as suitable for allylation reactions. The catalyst **Rh26** efficiently catalyzes the reactions and provides allylated benzamides in good yields and excellent selectivities. Along with these successful catalysis reactions, the researchers developed an unprecedented approach for axially chiral biaryl synthesis by C−H activation (*vide infa*). A handful of axially chiral biaryls were synthesized by direct C−H arylation of benzamides with diazonaphthoquinones in excellent yields and selectivities using the catalyst **Rh26**.

Development of an affordable synthetic pathway for chiral catalysts is an important aspect in terms of exploration of the strategy. Perekalin and co-workers developed a planar chiral rhodium catalyst [(C$_5$H$_2$^{t}Bu$_2$CH$_2$^{t}Bu)RhI$_2$]$_2$ in a very straightforward pathway from commercially available [(cod)-RhCl]$_2$ and *tert*-butylacetylene in two steps. They applied their catalyst system in the enantioselective dihydroisoquinolones synthesis from aryl hydroxamic acids and alkenes (Scheme 16).[41] A wide range of dihydroisoquinolones were synthesized

Scheme 16. Planar Chiral Rh(III)-Catalyzed Enantioselective Dihydroisoquinolones Synthesis from Aryl Hydroxamic Acids and Alkenes



with cyclic alkenes in very good yields and stereoselectivities (e.g., **3e−f**). However, acyclic terminal alkenes delivered moderate enantioselectivities (**3g−h**), presumably because of insufficient steric interactions between the cyclopentadienyl ligand and incoming alkenes. The enantioselectivity can be realized by the less hindered approach of the alkene to the open side of the proposed intermediate metallacycle (**81**) shown in Scheme 16, similarly with other studies.

In 2018, Matsunaga and co-workers demonstrated that a suitable chiral organic anion in combination with Cp*Rh(III) catalyst can efficiently induce enantioselectivity in C−H functionalization.[42] This study has shown an improved strategy in stereoselective Rh(III)-catalyzed C−H functionalization avoiding the complex multistep synthesis of the chiral Cp^x ligand. The hybrid catalysts, 1:1 composite of Cp*Rh(III) and (S)-BINSate derivatives (BINSate = 1,1′-binaphthyl-2,2′-disulfonate), were synthesized by treating chiral BINSA with

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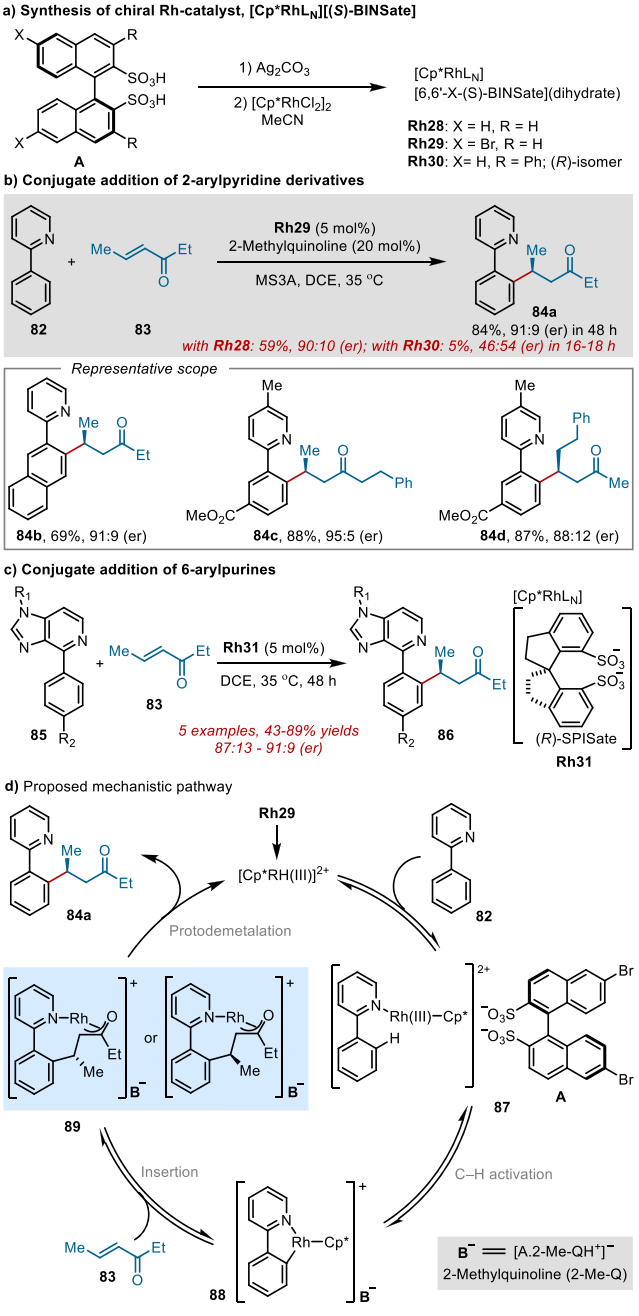
Ag_2CO_3 followed by $[Cp^*RhCl_2]_2$ in acetonitrile (Scheme 17a). The hybrid catalyst, Cp*Rh(III)/BINSate **Rh29**, efficiently catalyzed the enantioselective conjugate addition of 2-phenylpyridine with α,β-unsaturated ketone, providing the C−C coupled products (**84a−d**) in very good yields and enantioselectivities (Scheme 17b). While catalyst **Rh28** delivered the desired product in very low yield albeit similar steroselectivity, **Rh30** failed completely in terms of both yield and selectivity, possibly due to the over steric hindrance and unrecognized stereochemical faces of the catalyst derived from 3,3′-diphenyl BINSA. They expanded the scope of this concept with 6-arylpurine derivatives. Relatively lower enantioselectivity of the conjugate product of 6-arylpurine and α,β-unsaturated ketone was observed with Cp*Rh(III)/BINSate **Rh29**. Enantioselectivity was further improved with the chiral spirocycle counteranion (*R*)-SPISate (SPISate = 1,1′ -spirobiindane-7,7′ -disulfonate) and in the absence of additives, providing very good yields and enantioselectivities with the Cp*Rh(III)/SPISate **Rh31** (Scheme 17c). The plausible reaction pathway is attributed in Scheme 17d. Dissociation of the coordinating BINSate from Rh29 releases a coordinatively unsaturated Cp*Rh(III) species which activates the C−H bond by a concerted metalation deprotonation (CMD) mechanism and delivered rhodacycle intermediate **88**. Further subsequent insertion of α,β-unsaturated ketone and protodemetalation led to formation of the conjugate product. The released H^+ from the C−H activation step, confined by 2-arylpyridine or 2-methylquinoline, form ammonium-BINSate species with chiral organic anions. This chiral species provides the stereochemical environment around the C−H activated metallacycle intermediate for the incoming α,β-unsaturated ketone, thus helping to deliver enantioselective products.

Scheme 17. Rh(III)−Chiral Disulfonate Hybrid Catalysis for Enantioselective C−H Bond Functionalization



2.2. 3d Transition Metal Catalysis. Progress of enantioselective C−H functionalization methodologies mostly have developed based on 4d and 5d transition metal catalysts, in particular, rhodium, palladium, ruthenium, and iridium.[16,43] Whereas inexpensive earth-abundant 3d transition metal catalysts were successfully employed in enantioselective C−H bond functionalization in early stage, the chemistry remains underdeveloped over the time. However, recent development of suitable chiral ligand systems prompted the community to reinvestigate the 3d transition metals in enantioselective catalysis. In 2014, Hou and co-workers reported the enantioselective version of their previous developed method,[44] C−H bond addition of pyridines to various 1-alkenes employing scandium complex equipped with Cramer's chiral cyclopentadienyl ligand (Scheme 18a).[45] The developed method provided diverse enantio-enriched alkylated pyridine derivatives in good-to-excellent yields and enantioselectivities. The proposed mechanistic pathway reveals the involvement of cationic Sc-η2-pyridyl species, generated from **Sc1** by oxidation with an equimolar amount of $[Ph_3C][B(C_6F_5)_4]$ and subsequent deprotonation of 2-picoline at the C_6-position (**92**). Chiral backbone of the catalyst dictates the orientation of the incoming alkenes for coordination to the active metal center, leading to the preferential formation of diastereomeric intermediates **93** to avoid energetically unfavorable steric interaction between substituents of alkenes and the binaphthyl backbone of the ligand. Subsequent 2,1-migratory insertion of alkene into Sc−C bond and followed by σ-bond metathesis of another pyridyl moiety promotes the release the enantioenriched alkylated pyridine and regenerates the Sc-η2-pyridyl intermediate.

Recently, the same research group has developed an intramolecular asymmetric exoselective C−H cyclization of imidazoles bearing 1,1-disubstituted alkene by using chiral scandium catalyst **Sc2** (Scheme 18b).[46] The asymmetric cyclization provided a wide range of bicyclic imidazole derivatives having β-all-carbon-substituted quaternary stereocenters with excellent enantioselectivity (up to 97:3 er).

The continuous effort of the Cramer group in chiral catalyst development led them to devise a Co(III)-complexes bearing a trisubstituted chiral cyclopentadienyl ligand. They employed this chiral Co-catalyst in the synthesis of dihydroisoquinolones from *N*-chlorobenzamides and various alkenes by asymmetric C−H activation (Scheme 19).[47] Importantly, this catalyst

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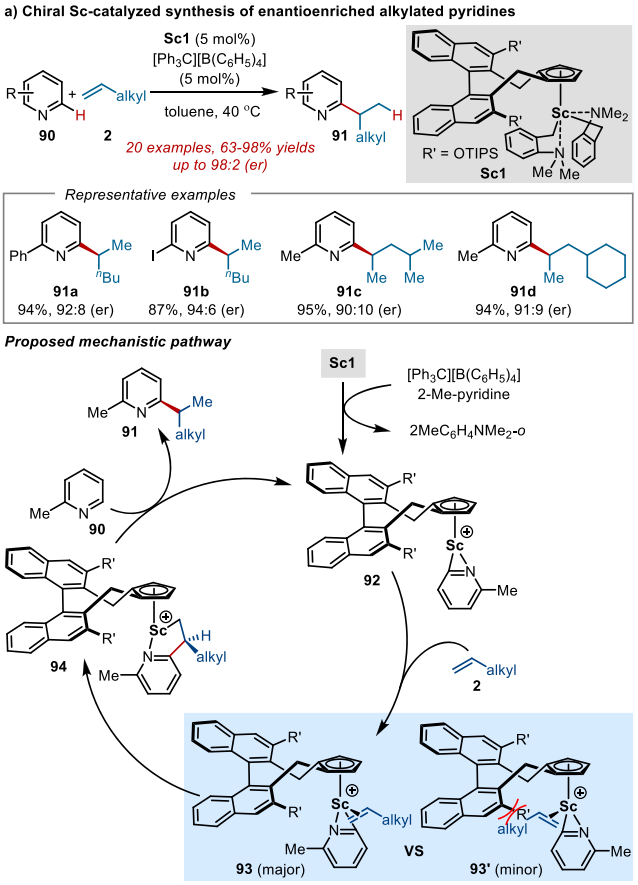
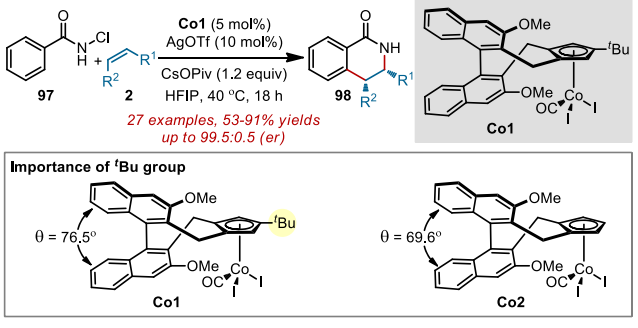
Scheme 18. Scandium-Catalyzed Enantioselective C−H Bond Functionalization



Scheme 19. Cp^{x}Co(III)-Catalyzed Enantioselective Synthesis of Dihydroisoquinolones from *N*-Chlorobenzamides Various Alkenes



turned out as superior over the Rh(I)-based catalyst for this class of reaction. Excellent enantioselectivity up to 99.5:0.5 (er) was achieved with the **Co1** catalyst. The finely design catalyst **Co1**, bearing a bulky *tert*-butyl group on the chiral Cp ligand, remotely affected the dihedral angle θ of the binaphthyl backbone of the Cp^x. The presence of the *tert*-butyl group on the Cp^x ligand (**Co1**) helps to open up the methoxy naphthyl portion of the pocket slightly more compared to unsubstituted **Co2** catalyst. The backwall of the chiral catalyst is responsible for the orientation and alignment of the metallocycle with incoming alkenes. A larger dihedral angle of **Co1** forces the gain of a specific orientation of the incoming alkenes, minimizing the steric repulsion and thus provides an excellent enantioselectivity.

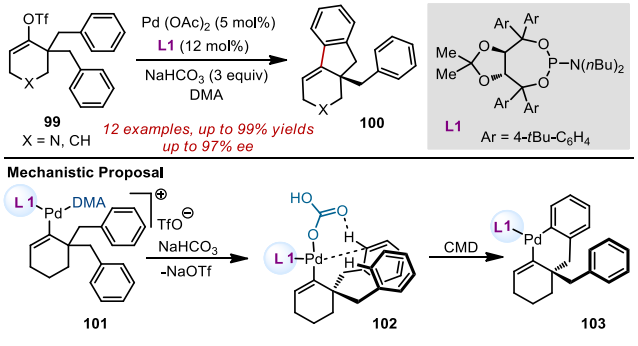
3. CHIRAL LIGAND CONTROL ASYMMETRIC C−H FUNCTIONALIZATION

The central area of asymmetric catalysis offers the development of new chiral ligands, which can enable stereoselective reactions with high levels of enantio-control and efficiency. Besides, the chiral ligand tunes the reactivity and selectivity of the metal center in transition metal-catalyzed asymmetric transformation in such a way that one of two viable enantiomeric products is formed preferentially. In general, various ligands such as TADDOL, BINOL, BINAP, etc. have been widely utilized in asymmetric catalysis. Considering the growing interest of the synthetic community in transition metal-catalyzed asymmetric C−H functionalization reactions, we intend to discuss thoroughly the utilization of the chiral ligands in this regard.

3.1. TADDOL-Based Chiral Phosphine Ligands. In 1987, Seebach and co-worker reported the first synthesis of TADDOLs and their derivatives.[48] Later in 1993, the Seebach group extended this protocol for the synthesis of TADDOL-derived phosphorus(III) ligands.[49] Afterward, these ligands have been utilized widely in enantioselective organic synthesis.[50] A variety of TADDOL-based phosphoramidites, phosphites, and phosphonites ligand have found in a wide range of applications in transition metal catalyzed asymmetric synthesis.[51] The monodentate TADDOL-phosphoramidites have shown excellent enantioselectivity in various types of coupling reactions.[50] In the last few decades, this class of chiral ligand has been extensively used in enantioselective C−H functionalization reactions.[52] In this part, we have addressed the monodentate TADDOL phosphorus ligand catalyzed enantioselective C(sp^2)−H functionalization.

In 2009, Cramer and co-workers developed Pd(II) catalyzed enantioselective C(sp^2)−H functionalization of aromatic compounds (Scheme 20).[53] The intramolecular direct arylation of vinyl triflates **99** delivered chiral indanes **100** with quaternary stereogenic centers. Initially, different classes of chiral ligands were tested. However, monodentate

Scheme 20. TADDOL-Based Phosphoramidites Catalyzed Enantioselective C(sp^2)−H Arylation



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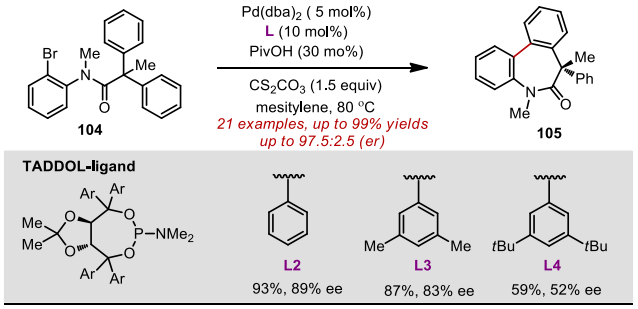
phosphine ligands showed the highest activity toward the desired arylation reaction. TADDOL derived phosphoramidite with 4-^{t}Bu-C$_6$H$_4$ substitution (**L1**) turned out to be an optimal ligand for this transformation. A variety of functionalities with regard to aryl substitution, as well heteroatom containing acyclic vinyl triflates, were well tolerated and delivered the desired products in good yields and moderate to excellent enantioselectivities. Several mechanistic models have been proposed in previous studies; one of such model proposed by Maseras, Echavarren, and co-workers,[54] and by Fagnou and co-workers[55] is illustrated in Scheme 20. Upon oxidative addition of vinyl triflate, it generates a cationic palladium(II) intermediate **101**, which subsequently undergoes a rapid association with carboxylate or carbonate anion of the base **102**. The carboxylate/carbonate anion then acts as ancillary base and facilitates the C−H activation of the aryl group through astereodetermining concerted metalation-deprotonation (CMD) pathway with the assistance of a bulky ligand and leads to the formation of palladacycle intermediate **103**. Reductive elimination of palladacycle **103** provided the cyclized product.

Cramer and Saget in 2013 extended this enantioselective C−H arylation strategy for the synthesis of functionalized dibenzazepinones with quaternary stereocenters **105** from *N*-acyl-2-bromoanilines **104** (Scheme 21).[56] The generation of

Scheme 21. Effect of TADDOL-Ligand on Asymmetric Dibenzazepinone Synthesis

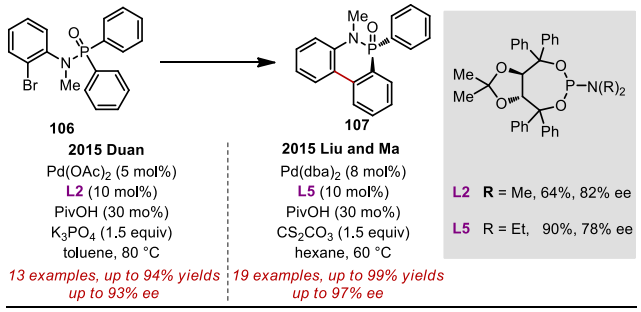


chirality of this transformation depends on the cooperative effects between a chiral phosphine ligand and a bulky carboxylate during the enantiotopical CMD step. A range of monodentate phosphine ligands were screened, especially TADDOL-based phosphoramidites showed promising results for the reaction. A simple phenyl substituent on the TADDOL backbone provided the desired cyclized products with excellent enantioselctivities.

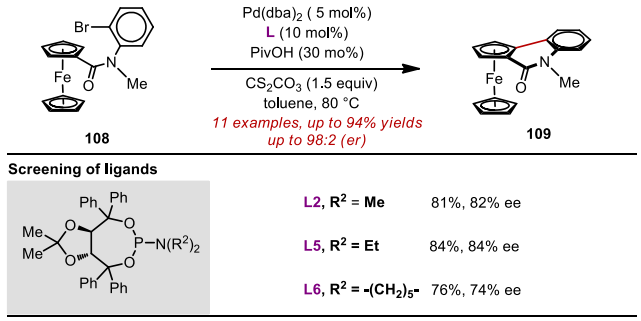
The group of Duan[57] and Ma[58] separately demonstrated the synthesis of cyclic *P*-chiral phosphinic amides via a Pd-catalyzed enantioselective C(sp^2)−H arylation of prochiral *N*-(2- haloaryl)-*P*,*P*-diphenylphosphincamides (Scheme 22). TADDOL-derived tetraphenyl phosphoramidites **L2** and **L5** provided the cyclized products in excellent yields and enantioselectivities.

Liu, Zhao, and co-workers reported an asymmetric synthesis of quinolinone-fused ferrocenes **109** (Scheme 23).[59] In contrast to the previously reported indenone-fused ferrocenes,[60] it was found that BINAP and other phosphine-based chiral ligands were poorly suited and provided low enantiomeric excess. Significant improvements in terms of both yields and enantioselectivities were observed by changing

Scheme 22. Asymmetric Synthesis of *P*-Stereogenic Phosphinic Amides via Phosphoramidite Ligand



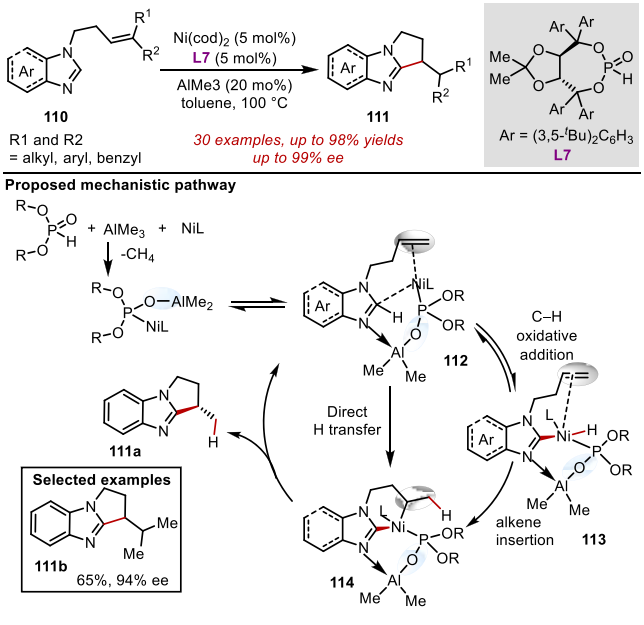
Scheme 23. Planar Chiral Quinolinone-Fused Ferrocene



the chiral backbone to TADDOL phosphoramidite (**L2**, **L5**, **L6**). TADDOL phosphoramidite having diethylamino substituents on the phosphorus atom (**L5**) delivered the desired product in 81% yield with 84% ee, while larger analogues **L6** furnished the cyclized product in lower enantiomeric excess.

In 2018, Ye and co-workers first reported nickel catalyzed enantioselective intramolecular *exo*-selective C−H cyclization of imidazole with alkene (Scheme 24).[61] The cooperative effect of chiral TADDOL-based phosphine oxide (SPO) ligand with Ni and Al helped to control the enantioselectivity efficiently. A series of bi- and polycyclic imidazoles with *β*-

Scheme 24. Nickel-Catalyzed Asymmetric Hydroarylation



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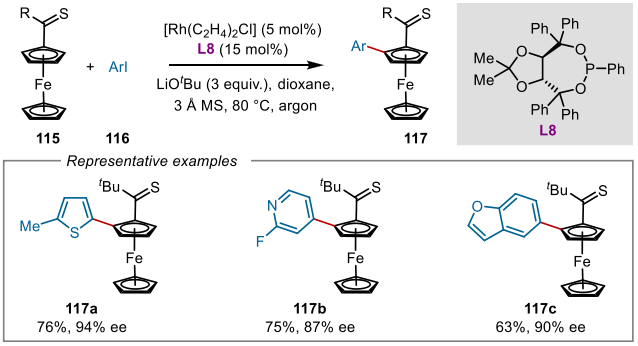
stereocenters **111** were afforded by this protocol. The bifunctional bis(t-butyl)phenyl-containing TADDOL-SPO ligand (**L7**) promoted Ni−Al bimetallic catalysis provided promising results in terms of both yields and enantioselectivities. Diversely substituted alkenes, as well as *N*-containing heterocycles, were also compatible under the optimized conditions. The mechanistic understanding could be rationalized by the binding nature of the SPO ligand. Experimental findings suggested that the SPO ligand could bind with the two metals and imidazole simultaneously. The nitrogen atom of imidazole could coordinate to the Al center of the complex precursor, and the nickel could interact with the olefin moiety **112**. This cooperative interaction would help to bring the olefinic part closer to the reaction center. Finally, ligand-to-ligand hydrogen transfer (LLHT) from imidazole to olefin led to a enanto-enriched cyclized product with the β-stereocenter.

Recently, You and co-workers developed thioketone-directed Rh(I)-catalyzed enantioselective C−H arylation of ferrocenes utilizing a TADDOL-based chiral phosphonite ligand **L8** (Scheme 25).[62] Under the optimized reaction

Scheme 25. Phosphonite-Catalyzed Thioketone-Directed Enantioselective C−H Arylation of Ferrocenes

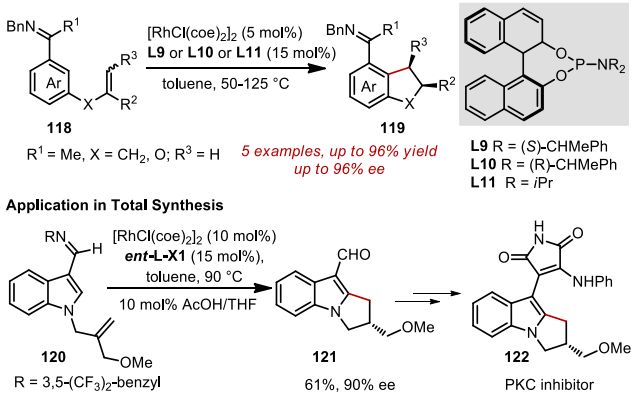


conditions, various aryl iodides reacted with ferrocenyl thioketones smoothly and provided the planar chiral ferrocenes with excellent enantioselectivities. Heteroaryl iodides also sustained well in this catalytic system, affording heteroaryl substituted ferrocenes **117a**, **117b**, and **117c** in good yields with promising enantioselectivity.

3.2. BINOL and Its Derivatives. Since 1990, the enantiomeric atropoisomer of 1,1′-binaphthyl-2,2′-diol (BINOL) provides one of the most widely used ligand for asymmetric catalysis.[63] Because of the versatility in the backbone of BINOL and its derivatives, these ligands control the reaction environment by changing their steric as well as their electronic properties toward the metal center. Thus, the merging of transition metal catalyst and catalytic BINOL derivatives has been an attractive approach for asymmetric C−H activation in recent times. In this section, we have discussed the developments on enantioselective C(sp^2)−H functionalization utilizing BINOL and their derivatives as crucial ligand systems.

In 2004, Ellman, Bergman, and co-workers reported the highly enantioselective catalytic reaction involving aromatic C−H bond activation.[64] The reaction proceeded through intramolecular imine-directed hydroarylation of ketimines **118**, under Rh(I)/Rh(III) catalysis, providing chiral fused heterocycles **119** with the assistance of chiral phosphoramidite ligands **L9**, **L10**, and **L11** (Scheme 26). The highest

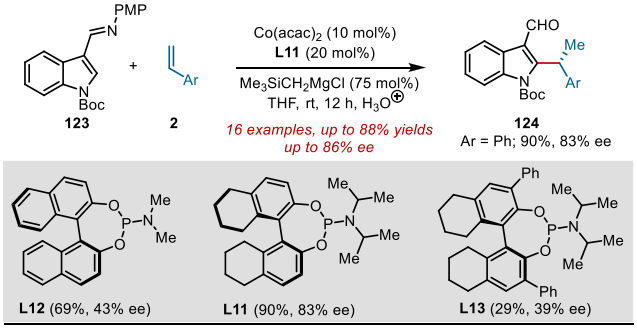
Scheme 26. Enantioselective Cyclization of Aromatic Imines



enantioselectivities indicated that asymmetric induction was predominately controlled by the BINOL backbone. They have also applied this methodology in the enantioselective synthesis of biologically active dihydropyrroloindole **121** and subsequently converted into PKC inhibitor.[65]

In 2014, Yoshikai and Lee utilized a BINOL-base chiral phosphoramidite ligand for cobalt-catalyzed imine-directed enantioselective C−H alkylation of indole **123** with styrene **2** (Scheme 27).[66] The reaction provided 1,1-diarylethane

Scheme 27. BINOL-Based Chiral Phosphoramidite



derivatives **124** in moderate to good yields with good enantioselectivities using chiral phosphoramidite catalyst under mild conditions. Initially, simplest BINOL-based phosphoramidite **L12** provided the desired product in low yield and enantioselectivity. Modifying the diol backbone and changing the amine substitution led to a significant increase in the catalytic activity. An H8-BINOL backbone and a diisopropyl moiety on amine (**L11**) were found to be optimal, affording the desired product in good yield and enantioselectivity. Further incorporation of the phenyl ring on the 3,3-positions of the H8-BINOL skeleton (**L13**) adversely affected the stereoselectivity presumably due to an over steric effect in the transition state.

In 2009, Shibata and co-workers reported cationic Ir/(*S*)-H8-BINAP-catalyzed enantioselective intramolecular cyclization of the pyruvamide derivative through C−H activation, leading to the chiral oxindole derivative.[67] Similarly, the Yamamoto group demonstrated a cationic iridium catalyzed synthesis of chiral 3-substituted 3-hydroxy-2-oxindoles **126** via a highly enantioselective intramolecular hydroarylation of α-ketoamides **125** (Scheme 28).[68] In this protocol, a chiral BINOL-based O-linked bidentate phosphoramidite ((*R*,*R*)-

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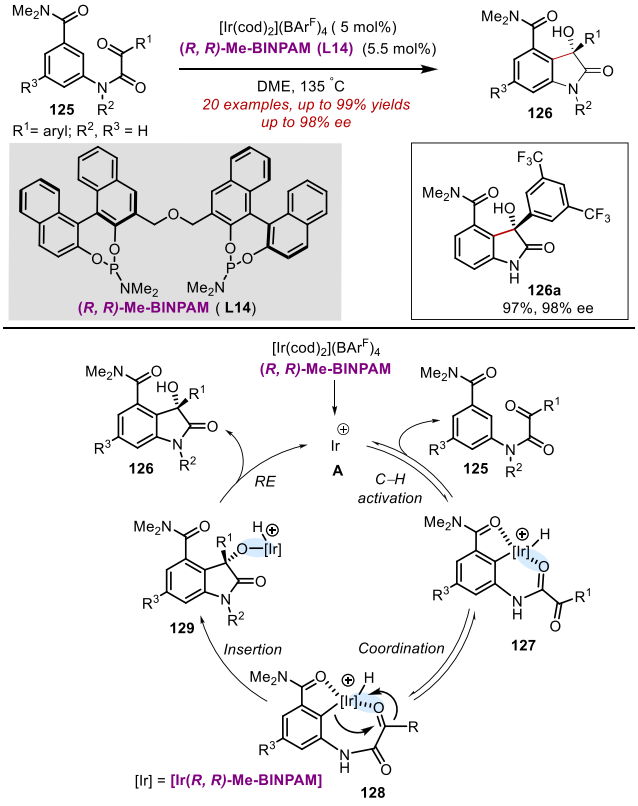
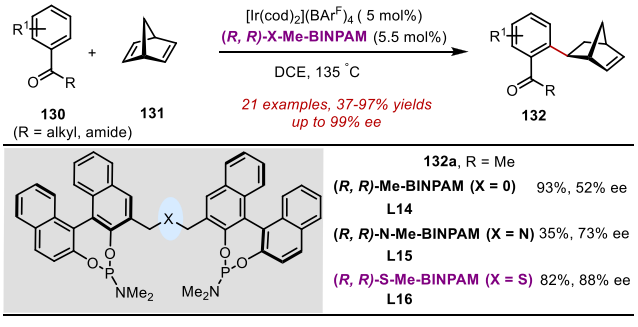
Scheme 28. Ir-Catalyzed Enantioselective Intramolecular Hydroarylation of Ketones



Me-BIPAM) **L14** was utilized as a ligand, and the *N,N* dimethyl carbamoyl group served as the directing group. A broad substrate scope was explored by using a variety of aromatic and aliphatic α-ketoamides, providing the chiral functionalized products with an excellent enantioselectivity. In the following year, the authors investigated thorough mechanistic studies of this transformation and suggested that C−H activation is not the turnover-limiting step.[69] Ir-catalyzed carbonyl directed C−H activation of the ketoamides led to the intermediate **127**, followed by insertion of the carbonyl group into the aryl-Ir bond (**129**), and subsequent reductive elimination led to the formation of cyclized product **126** and the regeneration of the active iridium species **A**.

In 2015, Yamamoto and co-workers disclosed an enantioselective intermolecular hydroarylation of bicycloalkenes using cationic iridium/(*R,R*)-S-Me-BIPAM complex (Scheme 29).[70]

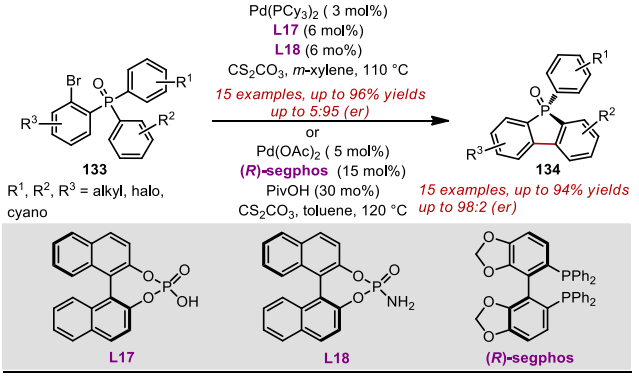
Scheme 29. S-Me-BIPAM-Catalyzed Asymmetric Hydroarylation of Bicycloalkenes



Ir-catalyed carbonyl directed C−H activation of aryl ketone or amides **130** with the assistance of newly synthesized sulfur-linked bis(phosphoramidite) ligand (S-Me-BIPAM), and subsequent reactions with bicycloalkanes **131** led to the formation of alkylated acetophenone or benzamide derivatives **132** in very good to excellent yields and enantioselectivities. Notably, changing the linker atom of the linked BINOL unit from oxygen **L14** to nitrogen **L15** and then sulfur **L16** substantially delivered the improved enantioselectivity of the desired alkylated product. Recently, the same research group extended the protocol to the acetanilide derivatives.[71]

In 2015, Tang and co-workers first reported the synthesis of P-chiral biarylphosphonates from diaryl 2-bromo arylphosphonates by enantioselective intramolecular cyclization using P-chiral biarylmonophosphorus ligands.[72] Moreover, BINOL-based chiral phosphoric amides/acids have been widely used to control stereoselectivity in various types of reactions over the years by different research groups.[73] Duan and co-workers disclosed Pd-catalyzed asymmetric C−H bond activation for the synthesis of P-stereogenic dibenzophospholes **134** from 2-bromoarylphosphine oxide via two different types of catalytic systems (Scheme 30).[74] Chiral phosphoric amides/acids

Scheme 30. BINOL-Phosphoric Acid/Amide Promoted Pd-Catalyzed Enantioselective Synthesis of Dibenzophosphole



(**L17**/**L18**) = 1/1 provided the desired cyclized product up to 5:95 er in the presence of $Pd(PCy_3)_2$, whereas (*R*)-segphos as the ligand was used to afford P-stereogenic dibenzophospholes in excellent yields and enantioselectivities.

3.3. BINAP and Other Chiral Phosphine Ligands. The axially chiral binaphthyl molecule 2′,2-bis-(diphenylphosphino)-1′,1-binaphthyl (BINAP) is another privileged chiral entity that has been widely used as a ligand and as well as catalyst in various stereoselective transformations.[75] Notably, numerous BINAP analogues and other binaphthylphosphine derivatives have also been employed as chiral ligands in a variety of transition metal-catalyzed reactions.[76] Herein, we highlight the BINAP and related phosphine ligands promoted enantioselective C(sp^2)−H activation reactions.

Several methodologies have been developed for the synthesis of planar chiral metallocenes via asymmetric C−H functionalization/cyclization reactions. These molecules are the precursors of planar chiral phosphine ligands, which have been demonstrated as high efficiency in transition metal-catalyzed asymmetric reactions.[77] In 2014, You,[60b] Kang and Gu[60a] groups independently reported highly efficient synthesis of planar chiral metallocenes (Fe and Ru) by enantioselective

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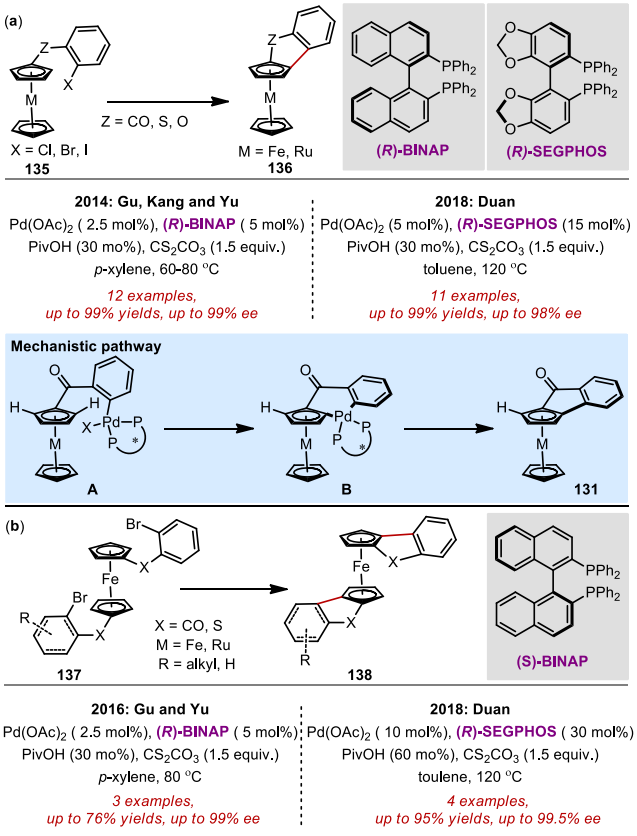
Pd-catalyzed intramolecular C−H arylation from metallocene derived haloarene **135** (Scheme 31a). With the assistance of

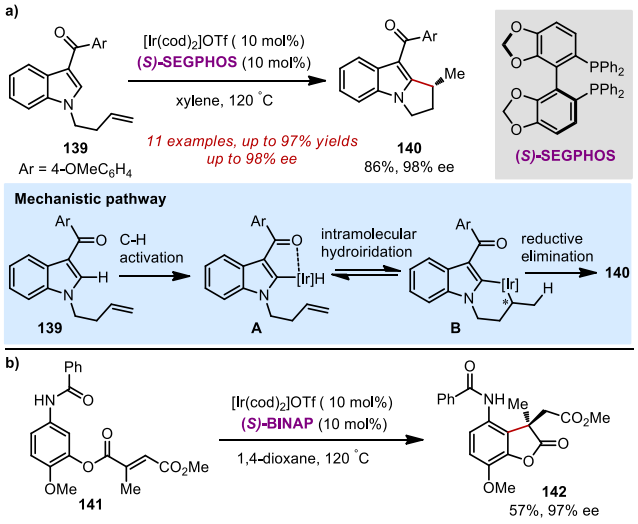
Scheme 31. Synthesis of Planar Chiral Metallocene via Enantioselective C(sp^2)−H Functionalization



(*R*)-BINAP ligand, one of the *ortho*-C−H bonds of the Cp ring was stereoselectively activated (**A**) and subsequently underwent intramolecular cyclization to form indenone derivatives **136** in high yields with excellent enantioselectivity (up to 99% ee). Further, they extended this approach to *N*-heterocyclic compounds using heteroaryl coupling partners.[78] In a subsequent report, Duan and co-workers utilized (R)-SEGPHOS ligand for the enantioselective intramolecular C−H arylation of ferrocenyl aryl sulfide, affording planar chiral thiophene compounds with a ferrocene skeleton.[79] This protocol was further extended to the synthesis of chiral ferrocenyl benzofuran. A series of chiral ferrocenyl derivatives were synthesized under the optimized conditions in excellent yields and enantioselectivities (up to 99% ee). In 2016, Gu, You,[80] and Guiry[81] groups demonstrated Pd-catalyzed intramolecular C−H alkenylation/arylation at both of the Cp rings of metalocene by employing (*S*)-BINAP as a chiral ligand (Scheme 31b). Duan and co-workers further demonstrated the synthesis of chiral bis-sulfides from the ferrocene moieties contaning an aryl sulfide moiety in each Cp ring (Scheme 31b).[79] Utilizing (*R*)-SEGPHOS as a ligand, chiral ferrocenyl bis-disulfide was afforded in high diastereoselectivities (>15:1) and enantioselectivities (up to 99.5% ee). Notably, the enantioselective and diastereoselective synthesis of planar chiral ferrocenes was realized by cascade C−H arylation and alkenylation reaction.

In 2015, Shibata and co-workers reported an Ir-catalyzed intramolecular enantioselective C-2 alkylation of *N*-alkenylindoles (**139**) via C_2−H bond activation (Scheme 32a).[82] A para-anisoyl group at the C-3 position of the indoles

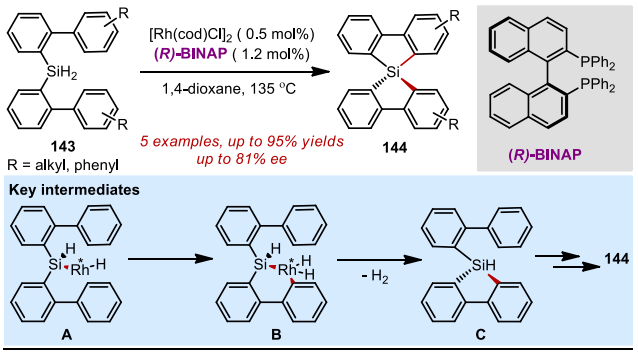
Scheme 32. Intramolecular Enantioselective C−H Functionalization via Diphosphine Ligand



functioned as an efficient directing group, and the chiral 1-substituted-2,3-dihydro-1*H*-pyrrolo[1,2- a]indoles (**140**) were afforded with the assistance of the chiral diphosphine ligand (*S*)-SEGPHOS, in high yields with excellent enantioselectivities (up to 98% ee). The reactions proceeded through the directed C_2−H bond activation of indoles (**A**), and subsequent intramolecular hydroiridation led to the generation of the stereogenic center (**B**), followed by reductive elimination providing the chiral 5-*exo*-type products. In 2018, the same group extended this protocol for benzoylamide directed enantioselective formal C−H conjugated addition to *β*-substituted *α,β*-unsaturated esters **141** using Ir-catalyst and (*S*)-BINAP as a ligand (Scheme 32b).[83] This intramolecular reaction furnished enantiomerically enriched *γ*-lactones with a quaternary all-carbon stereogenic center.

In 2013, Kuninobu, Takai, and co-workers disclosed the synthesis of chiral spirosilabifluorene derivatives **144** from bis(biphenyl)silane **143** via double dehydrogenative cyclization using a rhodium catalyst and chiral phosphine ligands (*R*)-BINAP (Scheme 33).[84] To rationalize the mechanistic understanding, plausible key intermediates are shown in

Scheme 33. (*R*)-BINAP Induced Asymmetric Synthesis of Spirosilabifluorene Derivatives



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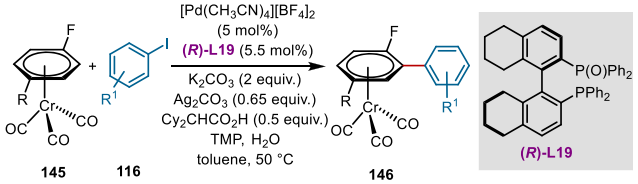
Scheme 33. The reaction is expected to follow the first Si−H bond activation by the Rh-catalyst via oxidative addition of bis(biphenyl)silane to the metal center (**A**), followed by sequential C−H activation of the aromatic C−H bond (**B**). Subsequent elimination of hydrogen and reductive elimination led to the formation of cyclized product **C**. Repeatation of all the steps led to formation of enantioselective spirosilabifluorenes **144**. The chirality of the spirosilabifluorenes was determined at the first dehydrogenative cyclization. The conformation of the intermediate **A** was expected to orient in such a way to minimize the steric interactions between the biphenyl of the bis(biphenyl)silane and chiral ligand of the catalyst, thus facilitating the reaction of Rh−H species enantioselectively with the closer biphenyl group. Then, the second dehydrogenative cyclization wasbcarried out between the remaining Si−H and biphenyl group.

Recently, Larosaa and co-workers demonstrated the Pd-catalyzed enantioselective C−H arylation of (η^6-arene)-chromium complexes **145** with the iodoarenes **116** to afford planar-chiral complexes (Scheme 34).[85] Notably, the afforded

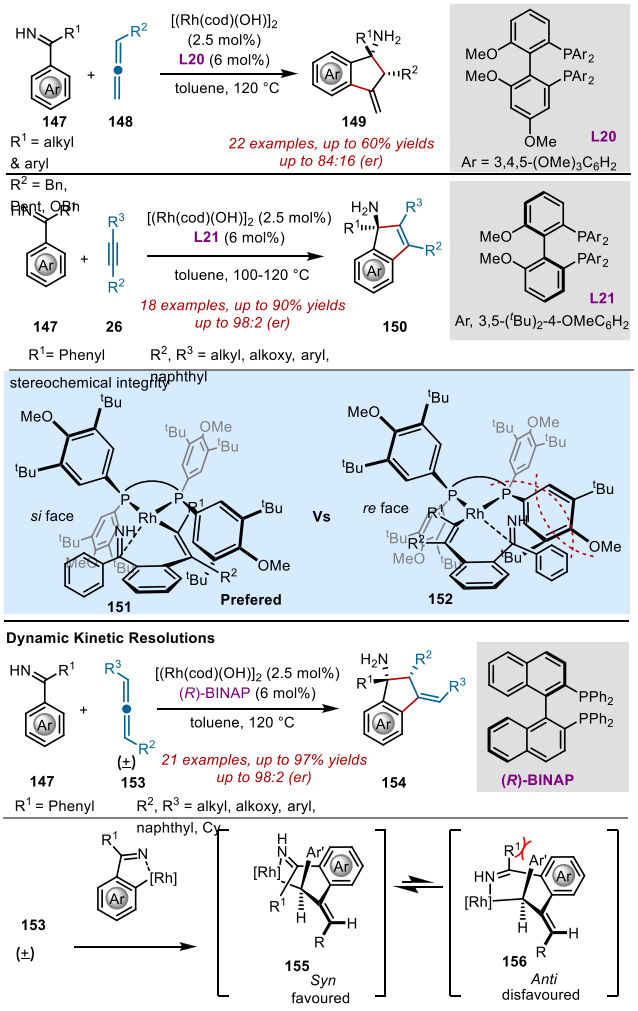
Scheme 34. Asymmetric C−H Arylation of (η^6-Arene)chromium Complexes



planar-chiral chromium derivatives can be easily transformed into a variety of planar chiral mono- or diphosphines. The hemilabile ligand H_8−BINAP(O) was found to be crucial for this transformation to obtain enantioenriched planar-chiral products **146** in high yields and selectivities (up to 98:2 er).

In 2010, Cramer and co-workers demonstrated rhodium(I)-catalyzed C−H functionalizations of unsubstituted ketimines **147** with terminal allenes **148** (Scheme 35).[86] Notably, the imine, which initially acts as a directing group for *ortho*-C−H activation, incorporated itself into the reaction and enhanced the diversity and molecular complexity of the developed products, resulting in the highly regio- and diastereoselective cyclized product **149**. The cyclized products were obtained in very good yields and enantioselectivities using the chiral biphosphine ligand **L20**. Further, Cramer and co-workers extended this protocol to both the symmetrical and unsymmetrical internal alkynes **26** for the synthesis of highly enantioselective indenamine derivatives **150** (Scheme 35).[87] The absolute configuration of the products can be rationalized from the stereochemical models **151** and **152**. It is clear that the imine moiety incorporated itself into the reaction preferentially through its *si* face. Intermediate **151** is preferred over **152** as it avoids an energetically unfavorable interaction of the ketimine and a DTBM residue of ligand (*S*)-**L21**. In 2013, Tran and Cramer disclosed a similar type of reaction for Rh-catalyzed dynamic kinetic resolution of racemic allenes **153** by [3 + 2] annulation of aryl ketimines **147** using (*R*)-BINAP as a chiral auxiliary.[88] The developed method furnished synthetically valuable indenylamines **154** up to 97% yield and up to 98% ee. The regioselectivity of the C−H activation was

Scheme 35. Enantioselective [3 + 2]-Annulation of Ketimines with Allenes and Alkynes



kinetically controlled, and excellent *E*/*Z*-selectivity, diastereo-, and enantioselectivity were observed. The authors proposed two competing modes of cyclization based on the two possible orientations of allene in the rhodacycle **155** and **156** (Scheme 35). The highly diastereoselective indenylamines were likely to form through the sterically favorable intermediate **155**.

Hartwig and co-workers reported an intermolecular asymmetric hydroarylation of bicycloalkenes **158** with C_2−H bonds of thiophenes, pyrroles, and furans in high yield with high enantiomeric excess (Scheme 36).[89] Notably, C_2−H alkylation was observed in unprotected indoles (**159b**), contrary to the innate selectivity at the C-3 position. The reaction proceeded with the oxidative addition of the heteroarene C−H bond to the Ir-catalyst (**160**), and subsequent syn addition of H atom to the olefin with the assistance of (*S*)-DTBM-SEGPHOS ligand led to formation of enantioenriched exo products **159** in very good yields (up to 98%) and excellent selectivities (up to 99% ee).

In 2015, the research group of He,[90] Murai, and Takai[91] independently disclosed Rh-catalyzed enantioselective C−H sillylation of the cyclopentadiene ring in the metalloacenes (Scheme 37). The C_2-symmetric electron rich and bulky chiral diphosphine ligands in combination with the Rh-catalyst efficiently catalyzed the dehydrogenative C(sp^2)−H sillylation

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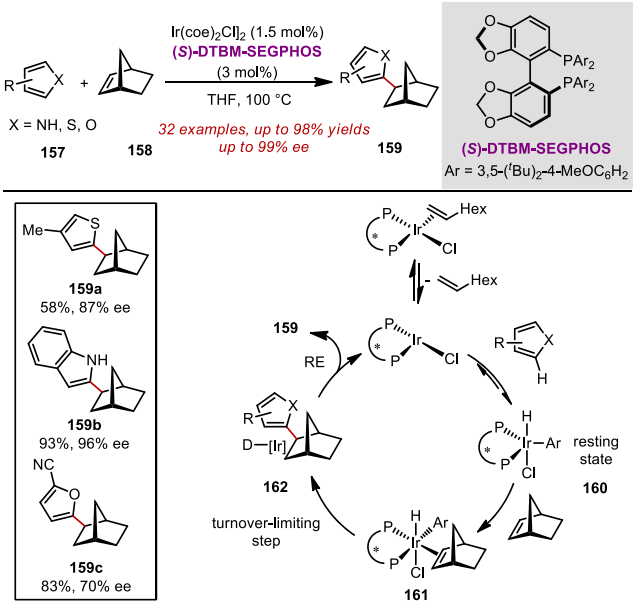
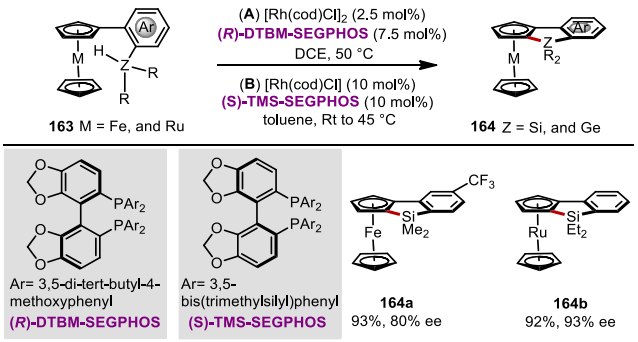
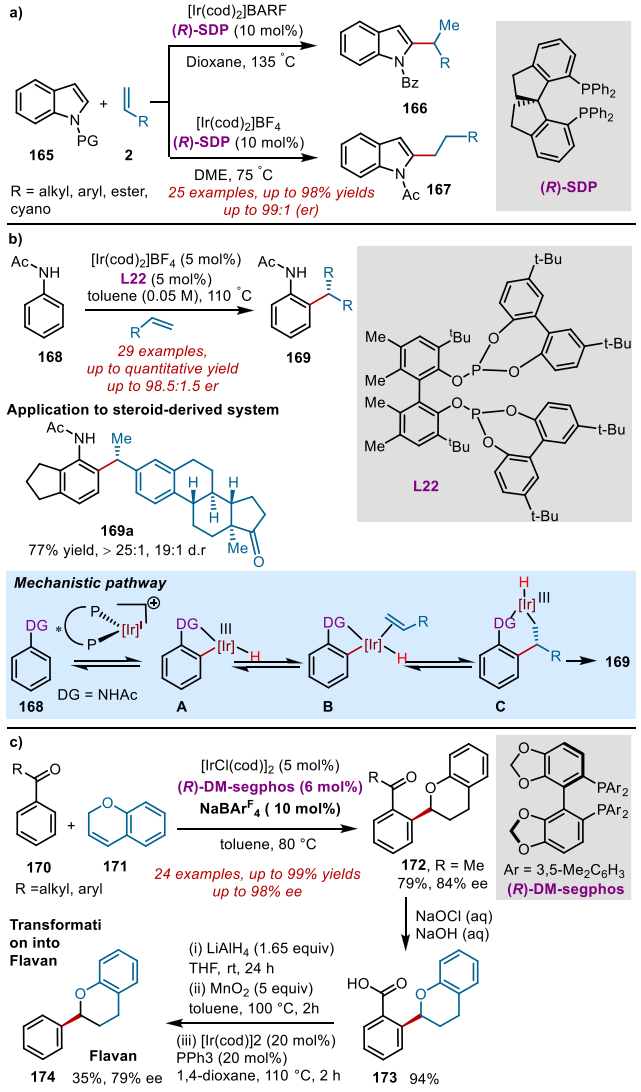
Scheme 36. Intermolecular Asymmetric Hydroheteroarylation of Bicycloalkenes



Scheme 37. Syntheses of Planar Chiral Metallocenes via Enantioselective C(sp²)−H Sillylation/Germanylation



Scheme 38. Enantioselective Intermolecular Hydroarylation



of metallocenes (**163**) leading to planar-chiral metallocene siloles (**164**). He and co-workers demonstrated the synthesis of metallocene siloles in very good yields and enantioselectivites utilizing (*S*)-TMS-SEGPHOS under very mild reaction conditions, whereas Takai and co-workers utilized (*R*)-DTBM-SEGPHOS for the synthesis of metallocene siloles and germoles.

In 2012, the Shibata group demonstrated Ir-catalyzed enantioselective C_2-alkylation of *N*-substituted indole **165** with a variety of alkenes using the chiral bisphosphine (*R*)-SDP ligand (Scheme 38a).[92] Depending on the directing group, two different types of alkylated products were achieved. Linear alkylated products **167** were obtained with the acetyl directing group, whereas with the benzoyl group branched selective products **166** were obtained in very good yields and enantioselectivities (up to 99:1 er). In 2018, Bower and co-workers reported that a chiral bisphosphine ligand **L22** promoted highly enantioselective Ir-catalyzed hydroarylations of styrenes and α-olefins (Scheme 38b).[93] The tertiary benzylic stereocenters were accessed directly through anilide *ortho*-C−H bond activation. The reaction was extended to afford steroid-derived complex molecule **169a**. Mechanistic studies revealed the reversibility nature of the stereocenter generating step. Very recently, Sakamoto and Nishimura reported an enantioselective hydroarylation of 2*H*-chromenes **171** with aromatic ketones **170** in the presence of a cationic iridium catalyst and chiral phosphine ligand, (*R*)-DM-SEGPHOS (Scheme 38c).[94] The reaction proceeded through olefin isomerization followed by enantioselective hydroarylation, leading to 2-arylchromanes **172** in high yields with excellent enantioselectivities. Aylchromane was further transformed into chiral flavan (**174**) by treating with aqueous NaOCl and NaOH and followed by deformylation through Ir catalysis.

Recently, Tang and co-workers demonstrated palladium-catalyzed intramplecular enantioselective C(sp²)−H carbamoylation of diarylmethyl carbamoyl chlorides **175** for the synthesis of chiral isoindolines derivaties **176** (Scheme 39).[95] Enantioenriched isoindoline derivatives (e.g., **176a−b**) were obtained in excellent yields and selectivities (up to 99% ee) using chiral monophosphorus ligand (*R*)-AntPhos. A carboxylate-assisted concerted metalation-deprotonation (CMD) pathway could lead to the formation of C−H activated intermediate (**177** or **178**). The stereochemistry of the product can be realized from the careful analysis of these two conformers.

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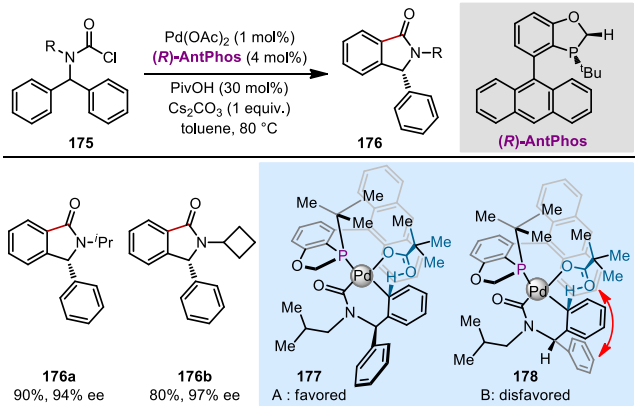
Scheme 39. Asymmetric C(sp²)-H Carbamoylation Reaction

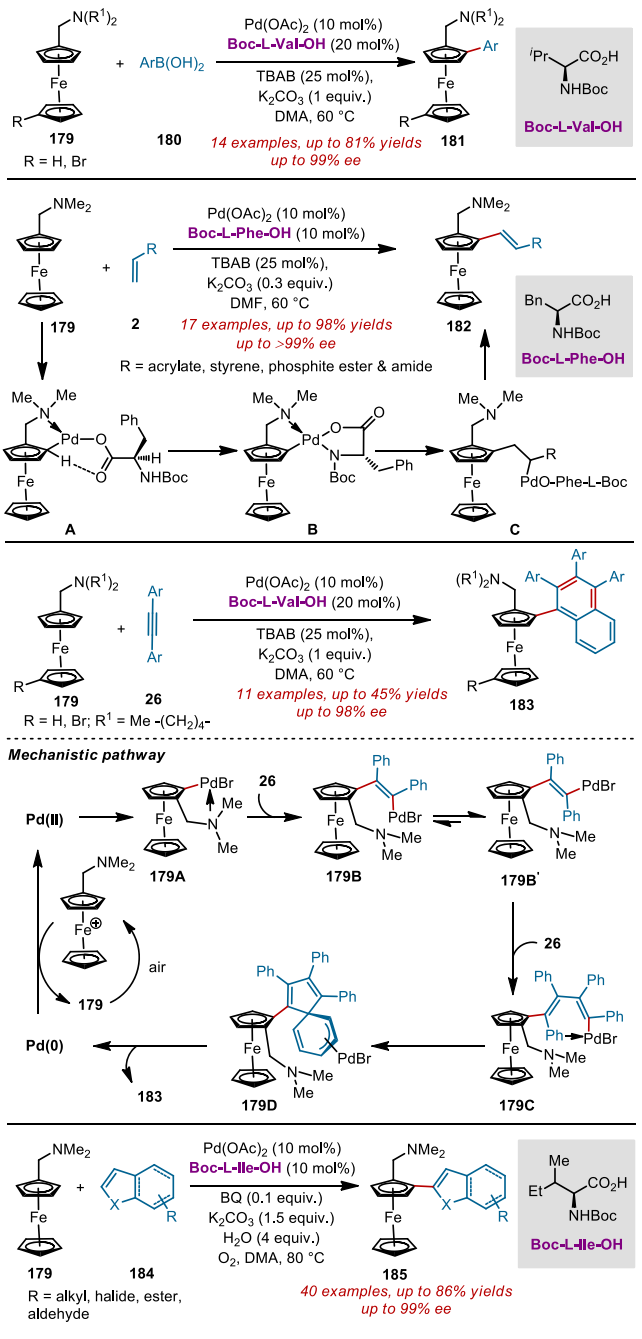


Energetically unfavorable interactions between the anthryl group of the ligand and one phenyl substituent of the substrate in the conformer **178** led to the minor isomer of the cyclized products, while the more stable conformer **177** leads to a highly enantio-enriched product.

3.4. Chiral Carboxylic Acid (CCA) Ligand. Chiral carboxylic acids (CCA) are an important class of ligands in transition metal catalysis as they can assist in the metalation-deprotonation step along with chiral induction. In 2008, Yu and co-workers[96] first introduced the usage of a catalytic amount of chiral mono-protected amino acids (MPAA) to induce chirality in the palladium-catalyzed enantioselective C−H functionalization process. Building on this pioneering work, several research groups have made a tremendous effort toward the development of chiral carboxylic acid promoted enantioselective C(sp²)−H functionalization.

The catalytic enantioselective synthesis of planar chiral ferrocenes by utilizing readily available chiral MPAA is highly desirable. In 2013, Gu, You, and co-workers reported a Pd(II)-catalyzed enantioselective arylation of aminomethyl ferrocenes **179** with arylboronic acids **180** using Boc-L-Val-OH as the chiral ligand (Scheme 40).[97] A wide range of planar chiral ferrocenes **181** were obtained under the optimized reaction conditions in 14−81% yields and up to 99% ee. In the same year, Cui, Wu, and co-workers[98] disclosed a Pd(II)-catalyzed enantioselective olefination reaction of *N,N*-dimethylamino-methylferrocene **179** using the monoprotected *α*-amino acid Boc-L-Phe-OH as the chiral ligand. A broad range of monosubstituted olefins **2** were amenable to this protocol to provide the desired chiral olefinated products in 65−98% yield and up to 99% ee. Mechanistically, the reaction proceeded through the formation of a cyclopalladated intermediate **B**. Subsequently, this intermediate undergoes syn-insertion of alkenes to provide intermediate **C**. Finally, *β*-hydride elimination of intermediate **C** leads to the formation of desired products **182**. Later, You and co-workers[99] described the enantioselective dehydrogenative annulation of *N,N*-substituted aminomethyl ferrocenes **179** with diarylethynes **26** under the same conditions, leading to highly enantioen-riched naphthyl-substituted ferrocene derivatives **183** in moderate yields. The proposed mechanistic pathway showed directed palladation to the ferrocene unit by a amine directing group, generating cyclopalladated intermediate **179A**. Then, the palladacycle **179A** was coordinated with alkyne **26**, followed by syn-insertion to provide intermediate **179B**. Subsequent cis−trans isomerization occurred, and then a

Scheme 40. Chiral MPAAs Promoted C(sp²)−H Functionalization of Ferrocenes



second alkyne was inserted to give the intermediate **179C**. Next, the intramolecular 5-exo-dig insertion of a benzene led to spiro palladium intermediate **173D**. The subsequent bond migration and reductive elimination generated **183** as well as the Pd(0) species which can be reoxidized into the active Pd(II) species by **179** to complete the catalytic cycle. In 2016, You and co-workers[100] reported the first example of Pd(II)/Pd(0)-catalyzed enantioselective biaryl coupling of ferrocenes **179** with heteroarenes **184** via a 2-fold C−H activation process. In this methodology, the dimethylamino group of **179** directed the first (stereochemistry-generating) C−H activation of the ferrocene backbone, whereas the regioselectivity of the second C−H activation was governed by the heteroatom of **184**. A variety of heteroaromatic-substituted planar chiral

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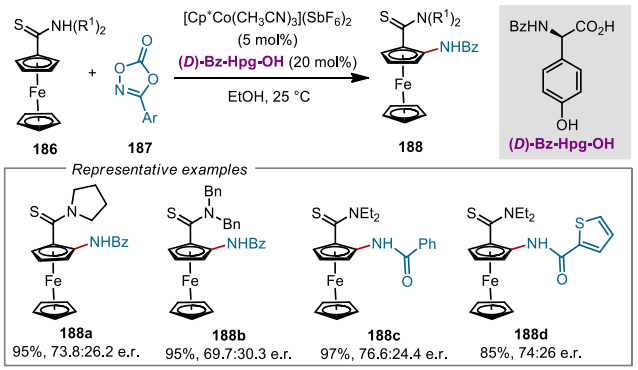
ferrocene derivatives **185** was synthesized with excellent regio- and enantioselectivity.

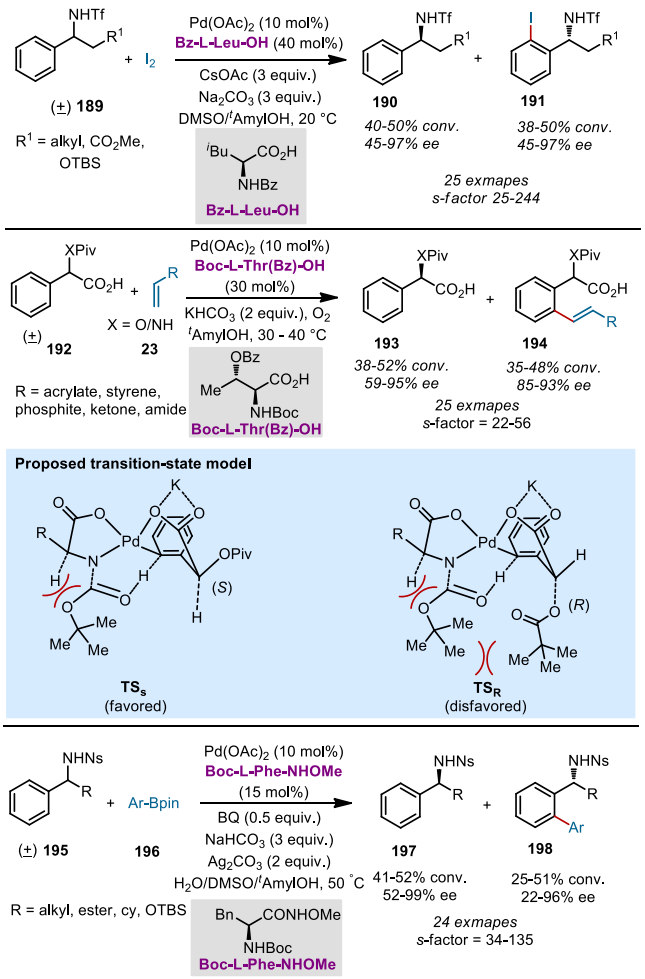
In 2019, Shi and co-workers disclosed a Cp*cobalt(III)-catalyzed enantioselective C−H amidation of ferrocenes **186** containing a thioamide directing group using monoprotected amino acids (D)-Bz-Hpg−OH as chiral ligands (Scheme 41).[101] Under the optimization condition, highly enantioenriched amidation of planar ferrocene derivatives (**188a−d**) was achieved.

Scheme 41. Enantioselective Amidation of Ferrocenes Directed by Thioamides



Kinetic resolution through aryl C(sp^2)−H bond functionalization has recently appeared as an efficient tool for synthesizing enantiopure compounds.[102] Yu and co-workers developed a highly efficient kinetic resolution of chiral arylalkylamines **189** by Pd catalyzed C−H iodination with an s-factor up to 244.[103] The reaction proceeded using a chiral MPAA ligand Bz-L-Leu-OH at ambient temperature. In addition to simple arylalkylamines, a wide range of β-amino acids and β-amino alcohols were compatible under the optimized reaction conditions to afford the desired chiral products with good to excellent enantioselectivities (Scheme 42). In 2016, Yu group described the kinetic resolution of racemic phenylacetic acids via *ortho*-C−H olefination.[104] In this protocol, a palladium(II)-catalyzed enantioselective C−H olefination of racemic α-hydroxy and α-amino phenylacetic acids **192** (X = O and NH) via kinetic resolution was developed to afford enantiomerically enriched olefinated mandelic acids **194** and phenylglycines **193** (Scheme 42). It was found that in the presence of Boc-L-Thr(Bz)-OH as the chiral ligand, the enantioselective C−H olefination of *rac*-**192** under the optimized conditions provided the desired products with high enantioselectivities. The differential reactivity can be realized from the proposed two transition-state model. In both TS_S and TS_R, Pd is coordinated with the MPAA ligand and the substrate in a square-planar coordination. The side-chain of amino acid points upward, which pushes the Boc groups below the Pd-coordination plane to avoid steric repulsion. In the C−H activation step, the transition state TS_R is expected to be disfavored relative to TS_S because of the steric repulsion between Boc and OPiv in TS_R and is consistent with the faster formation of the product with the S configuration. In the same year, Yu and co-workers described the kinetic resolution of N-nosyl benzylamine derivatives **195** via Pd (II)-catalyzed cross-coupling with arylboronic acid pinacol esters **196**.[105] Both chiral benzylamines **197** and ortho-arylated benzylamines **198** were obtained in high enantiomeric purity. In this protocol,

Scheme 42. Enantioselective C−H Functionalization via Kinetic Resolution



methylhydroxamic acid ligand Boc-L-Phe-NHOMe gave the best results. Notably, the usage of the nosyl (Ns) group as the directing group is a crucial practical advantage of this transformation. Authors suggested that the structures of the boronic acids did not show any significant impact on the s-factor, which is believed to be consistent with the fact that enantioselectivity is solely determined by the C−H activation step.

In 2018, the Ackermann group described the highly enantioselective cobalt(III)-catalyzed C−H activation enabled by chiral carboxylic acid (Scheme 43).[106] The reaction of *N*-pyridyl-indoles **199** with diversely functionalized allylbenzenes **2** afforded the desired C_2 alkylated indoles **200** with high regioselectivities and excellent levels of enantio-control. The newly designed C_2-symmetric carboxylic acid ligand **L23** was proven as the optimum ligand to exert a higher degree of stereoinduction in the C−H activation step. Later, Yoshino, Matsunaga, and their co-worker[107] extended this method for enantioselective 1,4-addition of indoles **201** to maleimides **202**. In this methodology, a binaphthyl-derived chiralcarboxylic acid **L24** served as the efficient ligand to control enantioselectivity. Authors proposed that a reversible insertion/protodemetalation mechanism is more likely to be operating via TS model **204**.

In recent times, enantioselective C−H functionalization using an achiral Cp^xM^{III} complex in combination with an

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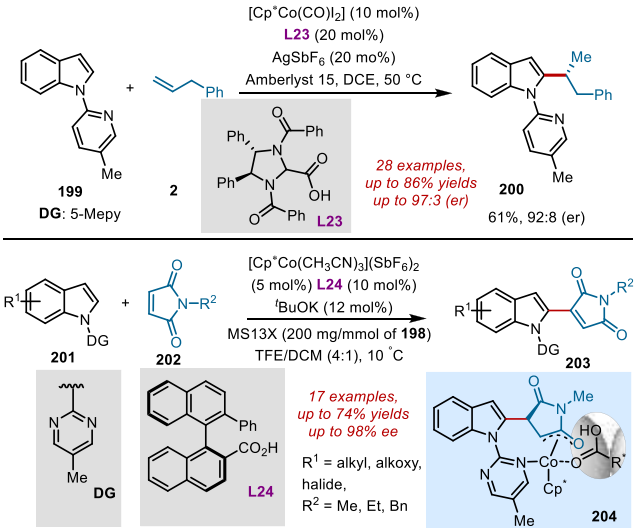
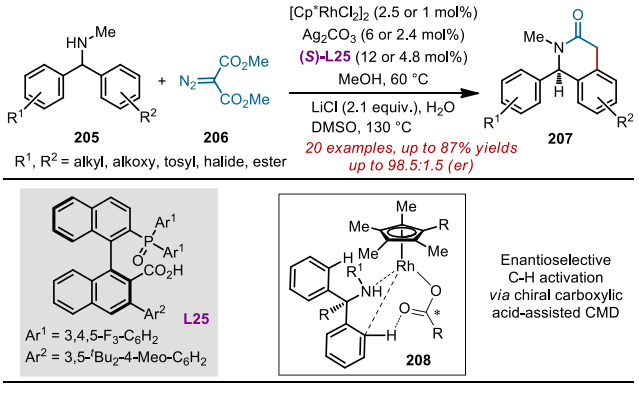
Scheme 43. Enantioselective Cobalt(III)-Catalyzed C−H Activation by Chiral Carboxylic Acid Cooperation



external chiral ligand is a highly evolving topic of discussion. In 2018, Matsunaga and co-workers disclosed an achiral Cp*Rh-(III)/chiral carboxylic acid (CCA) catalyzed asymmetric C−H alkylation of diarylmethanamines **205** with a diazomalonate **206**, followed by cyclization and decarboxylation to afford 1,4-dihydroisoquinolin-3(2*H*)-one derivatives **207** in very good yields and up to 98.5:1.5 e.r. (Scheme 44).[108] In this catalytic

Scheme 44. Chiral Carboxylic Acid Enabled Enantioselective C−H Alkylation

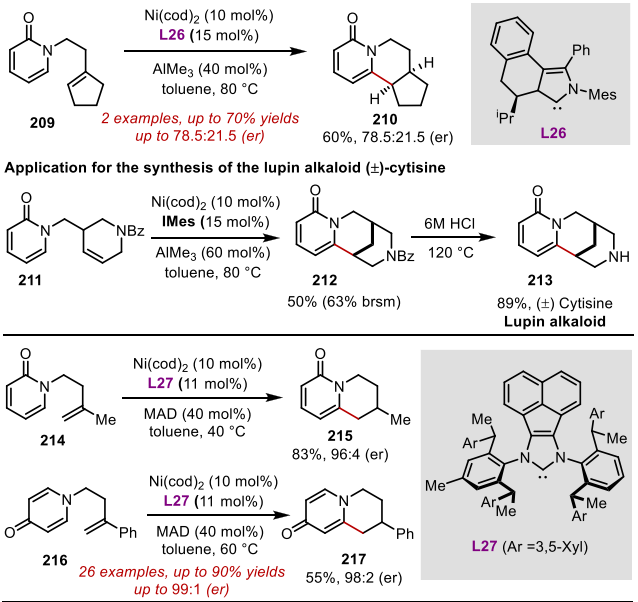


system, both secondary and nonprotected primary alkylamines were considered as the favored directing group, although enantioselectivity was achieved via a concerted metalation deprotonation (CMD) mechanism using sterically hindered binaphthyl-based chiral monocarboxylic acid **L25**.

3.5. Chiral NHC Ligands. Chiral *N*-heterocyclic carbene (NHC) ligands play a vital role in enantioselective transition-metal catalysis.[109] In 2001, Burgess reported the first highly enantioselective catalytic hydrogenation of olefins using chiral NHC ligand.[110] Later, Grubbs reported a newly designed monodentate NHC scaffold for the enantioselective ring-closing metathesis reaction.[111] Because of the rigid ligand backbone, multidentate nature (chelate effect), axis of C_2-symmetry, the usage of chiral NHC ligand scaffold reduces the number of possible transition states for the stereodetermining step and thereby increases the enantioselectivity. Herein, we have given an overview of chiral NHC ligands that have been exploited in catalytic enantioselective C(sp^2)−H functionalization reactions.

In 2015, Donets and Cramer reported a nickel-catalyzed intramolecular C−H alkylation of 2-pyridones **209** to afford racemic 1,6-annulated 2-pyridones **210**.[112] The preliminary investigation suggested that a catalytic asymmetric version of this endo cyclization event with a chiral *N*-heterocyclic carbene ligand **L26** could be achieved, resulting in the corresponding enantioenriched pyridones **210** in 78.5:21.5 e.r. (Scheme 45).

Scheme 45. Chiral NHC Control Enantioselectivity sp^2 C−H Functionalizations of Pyridone



A naturally occurring compound such as lupin alkaloid (±)-cytisine **213** was synthesized to showcase the practicality of the developed method. Later, this same group developed a sterically hindered and tunable *N*-heterocyclic carbene (NHC) ligand **L27** for the annulation of 2- and 4-pyridines (**214** and **216**) via enantioselective intramolecular olefin hydroarylation.[113] Notably, introduction of the acenaphthoimidazolylidene framework and 3,5-xylyl bulkier groups in the NHC backbone significantly improved the yield and enantioselectivity.

While various strategies have appeared for direct C−H functionalization of pyridines to deliver racemic products, methods for the enantioselective functionalization of pyridines via a C−H activation process are very rare.[45] In 2019, Shi and co-worker first reported a highly regio- and enantioselective Ni(0)-catalyzed endoselective intramolecular C−H alkylation of pyridines **218** (Scheme 46).[114] This asymmetric C−H alkylation at pyridyl 3- and 4-positions was accomplished by using bulky chiral NHC ligand **L28** in the presence of a bulky additive MAD. This protocol provided a series of chiral 5,6,7,8-tetrahydroquinolines and 5,6,7,8-tetrahydroisoquinolines **219** in moderate to high yields (up to 99% yield) and enantioselectivities (up to 99% ee). Shortly after, the Shi group extended this approach for the synthesis of enantioenriched fluorotetralins via asymmetric C−H alkylation of polyfluoroarenes **220** with alkenes by employing bulky chiral

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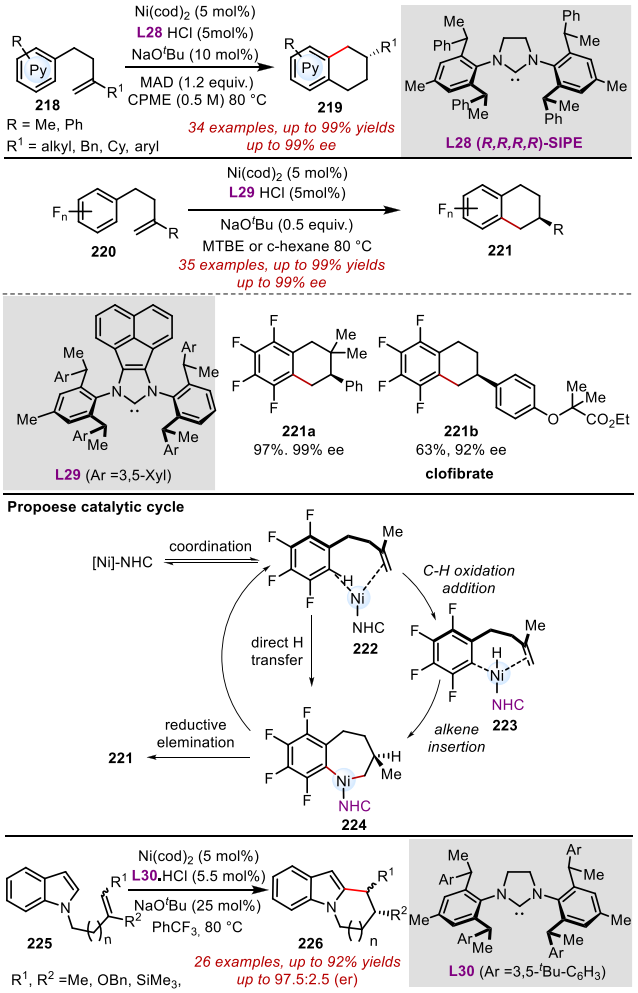
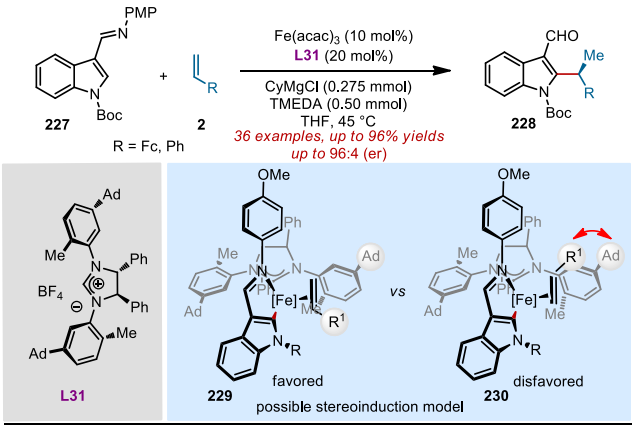
Scheme 46. Enantioselective C−H Cyclization of Alkenes by NHC Catalysis



N-heterocyclic carbene (NHC) **L29** (Scheme 46).[115] In this context, NHC-stabilized Ni(0) catalyst facilitated selective activation of C−H bonds over C−F bonds in polyfluoroarenes and predominantly improved the enantioselectivity chiral fluorotetralins. The proposed mechanistic study suggested that direct ligand-to-ligand hydrogen transfer from fluoroarenes to the alkene could be a favorable pathway. The utilization of highly sterically demanding and electron-donating chiral NHC ligands played a critical role to enable a challenging reductive elimination step and completed endoselective cyclization, thus leading to excellent chemo-, regio-, and enantio-control of the reaction. In the meantime, Cramer and co-workers applied the same protocol for the enantioselective Ni(0)-catalyzed C−H functionalizations of indoles and pyrroles **225** without using a Lewis basic directing group (Scheme 46).[116] This process provided a range of substituted tetrahydropyridoindoles and tetrahydroindolizines **226** with high yields and enantioselectivity. The authors suggested that the presence of bulky chiral SIPr carbene ligand **L30** holds the key factor for the C−H activation and stereoselectivity in the cyclized product.

Earth-abundant 3d transition metal catalyzed enantioselective C−H functionalization has drawn significant interest in recent times.[15c] In 2019, Ackermann's group developed the enantioselective iron-catalyzed C−H alkylation of (aza)indoles **221** (Scheme 47).[117] In this methodology, high levels of stereoselectivity was achieved by utilizing well designed NHC

Scheme 47. Asymmetric Fe-Catalyzed C−H Alkylation by Metasubstituted NHC Ligand

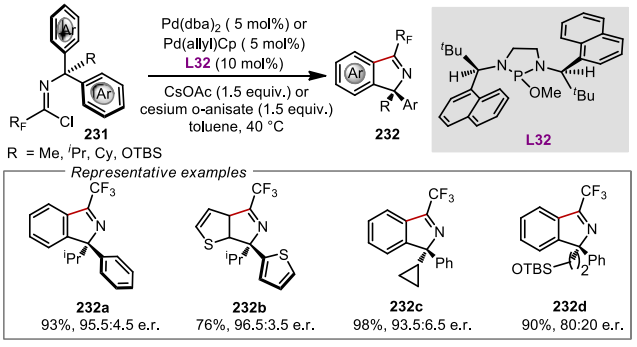


ligands **L31** with a bulky side arm. In addition to a broad range of indoles and azaindoles, diversely substituted olefins were compatible under the reaction conditions, affording the desired chiral C2-alkylated products **228** in excellent yields and up to 96:4 er. Mechanistic study suggested that the C−H activation step proceeds through a ligand-to-ligand H-transfer LLHT pathway. Moreover, authors proposed the stereoinduction to be arised by secondary interactions in the coordination-induced migratory insertion of **229.**

3.6. Miscellaneous. Mostly, metal-catalyzed enantioselective C−H functionalization has been developed by using well-known chiral frameworks such as BINOL, BINAP, chiral TADDOL, etc. (*vide supra*). However, this section covers the recent advances in enantioselective C(sp^2)−H functionalization utilizing different class of ligands, such as chiral transient ligand, phosphine oxides, sulfoxide-oxazoline, PyBox, and diene.

3.6.1. Chiral Phosphine Oxide Ligand. In 2019, Cramer and co-worker disclosed a catalytic enantioselective C−H functionalization for the synthesis of chiral 1*H*-isoindoles **232** bearing quaternary stereogenic centers using chiral diazaphospholane **L32** or TADDOL type ligand (Scheme 48).[118] The trifluoromethyl-substituted imidoyl chlorides **231** act as an electrophilic nature for the introduction of perfluoroalkyl substituent on the product. The use of phosphordiamidite

Scheme 48. Enantioselective 1*H*-Isoindole Synthesis via Chiral Diazaphospholane Ligand



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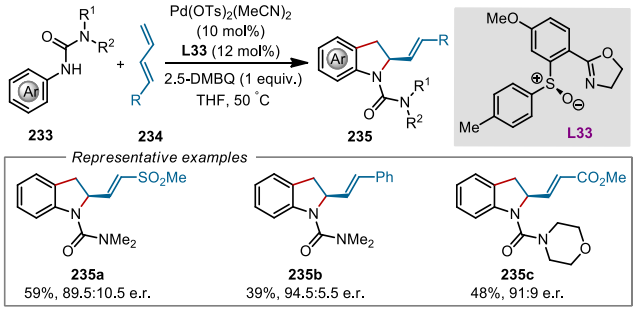
ligand **L32** provided in a very efficient way to enhance the high enantioselectivity. A variety of substituted arene substrates underwent competent C−H functionalization and allowed for the synthesis of isoindoles in good yield and excellent enantioselectivity.

3.6.2. Chiral Sulfoxide−Oxazoline Ligand. The development of enantioselective palladium-catalyzed cascade C−H bond activation offers a formidable challenge.[8b,16,43b] In 2017, Han and co-worker reported a Pd(II)-catalyzed cascade C(sp^2)−H functionalization/intramolecular asymmetric allylation reaction using an amide directing-group (Scheme 49).[119]

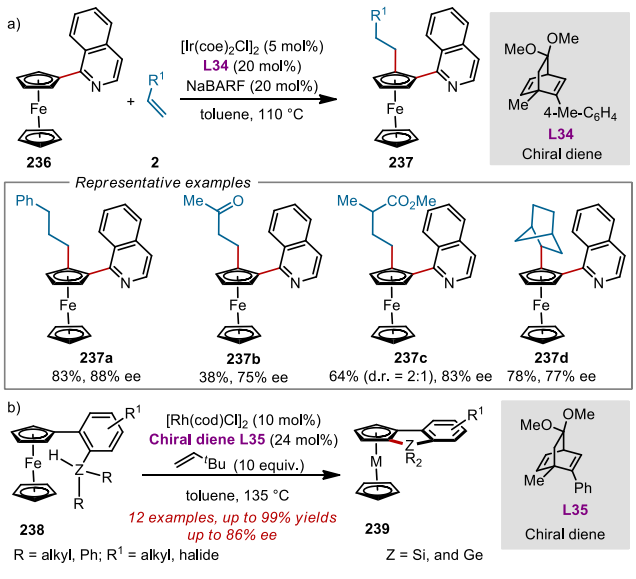
Scheme 49. Asymmetric Intramolecular Cascade C(sp^2)−H Allylation



In this reaction, a chiral sulfoxide-oxazoline (SOX) ligand containing chiral sulfur center **L33** was utilized to control stereoselectivity of the allylation step. The substrate scope was investigated with respect to aryl ureas **233** and 1,3-dienes **234**, providing a series of chiral indoline derivatives **235** with high yields and enantioselectivities.

3.6.3. Chiral Diene Ligand. The Shibata group discovered the first catalytic enantioselective C(sp^2)−H alkylation of ferrocene derivatives **236** with various alkenes **2** in the presence of a chiral diene ligand (Scheme 50a).[120] In this catalytic system, a cationic Ir-complex and a directing group 1-isoquinolyl moiety played a crucial role for the regio- and

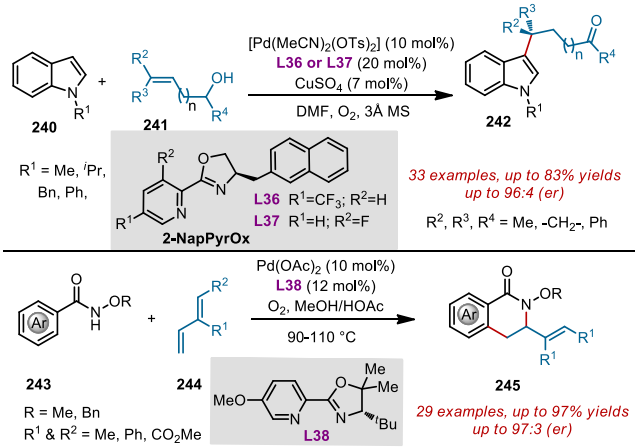
Scheme 50. Enantioselective C−H Alkylation of Ferrocenes Chiral Diene Ligand



enantioselective C−H activation of ferrocene. After several ligands were evaluated, an analogue of Carreira's diene,[121] tolyl-substituted derivative **L34**, was proven as the optimal chiral ligand and afforded the desired products **237** in 38−99% yields and up to 93% ee. A wide variety of alkenes were amendable to this reaction protocol (**237a−d**). Later, this same group extended this method for the synthesis of planar-chiral benzosiloloferrocenes derivatives (Scheme 50b).[122] This enantioselective cross dehydrogenative coupling of C(sp^2)−H bond of ferrocene with a Si−H bond proceeded efficiently with the use of a Rh catalyst and chiral diene ligand.

3.6.4. Chiral PyBox Ligand. In 2015, Sigman and co-workers disclosed an enantioselective intermolecular dehydrogenative Heck reaction of indoles **240** with trisubstituted alkenes **241** (Scheme 51).[123] It was found that the chiral

Scheme 51. C(sp^2)−H Functionalization via Chiral Pyrox Ligand



pyridine oxazoline ligand containing a naphthyl ring **L36** (PyrOx) could be effective for the synthesis of various chiral indoles **242**. Notably, authors have carried out a wide variety of ligand optimization by computationally for achieving a higher degree of stereocontrol in the desired product. Therefore, superior enantioselectivities were observed in the case of fluoro derivative **L37** over trifluoromethyl derivative **L36**. Two possible mechanism were proposed for the addition of indole to the alkene: (1) direct palladation through an electrophilic aromatic substitution and (2) a Wacker type addition. Later, the Han and Gong group developed a chiral Pd(II)-catalyzed cascade C(sp^2)−H functionalization/intramolecular asymmetric allylation of N-alkoxyaryl amides **243** with 1,3-dienes **244** using a novel chiral Pyrox as the ligand **L38**.[124] This method provided different types of chiral heterocycles derivatives with high yields and excellent enantioselectivities. Chiral pyridine-oxazoline based ligand bearing a methoxyl group at the C-5 position and a gem-dimethyl group on the oxazoline moiety is seen to be crucial for the stereocontol.

3.6.5. Chiral Transient Directing Group (TDG). In 2016, the concept of chiral TDG enabled asymmetric C−H activation reaction was first realized by Yu and co-workers.[125] They described enantioselective benzylic C(sp^3)−H arylation of aldehydes by using L-*tert*-leucine as a chiral TDG. However, the usage of chiral TDG in achieving asymmetric C(sp^2)−H functionalization is in the infancy stage. In early 2019, Wang and co-workers developed an efficient catalytic systems for the

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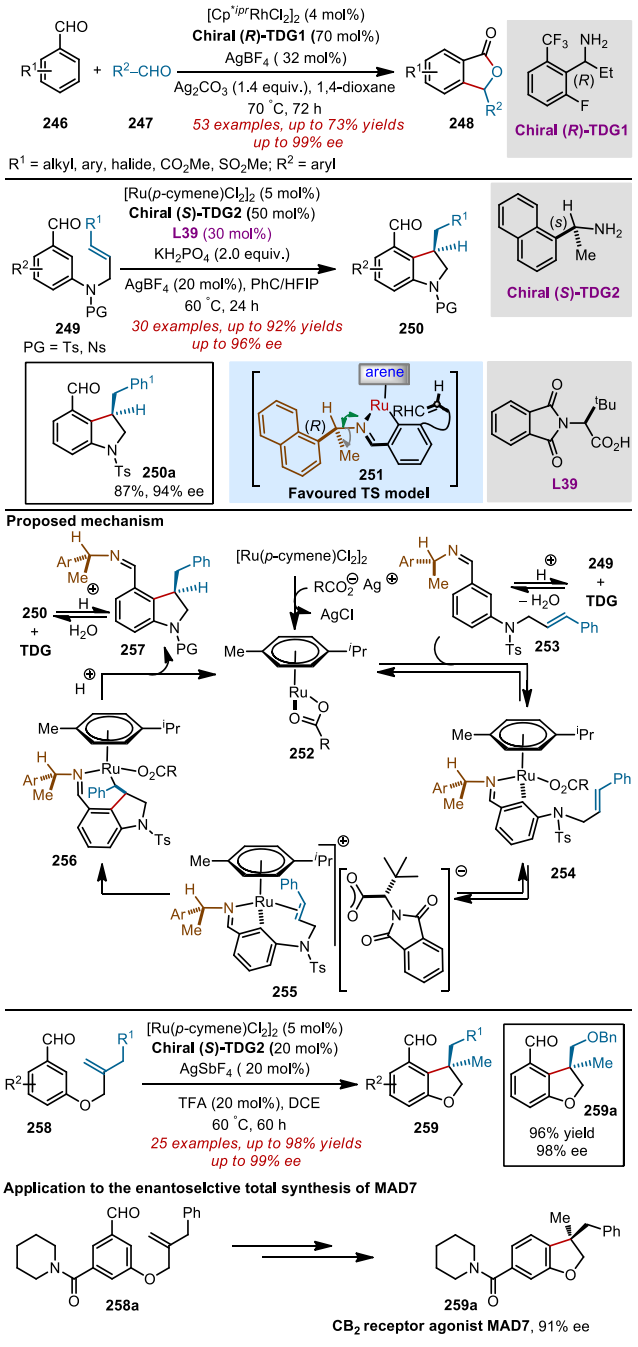
synthesis of various chiral phthalides **248** from simple aldehydes **246** and **247** by combining catalytic amount of chiral amine as a transient directing group along with a achiral rhodium(III) catalyst (Scheme 52).[126] After several chiral

Scheme 52. Asymmetric C(sp²)-H Functionalization by Chiral Transient Directing Group



TDG were evaluated, the chiral amine bearing fluoro- and trifluoromethyl groups at 2- and 6-positions of the phenyl ring, TDG1 was found to be superior under the optimized reaction conditions to afford the desired chiral products **248** in good yields and enantioselectivities. In the same year, Cui et al. described a Ru-catalyzed enantioselective C−H hydroarylation reaction for the synthesis of indoline derivatives **250** using α-methyl amine, TDG2 as the chiral transient directing group.[127]

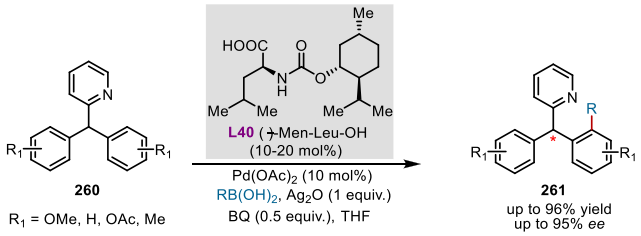
The reaction proceeded with the formation of chiral transient imine intermediate **253**, which then undergoes a reversible Ru(II)-catalyzed C−H activation process in acidic media to form ruthenacycle **254**. The bulky chiral carboxylate ligand not only assists in the metalation/deprotonation step but also controls the enantioselectivity by forming an ion pair intermediate **255**. The enantio-determining alkene insertion step occurs via favored intermediate **251**, in which the alkene moiety approaches the Ru-center from the less sterically hindered side of the chiral carbon to afford the favored enantiomer with a high degree of enantioselectivities. Recently, the Wang group extended this protocol for the synthesis of highly enantio-enriched 2,3-dihydrobenzofuran derivatives **259** by using similar chiral TDG (Scheme 52).[128] By taking advantage of this methodology, a novel asymmetric total synthesis of CB2 receptor agonist MDA7 **259a** was explored.

4. ENANTIONSELECTIVE C(SP²)−H ACTIVATION VIA DESYMMETRIZATION

Desymmetrization of prochiral *gem*-diaryl compounds offer an alternate efficient strategy for achieving enantioselective aromatic C−H functionalization reactions. However, advances hitherto have clearly shown that both intra- as well as intermolecular C−H functionalization reactions could accomplish the construction of quaternary carbon stereocenters.

4.1. Enantioselective Intermolecular C−H Functionalization Reactions. In 2008, Yu and co-workers described Pd(II)-catalyzed enantioselective desymmetric C−H alkylation of prochiral diaryl(2-pyridyl)methane **260** using alkyl boronic acids as coupling partner and monoprotected amino acid as a chiral ligand (Scheme 53).[14] After several ligands were

Scheme 53. Palladium-Catalyzed Enantioselective C−H Alkylation



screened, bulkier menthoxycarbonyl group protected ligand **L40** was found to be the optimal ligand and afforded the desired products **261** in excellent yields and enantioselectivities.

The proficiency of chiral Pd(II)-MPAA complex to induce enantioselective C−H bond cleavage was further investigated by employing it for the desymmetric C−H functionalization of weakly coordinating functional group bearing substrates. In 2010, Yu and co-workers reported enantioselective desymmetric C−H olefination of sodium α,α-diphenylacetates **262** with styrenes **263** using *N*-Boc-L-isoleucine **L41** as the chiral ligand (Scheme 54).[129] They hypothesized that the σ-chelation of the carbonyl oxygen of the carboxylate salt with chiral Pd(II)-MPAA complex was responsible for the cleavage of proximal C−H bond, resulting in the formation of chiral carbon−Pd intermediate **265**. Subsequently, this intermediate underwent olefination to provide the desired chiral products **264** in good yields and enantioselectivities.

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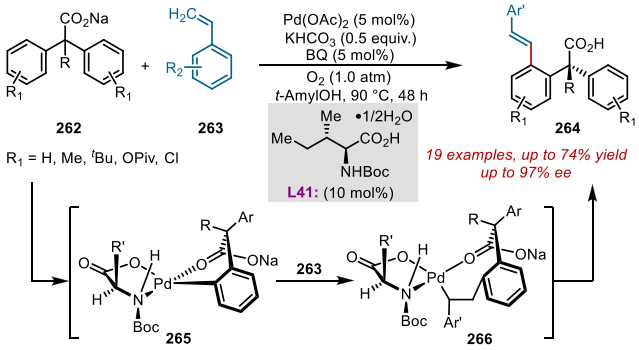
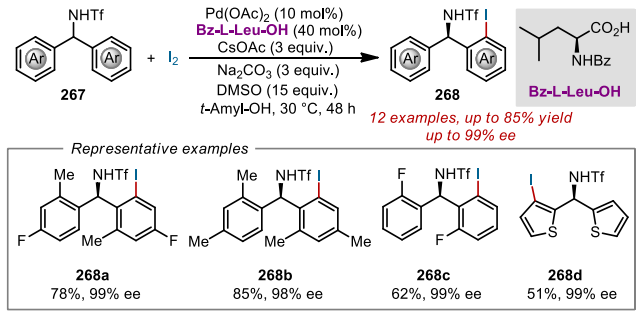
Scheme 54. Palladium(II)-Catalyzed Enantioselective C−H Olefination *α,α*-Diphenylacetic Acids



Enantiopure diarylmethylamines are prevalent in bioactive compounds. In 2013, Yu described a Pd-catalyzed enantioselective C−H iodination reaction for the preparation of enantioenriched chiral diarylmethylamines **268** using monoprotected amino acid as a chiral ligand (Scheme 55).[130] In the

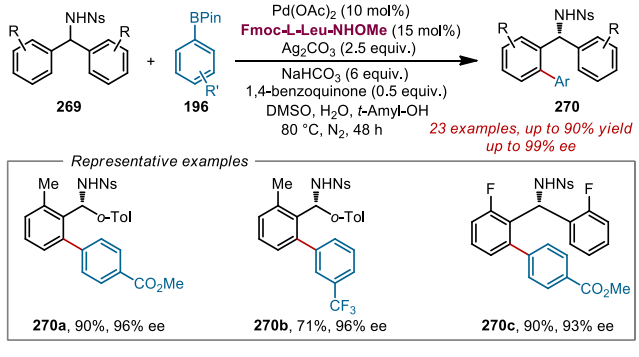
Scheme 55. Palladium-Catalyzed Enantioselective C−H Iodination



presence of I_2 as the sole oxidant, along with Bz-Leu-OH as the optimal ligand, the combination of CsOAc and Na_2CO_3 as base and DMSO as the additive, a variety of desired products were obtained in 51−85% yield and up to 99% ee.

With their continuing interest in synthesizing enantiopure diarylmethylamines, in 2015 Yu described a Pd-catalyzed enantioselective C−H arylation of nosyl-protected prochiral diarylmethylamines **269** with arylboronic acid pinacol esters **196** using monoprotected amino acid as chiral ligand (Scheme 56).[131] After several chiral MPAA ligands were evaluated, it

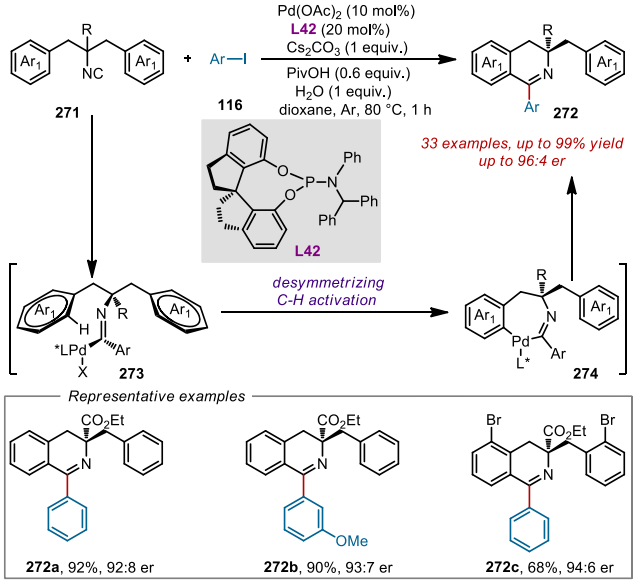
Scheme 56. Palladium-Catalyzed Enantioselective C−H Arylation



was found that by converting the acid moiety of the ligand to an *N*-methoxyamide group both reactivity and enantioselectivity was improved significantly. In the presence of 10 mol % of Pd-catalyst, along with 15 mol % Fmoc-Leu-NHOMe as the chiral ligand, a combination of Ag_2CO_3 and 1,4-benzoquinone as the oxidant and $NaHCO_3$ as the base, a variety of desired enantioenriched diarylmethylamines **270** were obtained in good to moderate yields with excellent enantioselectivities.

In 2017, Zhu and You reported a palladium-catalyzed enantioselective desymmetric C(sp^2)−H imidoylation reaction of dibenzyl isocyanides **271** (Scheme 57). After several ligands

Scheme 57. Pd-Catalyzed Enantioselective Synthesis of 3,4-Dihydroisoquinolines via Desymmetrization



were evaluated, SPINOL-derived phosphoramidite ligand **L42** was proven as the optimal chiral ligand and afforded the desired 3,4-dihydroisoquinolines **272** containing a chiral quaternary carbon center in good to excellent yields and up to 96:4 er. The reaction proceeded with the formation of an imidoyl palladium-(II) intermediate **273**, which is actually a stereodetermining step.[132]

P-Stereogenic phosphorus compounds are an important structural motif in enantioselective catalysis and medicinal chemistry.[133,134] In 2015, Han and co-workers reported a Pd(II)-catalyzed enantioselective desymmetric C−H arylation for the synthesis of P-stereogenic phosphinamides (Scheme 58).[135] In the presence of 10 mol % of $Pd(OAc)_2$ as the catalyst, along with 20 mol % of Boc-protected amino acid **L43** as the chiral ligand, Ag_2CO_3 as the oxidant, Li_2CO_3 as the base, and benzoquinone (BQ) as the additive, the reaction of prochiral diarylphosphinamides **275** with aryl boronic esters **196** afforded the desired P-stereogenic products **276** in 48−74% yields and up to 98% *ee*.

The synthesis of enantiopure arylboron compounds are of significant interest in drug discovery, synthetic organic chemistry, and catalysis.[136] In 2017, Hartwig and co-workers reported the Ir-catalyzed enantioselective C−H borylation through a silyl-directed desymmetrization process (Scheme 59).[137] The combination of $[Ir(cod)OMe]_2$ and chiral quinolyl oxazoline-typeligand **L44** was proven as an efficient catalytic system for providing the desired borylated products **379** in

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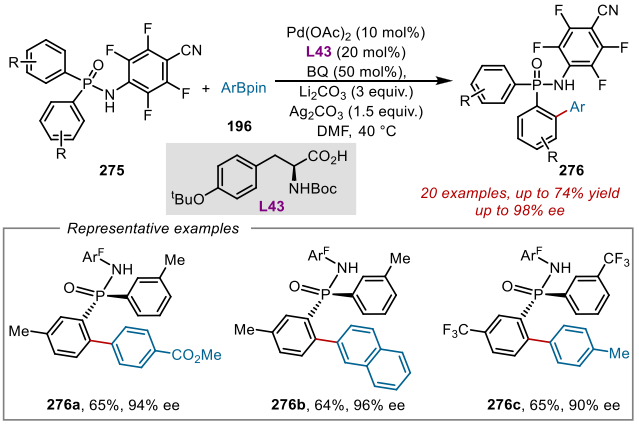
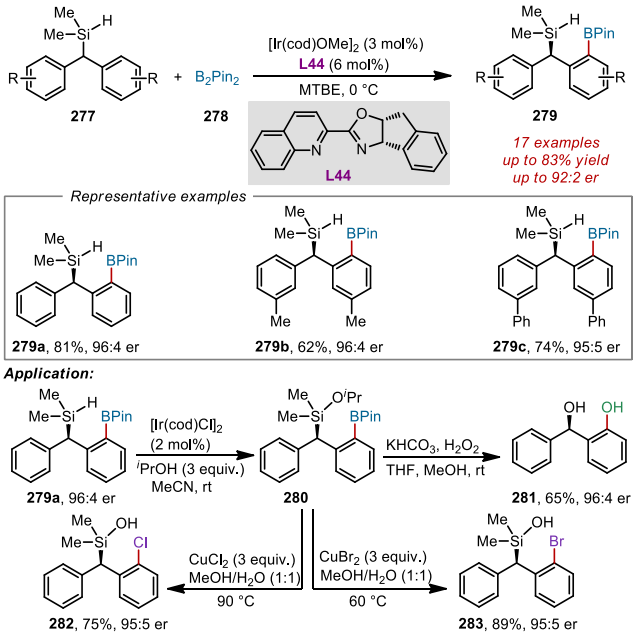
Scheme 58. Palladium(II)-Catalyzed Enantioselective C−H Arylation of Diarylphosphinamides



Scheme 59. Iridium-Catalyzed Enantioselective C−H Borylation and Its Applications

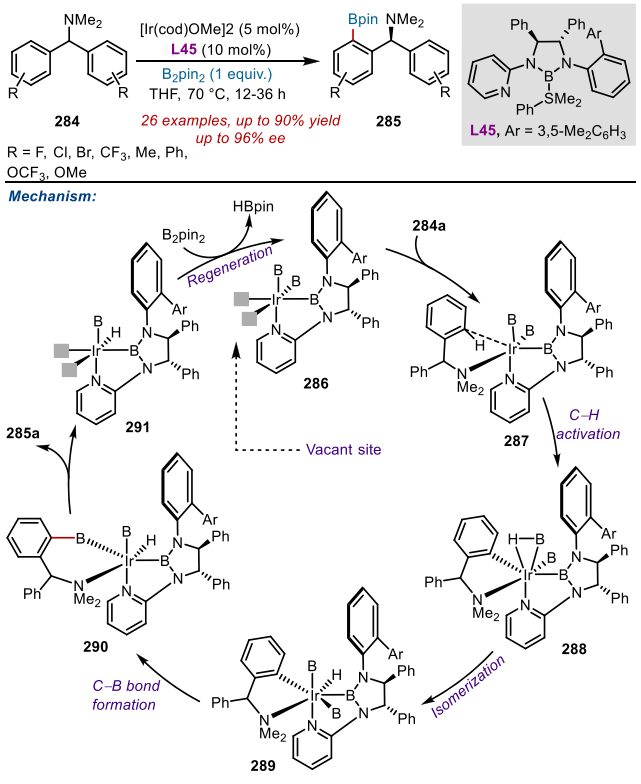


55−83% yields and up to 98:2 er. Further, they demonstrated a variety of transformations of C−B bonds and C−Si bonds in compound **279a** without any significant reduction in enantioselectivity.

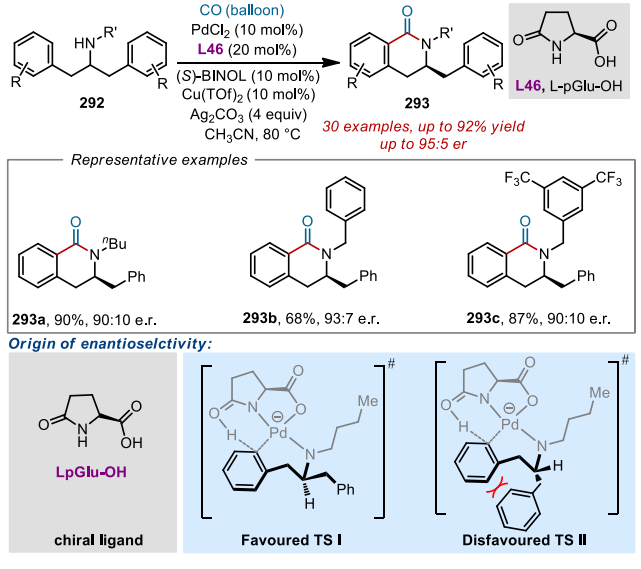
In 2019, Xu described a chiral bidentate boryl ligand enabled Ir-catalyzed enantioselective C−H borylation of prochiral diarylmethylamines **284** through a free amine directed desymmetrization process (Scheme 60).[138] In the presence of 5 mol % of chiral ligand L45 derived Ir-catalyst, a variety of desired borylated products 285 were obtained in 60−90% yields and up to 96% ee. Mechanistically, this reaction occurs with the involvement of four elementary steps such as (a) C−H oxidative addition, (b) isomerization, (c) C−B bond formation, (d) regeneration of the active catalytic species. The proposed catalytic cycle is as shown in Scheme 60.

In 2019, Xia and co-workers reported an elegant approach for the synthesis of enantioenriched isoquinolinones via Pd-catalyzed enantioselective desymmetric C−H aminocarbonylation (Scheme 61).[139] In the presence of 10 mol % of $PdCl_2$,

Scheme 60. Iridium-Catalyzed Enantioselective C−H Borylation of Diarylmethylamines



Scheme 61. Palladium-Catalyzed Enantioselective C−H Aminocarbonylation



along with 20 mol % of L-pyroglutamic acid **L46** as the chiral ligand, a combination of 10 mol % of (*S*)-BINOL and 10 mol % of $Cu(OTf)_2$ as additive, and Ag_2CO_3 as the oxidant, a variety of desired chiral isoquinolinones **293** were obtained in 28−92% yield and up to 95:5 er. The authors hypothesized that the OH group of the additive (S)-BINOL can coordinate with palladium and thereby preventing the deactivation of active catalyst to Pd black. Mechanistically, enantioselectivity is originated in the C−H activation step via favored transition state **TS I**.

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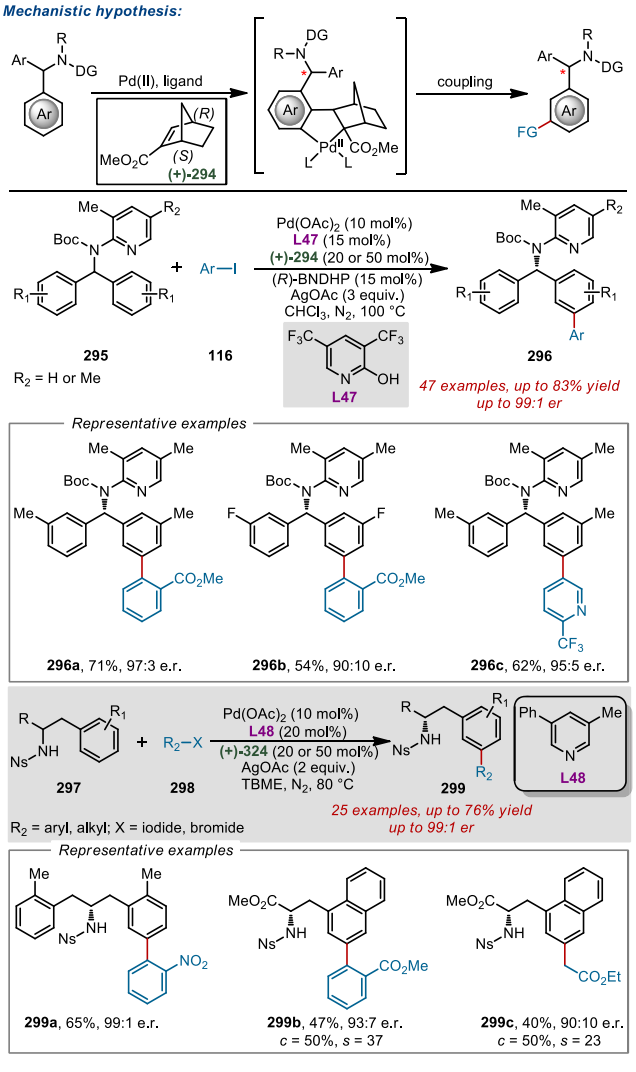
Till now we have discussed the enantioselective desymmetric proximal C−H functionalization reactions, whereas achieving enantioselectivity in remote C−H functionalization process is a formidable challenge. In 2018, Yu and co-workers developed an elegant strategy for Pd(II)-catalyzed enantioselective *meta*-C−H arylation of diarylmethylamines **295** by employing a strong coordinating pyridine-type directing group and chiral norbornene (+)-**294** as the transient mediator (Scheme 62).[140] Mechanistically, the insertion of enantioen-

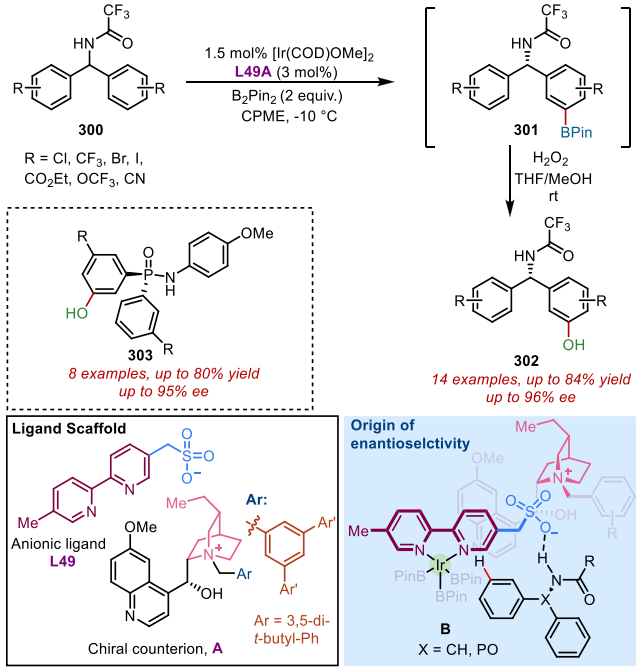
Scheme 62. Pd(II)/Chiral Norbornene-Catalyzed Enantioselective *meta*-C−H Arylation



riched norbornene (+)-**294** to the *ortho* palladate intermediate is believed to be chirality inducing step. Several control experiments revealed that the addition of catalytic amount of (R)-BNDHP (1,1′-binaphthyl-2,2′-diyl hydrogen phosphate) as an additive along with chiral norbornene afforded the desired products **296** in good to moderate yields with excellent enantioselectivities. In addition, they also demonstrated the enantioselective *meta*-C−H arylation and alkylation of nosyl (Ns)-protected homobenzylamines **297** via either desymmetrization or kinetic resolution using similar Pd(II)/chiral norbornene cooperative catalysis strategy.

Very recently, Phipps and co-workers introduced an attractive ion-pair interaction strategy to achieve long-range asymmetric induction (Scheme 63).[141] They described a chiral cation enabled iridium-catalyzed enantioselective *meta*-C−H

Scheme 63. Noncovalent Interaction Guided Enantioselective *meta*-C−H Borylation



borylation of prochiral geminal diaryl motif through desymmetrization. The authors hypothesized that the regioselectivity was governed by the specially designed anionic sulfonate tether containing bipyridine ligand, which can act as a hydrogen bond acceptor for benzhydrylamides **300** and diarylphosphinamides, whereas the ion-pair interaction involving a chiral cation and ligand **L49** was responsible to induce enantioselectivity. After several chiral cations were evaluated, *N*-benzyl substituted dihydroquinine (DHQ) derived chiral cation **A** was found to be optimal for affording desired ***C***-chiraland ***P***-chiral compounds (**302** and **303** respectively) in good to moderate yields and excellent enantioselectivities. It is important to mention over here that they converted the resulting borylated products to the corresponding alcohols by treating with H_2O_2 for the ease of purification.

4.2. Enantioselective Intramolecular C−H Functionalization Reactions. *4.2.1. Desymmetric C−H Activation/C−O Cyclization.* In 2013, Wang, Yu and co-workers disclosed a Pd(II)-catalyzed enantioselective C−H activation/C−O bond formation sequence via desymmetrization of *α,α*-diarylacetic acids **304** employing monoprotected amino acid Boc-L-Ile-OH as the chiral ligand (Scheme 64).[142] A variety of functional groups such as methyl, chloro, thiomethyl, and methoxy were well tolerated under the reaction conditions, affording the desired *α,α*-disubstituted benzofuran-2-ones **305** in good to moderate yields and high enantioselectivities. Notably, this transformation represents the first example of Pd(II)/Pd(IV) redox catalytic cycle enabled enantioselective C−H functionalization.

4.2.2. C/Si−X Bond Directed Desymmtric C−H functionalization (X = halogen, OTf, hydrogen). In 2009, Cramer and co-workers disclosed a Pd(0)-catalyzed intramolecular arylation of vinyl triflates **99** for the enantioselective construction of

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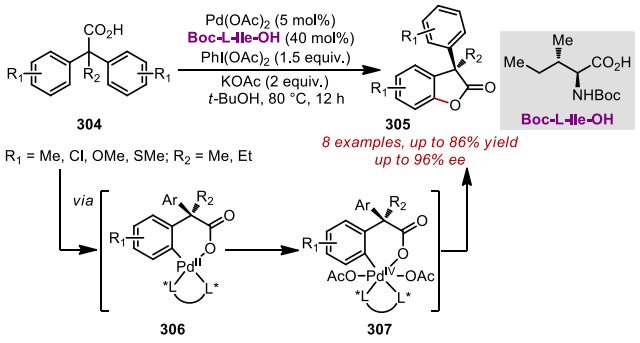
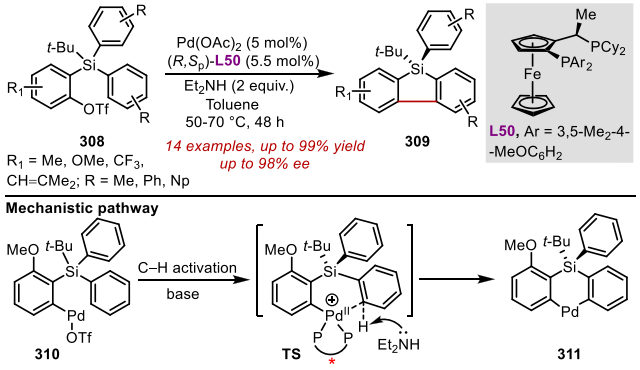
Scheme 64. Pd(II)-Catalyzed Desymmetrizing C−H Activation/C−O Cyclization



indanes **100** with quaternary stereogenic centers exploiting taddol-based phosphoramidite ligand **L1** (*vide supra*, Scheme 20).[53] Dibenzosiloles, having an extended π-conjugated systems, are an important structural motif in materials science such as light-emitting diodes, thin-film transistors, solar cells, and detectors for explosives.[143] As a consequence, the synthesis of enantioenriched chiral dibenzosiloles is of immense interest. In 2012, Shintani and Hayashi reported a Pd-catalyzed enantioselective C−H arylation of prochiral 2-(arylsilyl)aryl triflates **308** for the contruction of chiral dibenzosiloles with a Si stereogenic center (Scheme 65).[144] After various electron-

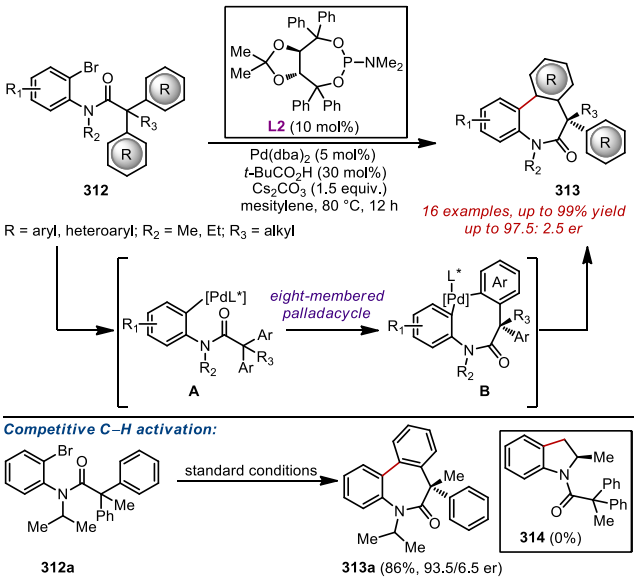
Scheme 65. Pd-Catalyzed Enantioselective C−H Arylation of Prochiral 2-(Arylsilyl)aryl Triflates



rich bisphosphine ligands were evaluated, Josiphos-type ligand **L50** was found as the optimal ligand and afforded the desired products **309** in excellent yields and enantioselectivities. Mechanistically, this transformation is initiated by the oxidative addition of C−OTf bond to Pd(0) to form arylpalladium species **310**. Subsequently, base promoted enantioselective intramolecular C−H cleavage leads to the formation of intermediate **311**, which then undergoes reductive elimination to provide the desired chiral product.

In 2013, Saget and Cramer described a Pd(0)-catalyzed intramolecular enantioselective C−H arylation of *o*-bromoaniline-derived α,α-diaryl-substituted amides **312** for the synthesis of chiral dibenzazepinones **313**, an important class of nitrogen-containing heterocyclic motif with interesting biological properties (Scheme 66).[56] This reaction represents a rare example of construction of seven-membered ring through the formation of an eight-membered palladacycle intermediate **B**. The taddol-based phosphoramidite ligand **L2** was crucial for

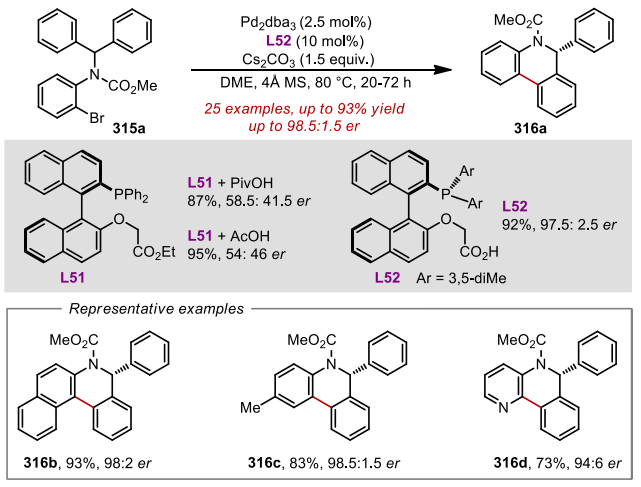
Scheme 66. Palladium-Catalyzed Enantioselective Intramolecular C−H Arylation of Dibenzazepinones



controlling the enantioselectivity of the reaction. A variety of functional groups were well tolerated under the optimized reaction conditions affording the desired products in excellent yields and enantioselectivities. It is worth mentioning here that this catalytic system provided complete selectivity for C(sp^2)−H activation over competing C−H activations, which could give undesired five- or six-membered rings.

Recently, Baudoin and co-workers reported a new class of binaphthyl scaffold based chiral bifunctional ligands and utilized them in intramolecular enantioselective desymmetrizing C(sp2)-H arylation of aryl bromide **315** leading to 5,6-dihydrophenanthridines (Scheme 67).[145] The chiral bifunctional ligand comprising both phosphine and carboxylate moiety provided a range of substituted 5,6-dihydrophenanthridines **316** in excellent yields and enantioselectivities under the optimized conditions. The importance of the bifunctional ligand **L52** was realized when monofunctional ligand **L51**,

Scheme 67. Bifunctional Phosphine-Carboxylate Ligand Assisted Pd-Catalyzed Enantioselective Desymmetrizing C−H Arylation



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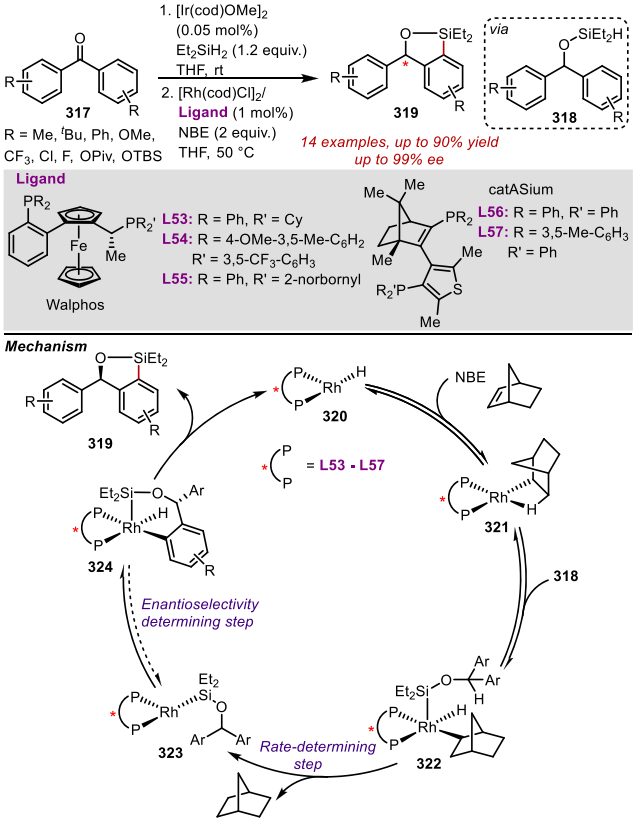
lacking a carboxylic acid moiety, was used in the reaction with additional carboxylic acids, delivering very low enantioselectivities.

Arylsilanes are valuable synthetic intermediates in medicinal chemistry, agrochemicals, and material science. In 2015, Hartwig and co-workers reported a Rh-catalyzed enantioselective desymmetric C−H silylation of (hydrido)silyl ethers **318**, which are generated in situ by the Ir-catalyzed hydrosilylation of benzophenone derivatives **317** (Scheme 68).[146] In the presence of 1.0 mol % of chiral Walphos (**L53**−**L55**) and catASium (**L56**, **L57**) classes of ligands derived Rh-catalyst, along with 1.2 equiv of norbornene as an H_2 acceptor, a variety of benzoxasiloles **319** were obtained in 54−90% yield and up to 99% *ee*. The authors proposed that the addition of (hydrido)silyl ethers **318** to **321** generates intermediate **322**, which then undergoes reductive elimination to form intermediate **323** and norbornane. Subsequently, the oxidative addition of arene C−H bond to the intermediate **323** leads to the formation of intermediate **324**. Finally, reductive elimination occurs to provide the desired product **319** and rhodium hydride species **320**.

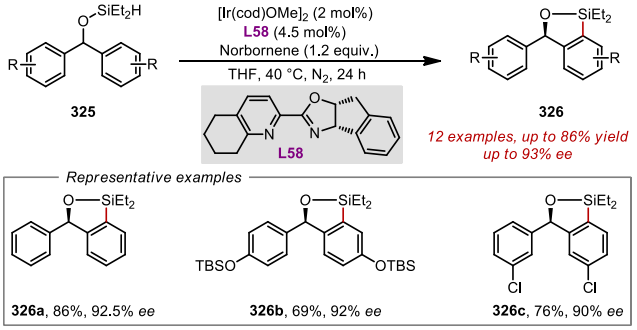
In 2017, the same group reported the Ir-catalyzed enantioselective C−H silylation of (hydrido)silyl ethers **325** through chiral pyridinyloxazoline-type ligand promoted desymmetrization (Scheme 69).[147] After various chiral dinitrogen ligands were screened, the more electron donating **L58** was proved as the optimal ligand and afforded the desired products **326** in good yields and enantioselectivities.

Shortly after, Nozaki and co-workers described a Pd-catalyzed enantioselective synthesis of 5,10-dihydrophenazasilines with a Si-stereogenic center through 1,5-Pd migration induced desymmetrization (Scheme 70).[148] In the presence of 5 mol % of $Pd(OAc)_2$ as the catalyst, along with 5.5 mol % of 4,4′-bis(trimethylsilyl) (*R*)-Binap as the chiral ligand, and 2 equiv of triethylamine as the base, a variety of chiral 5,10-dihydrophenazasilines **328** were obtained in 61−89% yields and up to 98% *ee*. Mechanistically, this reaction is initiated by the oxidative addition of C−OTf bond to Pd(0) to arylpalladium(II) species **329**. Subsequent enantioselective 1,5-palladium migration leads to the formation of intermediate **330**. A kinetic isotope effect study (K_H/K_D = 1.31) suggested that this 1,5-palladium migration step is not involving in the

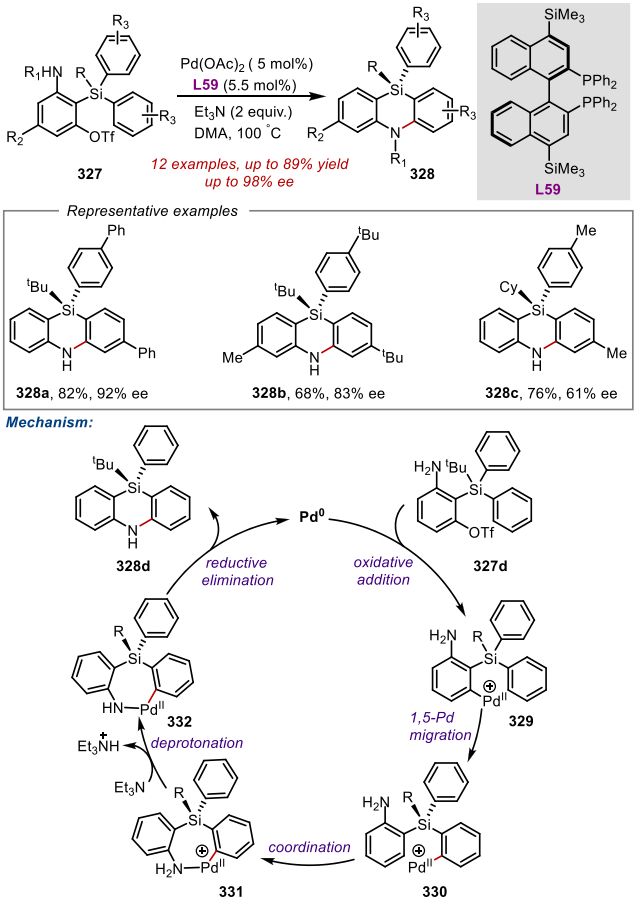
Scheme 68. Rhodium-Catalyzed Enantioselective C−H Silylation



Scheme 69. Iridium-Catalyzed Enantioselective C−H Silylation



Scheme 70. Palladium-Catalyzed Enantioselective Synthesis of 5,10-Dihydrophenazasilines



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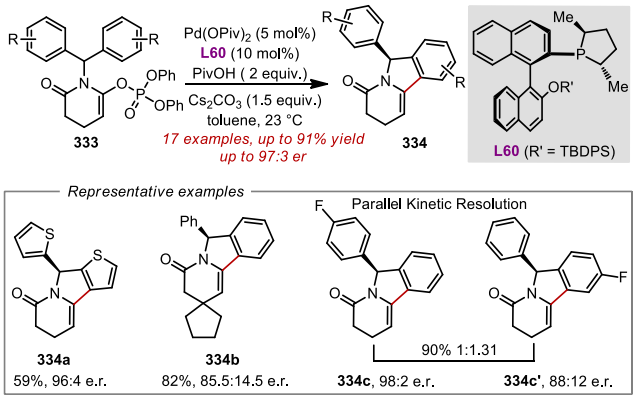
rate-determining step. Intramolecular coordination of the amino group to the electrophilic Pd-center followed by deprotonation provides intermediate **332**. Finally, reductive elimination occurs to afford the desired product **328d** along with regeneration of Pd(0).

In 2017, Cramer and co-workers reported a Pd(0)-catalyzed enantioselective C−H alkenylation of ketene aminal phosphates **333** to provide chiral isoindolines **334** via either desymmetrization or kinetic resolution (Scheme 71).[149] After

Scheme 71. Palladium-Catalyzed Enantioselective Synthesis of Isoindolines



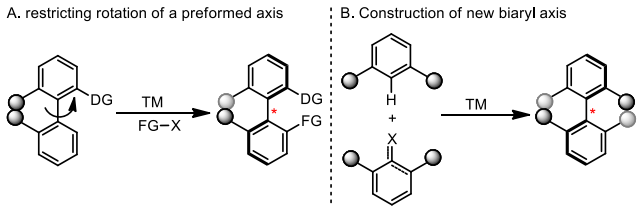
several chiral ligands were evaluated, the monodentate electron-rich phosphine-based ligand **L60** containing both the point chirality and axial chirality was found to be optimal for affording the desired products **334** in good yields and excellent enantioselectivities. Notably, the ligand **L60** not only induce chirality but also accelerated the oxidative addition of alkenyl phosphates to Pd(0) species. Mechanistically, C−H activation step through the CMD pathway is believed to be the enantioselectivity generating step.

5. ATROPO-ENANTIOSELECTIVE C−H FUNCTIONALIZATION

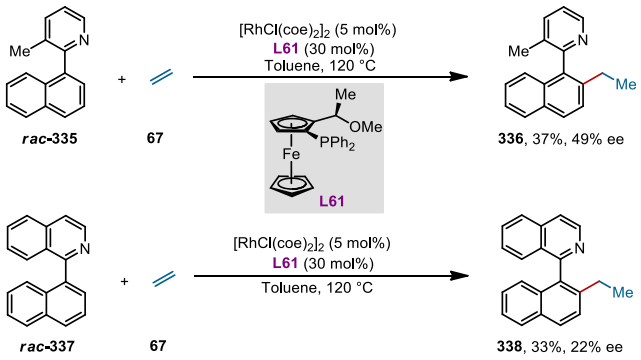
Axially chiral biaryls are prevalent in natural products, drug molecules, and pharmaceuticals as the important structural motifs.[150] Moreover, they are widely used in asymmetric catalysis as privileged ligands.[63a,151a] As a consequence, the enantioselective synthesis of axially chiral biaryls skeletons through transition metal catalyzed C−H functionalization has drawn immense attention in recent times.[152] The axial chirality of biaryls is generated by restricting rotation of the aryl−aryl bond, which results from the nonplanar arrangement of four *ortho*-substituents in proximity to the biaryl axis. Hence, the key features of axial chirality in biaryls are (a) a rotationally stable axis, and (b) the presence of different substituents on both sides of the axis.[153] In general, two main strategies have been developed to accomplish atroposelective synthesis of axially chiral biaryls. In the first strategy, axially chiral biaryls were synthesized by restricting the free rotation of a preformed axis via (dynamic) kinetic resolution or desymmetrization processes (Scheme 72A). The second strategy is the construction of a new biaryl axis via C−H activation/asymmetric coupling (Scheme 72B).

5.1. Restricting Rotation of a Preformed Biaryl Axis via (Dynamic) Kinetic Resolution or Desymmetrization. *5.1.1. Chiral Ligand or Chiral Catalyst Controlled Atropo-Enantioselective C−H Functionalization.* In 2000, the Murai group first reported a Rh(I)-catalyzed atropo-enantioselective C(sp^2)−H alkylation of 2-(1-naphthyl)pyridine or 1-(1-naphthyl)isoquinoline derivatives via dynamic kinetic resolution (Scheme 73).[154] In the presence of 5 mol % of

Scheme 72. Transition-Metal-Catalyzed Atroposelective C−H Functionalization



Scheme 73. Rh(I)-Catalyzed Atropo-Enantioselective C−H Alkylation Using a Chiral Ferrocenyl Phosphine Ligand



$[Rh(coe)_2Cl]_2$ as the catalyst and 30 mol % of (*R*,*S*)-PPF-OMe **L61** as the chiral ligand, the reaction of *rac*-**335** with ethylene afforded the desired axially chiral biaryl **336** in 37% yield with 49% ee, whereas the quinoline derivative *rac*-**337** proved to be detrimental by providing the product **338** in lower yield and enantioselectivity (33% yield, 22% ee) under similar reaction conditions.

In 2014, You and co-workers demonstrated the usage of preformed chiral cyclopentadienyl complex to achieve high enantioselectivity for this class of reaction (Scheme 74).[26] Isoquinoline-based biaryls **22** were alkenylated with a wide range of terminal alkenes **23** by employing BINOL-derived chiral [$Cp^xRh(III)$] catalyst **Rh-8** and a combination of $Cu(OAc)_2$ and Ag_2CO_3 as oxidants. The reaction proceeds through the formation of a five-membered cyclometalated intermediate. The atropisomeric products **24** were obtained in 24−99% yields and up to 86% ee. Two years later, the same group developed a novel class of SPINOL-derived chiral Rh-complex **Rh-15**, which was found to be superior for providing excellent enantio-selectivites (up to 96%) in a similar type of asymmetric oxidative coupling reaction of biaryls **22** with alkenes **23**.[155]

Since the pioneering discovery of Yu and co-workers, chiral mono-*N*-protected amino acids (MPAAs) have been recognized as privileged ligands for various types of enantioselective C−H functionalization reactions.[14,129,156] In 2014, You and co-workers first reported the Pd/MPAA-catalyzed atroposelective C−H iodination of *rac*-**339** via kinetic resolution (Scheme 75).[102] In this reaction, *N*-iodosuccinimide (NIS) was used as a iodinating reagent, and *N*-monoprotected phenylalanine **L62**

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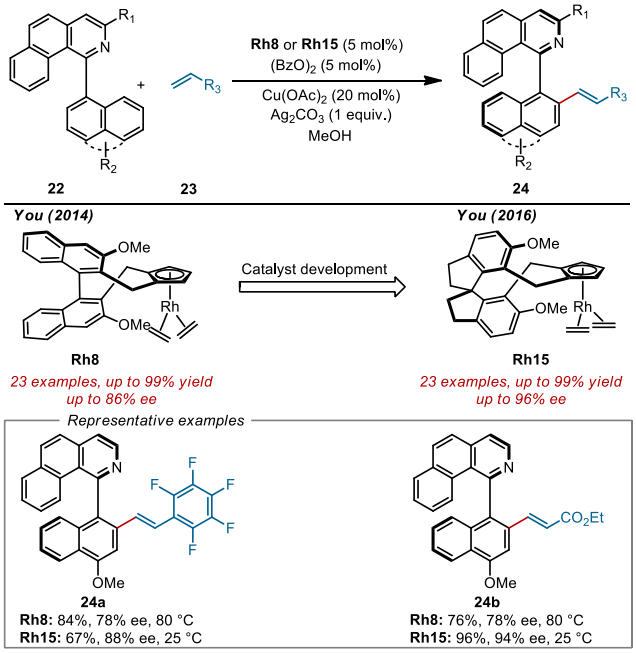
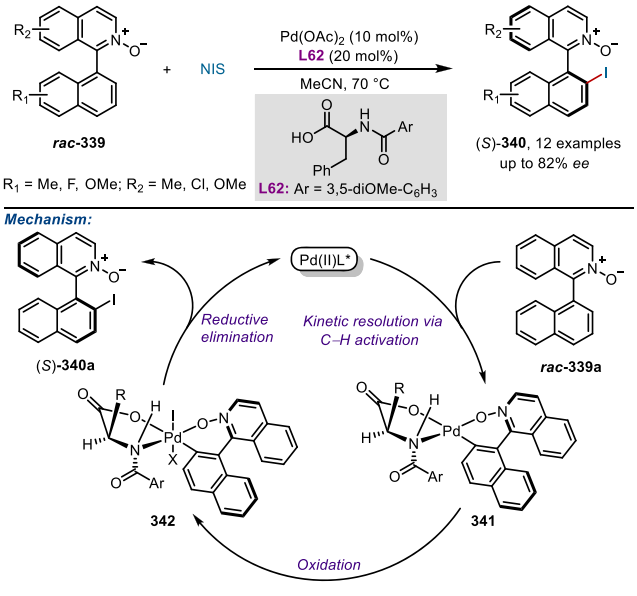
Scheme 74. Chiral Rhodium-Catalyst Enabled Atropo-Enantioselective C−H Alkenylation of Biaryls



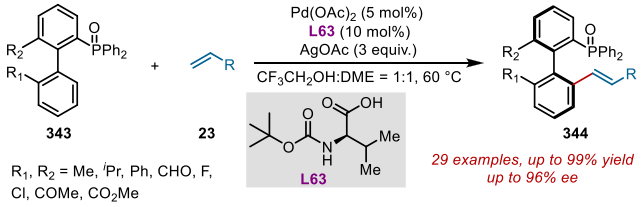
Scheme 75. Pd-Catalyzed Atroposelective C−H Iodination



was used as the optimal chiral ligand to achieve desired axially chiral biaryls (*S*)-**340** in good yields and enantioselectivities. The authors hypothesized that in the presence of Pd/MPAA catalytic system, enantioselective C−H bond cleavage of *rac*-**339a** via the CMD pathway led to the formation of intermediate **341**, which was then oxidized by NIS to generate a reactive intermediate **342**. Finally, this intermediate underwent reductive elimination to provide the desired product (*S*)-**340a**.

In 2017, Yang and co-workers described a Pd-catalyzed atroposelective C−H olefination for the synthesis of axially chiral biaryls by employing chiral MPAA ligand and $P(O)Ph_2$ as the directing group (Scheme 76).[157] In the presence of 5 mol % of $Pd(OAc)_2$ as the catalyst, along with 10 mol % of

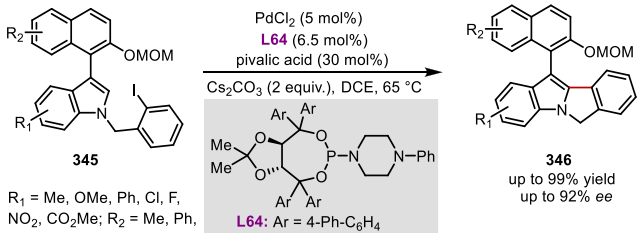
Scheme 76. Pd-Catalyzed Atroposelective C−H Olefination Using Chiral MPAA Ligand



Boc-L-Val-OH (**L63**) as the chiral ligand, a wide range of racemic biaryl phosphines **343** underwent olefination via a dynamic kinetic resolution process to provide the desired chiral biaryl phosphine−olefin compounds **344** in excellent yields (up to 99%) and enantioselectivities (up to 96% ee).

Indoles are an important structural motif widely found in natural products and bioactive molecules. In 2017, Gu and co-workers reported a Pd-catalyzed intramolecular enantioselective C−H arylation for the synthesis of indole-based biaryl atropisomers (Scheme 77).[158] After several chiral ligands were

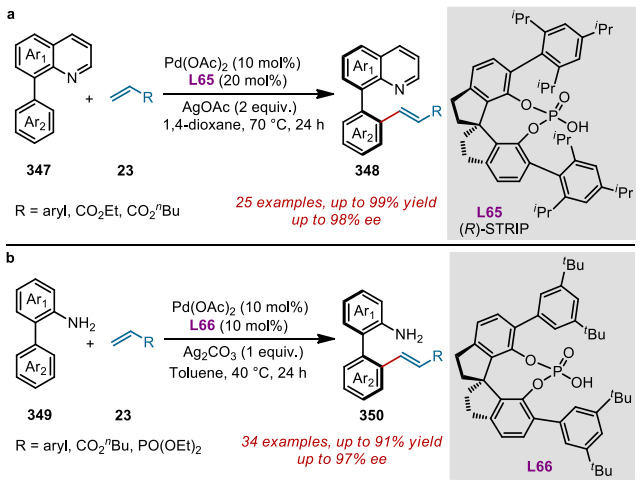
Scheme 77. Palladium-Catalyzed Intramolecular Atroposelective C−H Cyclization



evaluated, TADDOL-based phosphoramidite ligand **L64** was proved as the optimal ligand and provided the desired products **346** in excellent yields and up to 92% *ee*.

In 2019, Shi and co-workers reported a Pd(II)-catalyzed atroposelective C−H olefination of quinoline-derived biaryls **347** by using chiral spiro phosphoric acids (SPAs) ligands (Scheme 78a).[159] In this reaction (*R*)-STRIP **L65** was proven as the optimal chiral ligand and exhibited superior stereo-

Scheme 78. Pd(II)-Catalyzed Atroposelective C−H Olefination Using Chiral Spiro Phosphoric Acid Ligand



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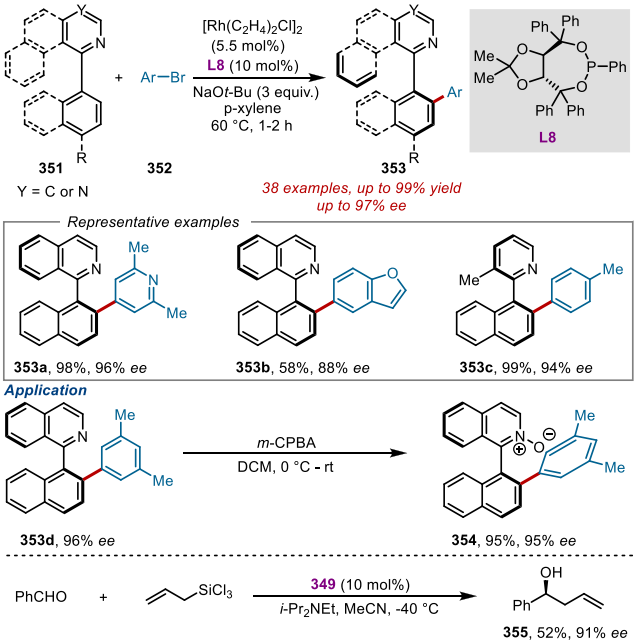
control than BINOL-derived ligand, which may be due to its better steric interaction with the substrates. A wide variety substrates were compatible under the reaction conditions to afford the desired axially chiral products **348** in excellent yields and enantioselectivities. Mechanistically, a C−H activation step through the CMD pathway was identified as the enantioselectivity generating step. Shortly after, the same group reported a free-NH_2 directed Pd-catalyzed enantioselective C−H olefination for the synthesis of axially chiral biaryl-2-amines (Scheme 78b).[160] In the presence of 10 mol % of $Pd(OAc)_2$ as the catalyst, along with 10 mol % of chiral spiro phosphoric acid **L66** as the chiral ligand, and Ag_2CO_3 as the oxidant, a variety of desired atroposelective products **350** were obtained in excellent yields and enantioselectivities (up to 97% ee).

In 2019, You and co-workers described a Rh(I)-catalyzed atroposelective C−H arylation of heterobiaryls **351** (Scheme 79).[161] In the presence of 5.5 mol % of $[Rh(C_2H_4)_2Cl]_2$ as the

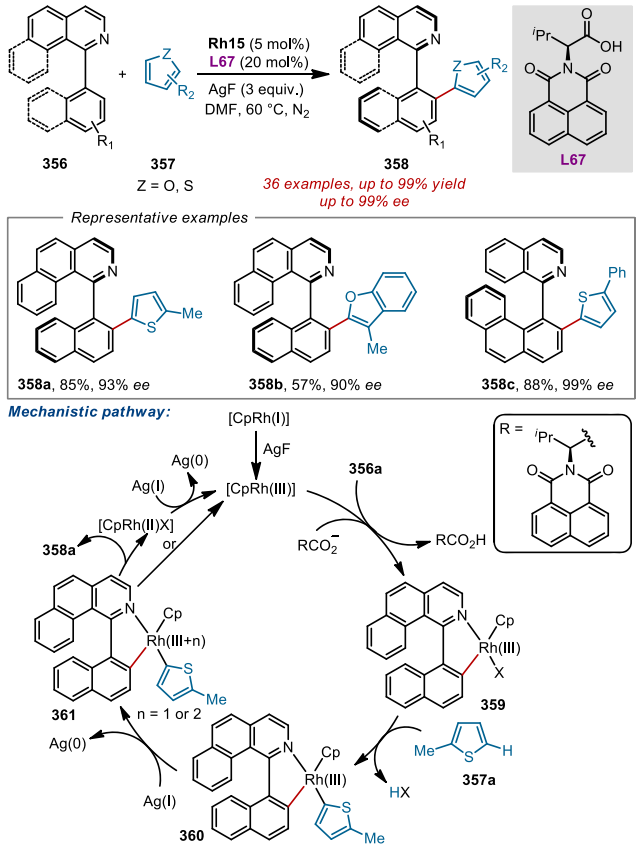
Scheme 79. Rh(I)-Catalyzed Atroposelective Synthesis of Axially Chiral Heterobiaryls and Its Application



catalyst, along with 10 mol % of TADDOL-derived monodentate phosphonite **L8** as the chiral ligand, and hetero(aryl) bromides **352** as the coupling partner, a wide range of axially chiral heterobiaryls **353** were obtained in good to excellent yields and up to 97% *ee*. Furthermore, they also demonstrated the potential utility of this transformation by synthesizing a chiral *N*-oxide **354**, which could act as an efficient catalyst in asymmetric allylation reaction of benzaldehyde with allyltrichlorosilane.

In the following year, the same group reported a Rh(III)-catalyzed atropoenantioselective oxidative C−H/C−H cross-coupling reaction between 1-aryl isoquinoline derivatives **356** and electron-rich heteroarenes **357** (Scheme 80).[162] In the presence of 5 mol % of chiral [SCpRh] complex, along with 20 mol % of chiral carboxylic acid as the additive, and 3 equiv of AgF as the oxidants, a wide variety of desired axially chiral heterobiaryls **358** were obtained in good to excellent yields and up to 99% *ee*. Kinetic isotope effect studies suggested that both

Scheme 80. Rh(III)-Catalyzed Atroposelective Synthesis of Axially Chiral Heterobiaryls via Oxidative C−H/C−H Cross-Coupling



C−H bond cleavages are not likely rate-determining step. Mechanistically, the initial rhodacycle intermediate **359** was generated through coordination with **356a** and followed by carboxylate-assisted enantioselective C−H bond cleavage in a concerted-metalation-deprotonation (CMD) pathway. Then, this intermediate reacts with **357a** via electrophilic C−H substitution (S_EAr) to form intermediate **360**. Subsequently, the rhodacycle intermediate **360** undergoes oxidation by the Ag(I) salt to generate high-valent Rh-species **361**. Finally, reductive elimination occurs to afford the desired product **358a** and either a CpRh(III) or CpRh(II) complex.

In 2020, the Shi group also described a Pd(II)-catalyzed enantioselective C−H alkenylation and alkynylation for the synthesis of axially chiral styrenes by employing a pyridine-type directing group and L-pyroglutamic acid **L46** as the chiral ligand (Scheme 81).[163] The reaction demonstrated good substrate scope, affording a range of axially chiral molecules (e.g., **363**, **364**) in good yields and excellent enantioselectivities.

5.1.2. Transient Chiral Auxiliary. Over the last few decades, a variety of covalently attached directing groups have been utilized for site selective C−H functionalization.[5b] Recently, a transient directing group strategy has emerged as a special case to address the selectivity issue in the C−H functionalization process due to its ease of installation and removal.[164] A pioneering work by Yu and co-workers demonstrated the utilization of a transient chiral auxiliary for the creation of point chirality.[165] Inspired by this work, Shi and co-workers reported several examples of transient auxiliary assisted Pd(II)-

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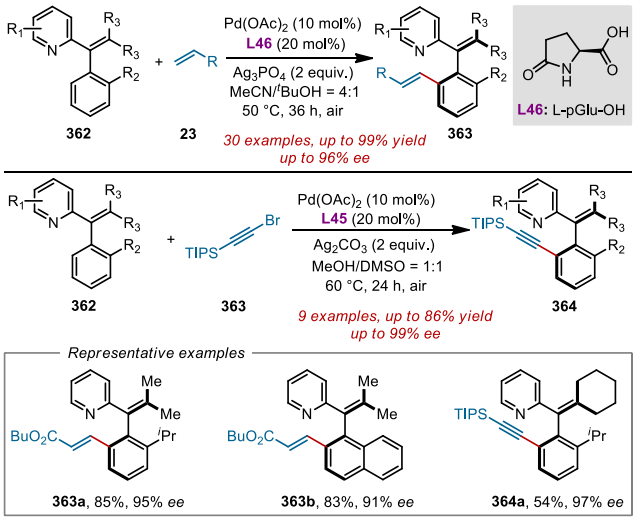
Scheme 81. Pd(II)-Catalyzed Atroposelective C−H Olefination and Alkynylation for the Synthesis of Axially Chiral Molecules

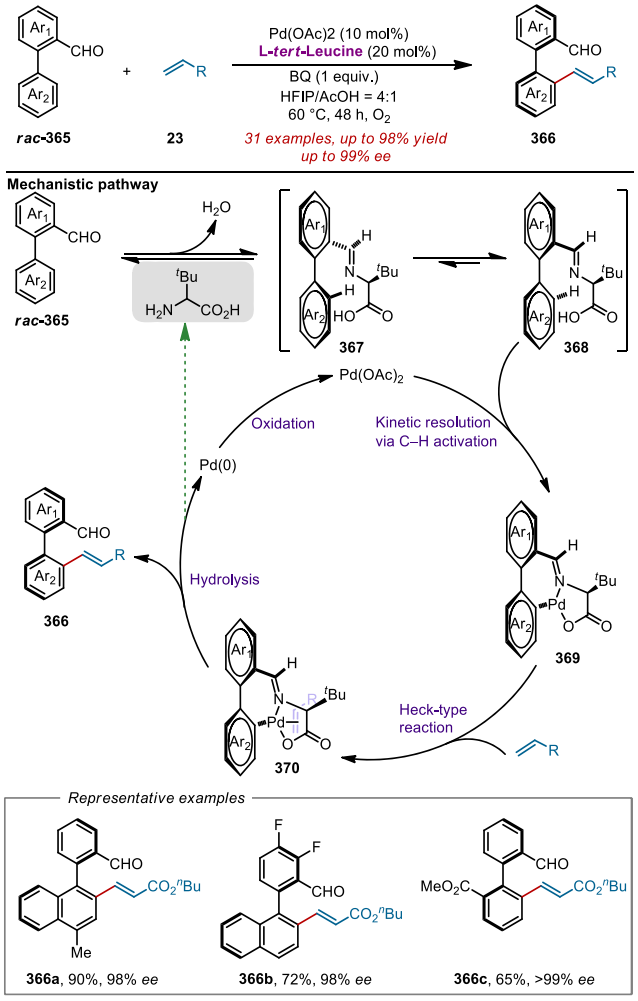


catalyzed atroposelective synthesis of axially chiral biaryls via C−H functionalization. Here, chiral transient auxiliary serves the dual role of a catalytic directing group by virtue of its better σ-donor ability and chiral ligand for asymmetric induction. In 2017, the Shi group first realized the atroposelective C−H olefination of biaryl aldehydes *rac*-**365** by employing commercially available L-*tert*-leucine as the transient chiral auxiliary (Scheme 82).[166] The reaction proceeded via a Pd(II)/Pd(0) catalytic cycle, furnishing the desired olefinated axially chiral biaryls in good yields and excellent enantioselectivities (up to >99% ee). The authors proposed that the reversible reaction of biaryl aldehydes *rac*-**365** with the L-*tert*-leucine led to the formation of imines **367** and **368**. Because of the steric factors, one of the diastereomers **368** underwent C−H activation, affording the axially enantioenriched biaryl palladacycle intermediate **369**. Subsequently, this chiral intermediate underwent a Heck-type reaction with olefin **2** to generate the intermediate **370**. Eventually, in situ hydrolysis occurs to afford desired products **366** with excellent enantioselectivities. The resulting Pd(0) species reoxidizes to the catalytically active Pd(II) by BQ and O_2.

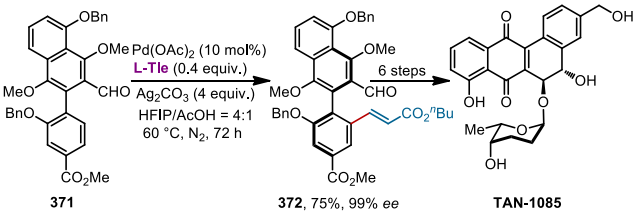
In 2019, the Shi group also demonstrated the synthetic utility of this protocol by the total synthesis of TAN-1085 (Scheme 83).[167] The key step for this total synthesis relies on the atropo-enantioselective construction of chiral biaryl aldehyde **372** using transient chiral auxiliary mediated Pd(II)-catalyzed asymmetric C−H olefination. It is worth mentioning here that owing to the electron-rich properties of **371**, poor yield and low *ee* value were obtained under their previously reported conditions.

In 2019, Xie and co-workers reported a Pd(II)-catalyzed atropoenantioselective C−H olefination of N-arylindoles **373** by employing amino acid as transient chiral auxiliary (Scheme 84). In the presence of 10 mol % of $Pd(OAc)_2$ as the catalyst, along with 20 mol % of either L-valine or L-*tert*-leucine as the chiral ligand, AgTFA/benzoquinone as the oxidant, and 2 equiv of $NaHCO_3$ as the base, a wide range of axially chiral olefinated *N*-arylindoles **375** with the N−C chiral axis were obtained in good to moderate yields and excellent enantioselectivities.[168]

Scheme 82. Pd-Catalyzed Atroposelective C−H Olefination of Biaryl Aldehyde Using L-*tert*-Leucine as Transient Chiral Auxiliary



Scheme 83. Total Synthesis of TAN-1085 Using Atroposelective C−H Olefination as the KeyStep



By adopting a similar strategy, in 2018, the Shi group described a Pd(II)-catalyzed atropo-enantioselective C−H alkynylation of biaryl aldehydes *rac*-**355** (Scheme 85).[169] In the presence of 10 mol % of $Pd(OAc)_2$, along with 30 mol % of L-*tert*-leucine, AgOAc as the oxidant, and KH_2PO_4 as the additive, a variety of axially chiral alkynylated biaryls **376** were obtained in good yields and excellent enantioselectivities. Further, the potential utility of this method was demonstrated by the gram-scale formal syntheses of (+)-isoschizandrin **378** and (+)-steganone **380**.

Very shortly, they extended this approach to the Pd-catalyzed atroselective C−H allylation of diverse range of racemic biaryl aldehydes *rac*-**355** (Scheme 86).[170] By using

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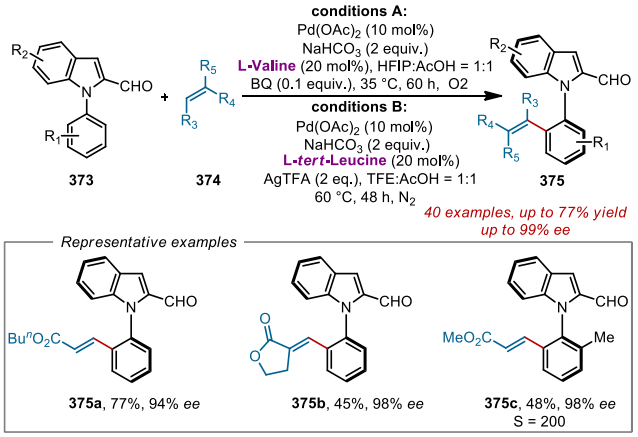
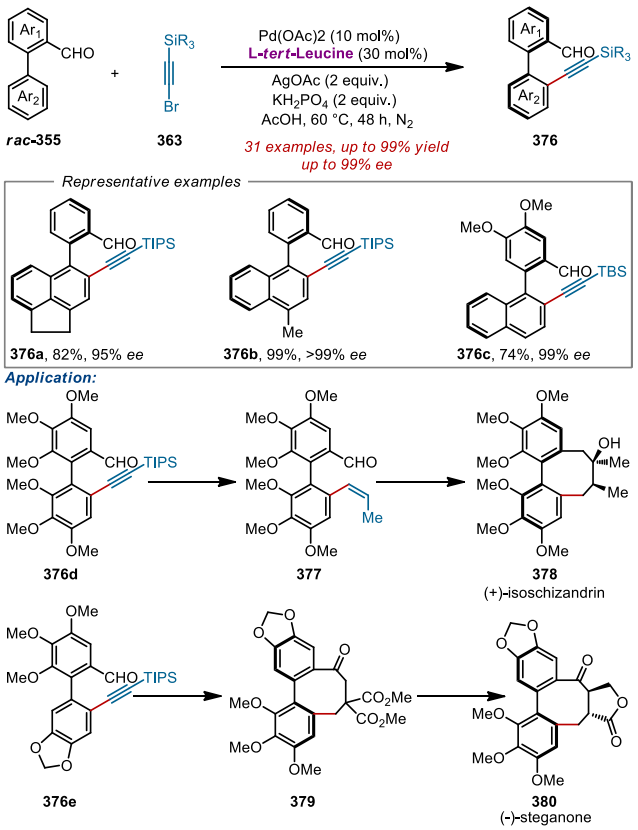
Scheme 84. Pd(II)-Catalyzed Atropoenantioselective C−H Olefination of N-Arylindoles



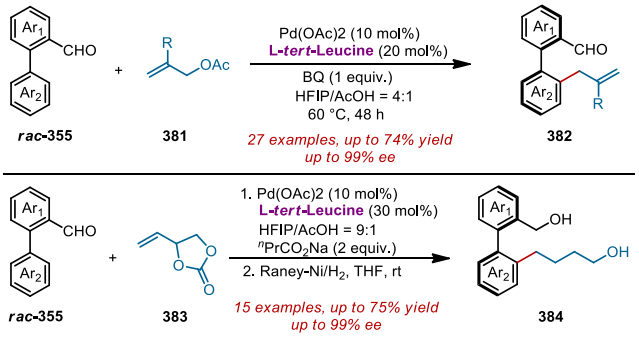
Scheme 85. Pd-Catalyzed Atroposelective C−H Alkynylation



Morita−Baylis−Hillman (MBH) acetates **381**, a variety of allylated axially chiral biaryls **382** were obtained in good yields and excellent enantioselectivities. In addition, 4-vinyl-1,3-dioxolan-2-one **383** was also compatible as a allylic surrogate under the reaction conditions, affording a mixture of *Z*/*E* isomers. The resulting mixture of allylated products was treated with Raney-Ni to provide the reduced axially chiral biaryls **384** in 33−75% yield and up to >99% *ee*.

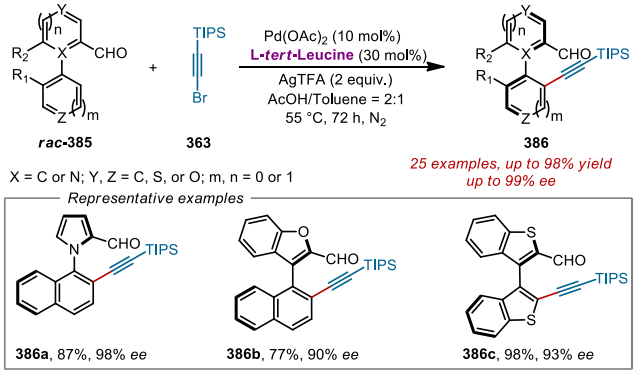
Despite these advancements, the atropo-enantioselective synthesis of pentatomic biaryls remains an arduous task due to the lower rotational barriers of these five-membered ring containing atropisomeric species.[171] In 2019, Shi group

Scheme 86. Pd-Catalyzed Atroposelective C−H Allylation

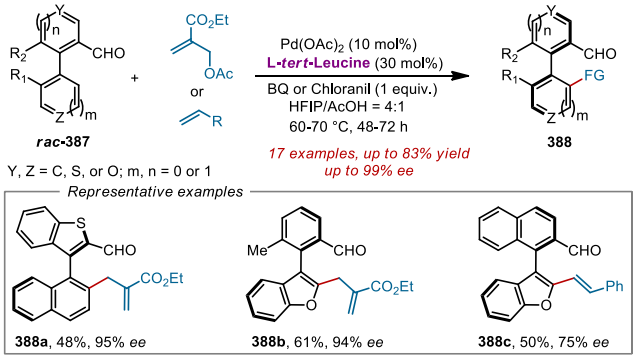


described a rare example of Pd-catalyzed atroposelective C−H alkynylation, allylation, and alkenylation for the synthesis of axially chiral pentatomic heteroaryls using transient chiral auxiliary strategy (Schemes 87 and 88).[172] A wide variety of

Scheme 87. Pd(II)-Catalyzed Atroposelective C−H Alkynylation for the Synthesis of Axially Chiral Heteroaryls



Scheme 88. Pd(II)-Catalyzed Atroposelective C−H Allylation and Alkenylation for the Synthesis of Axially Chiral Heteroaryls



five-membered heteroarenes, including pyrroles, thiophenes, benzothiophenes, and benzofurans were very compatible under this reaction protocol, affording the desired axially chiral heteroaryls **386** and **378** in good yields and enantioselectivities. Moreover, atropisomers containing two five-membered rings were also obtained in good yields and up to 93% *ee* (e.g., **386c**).

In 2019, Shi and co-workers reported a Pd(II)-catalyzed atroposelective C−H naphthylation using 7-oxabenzonorbornadienes **389** as the coupling partner and L-*tert*-leucine as the

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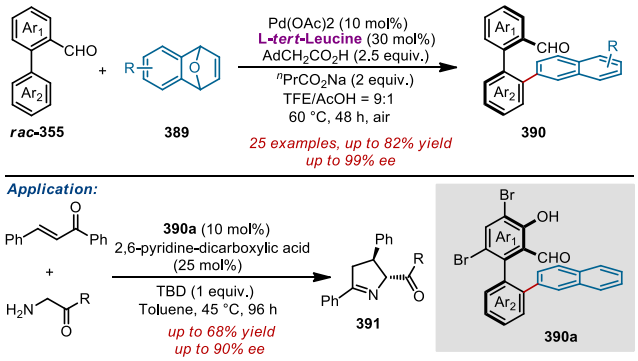
transient chiral auxiliary (Scheme 89).[173] A wide range of substrates were compatible under the reaction conditions to

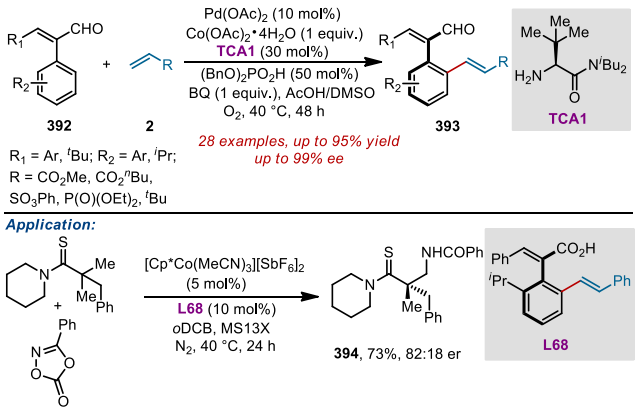
Scheme 89. Pd-Catalyzed Atroposelective C−H Naphthylation and Its Application



afford the desired axially chiral products **390** in good yields and excellent enantioselectivities. Furthermore, they also demonstrated the potential utility of this method by synthesizing the axially chiral biaryl **390a**, which exhibited much better catalytic reactivity and chiral induction as the organocatalyst in the asymmetric reaction of (*E*)-chalcone with glycine derived amides and dipeptides.

Recently, Shi group reported a Pd-catalyzed atroposelective C−H olefination for the synthesis of axially chiral styrenes using a bulky amino amide **TCA1** as the transient chiral auxiliary (Scheme 90).[174] A wide variety of axially chiral

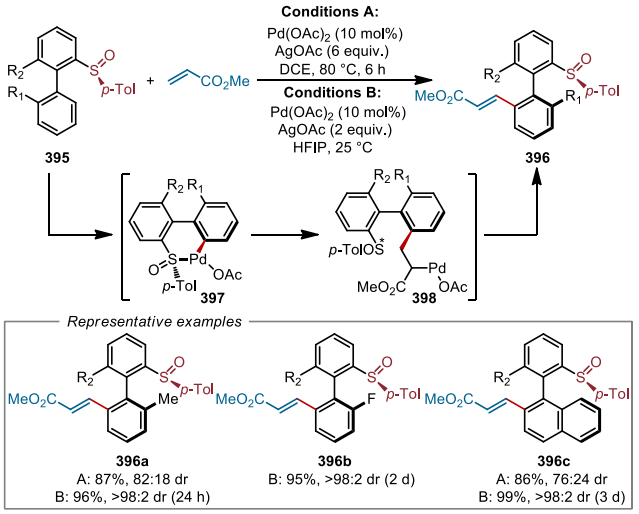
Scheme 90. Pd(II)-Catalyzed Atroposelective C−H Olefination Using a Bulky Chiral Transient Amino Amide and Its Application



styrenes **393** were obtained under the reaction protocol in good to excellent yield and up to 99% *ee*. Importantly, chiral carboxylic acids **L68** derived from the axially chiral styrenes **393** exhibited superior seterocontrol in Co(III)-catalyzed enantioselective C(sp^3)−H amidation of thioamide.

5.1.3. Diastereoselective C−H Functionalization. Diastereoselective C−H functionalization has also been recognized as a potential strategy to accomplish the construction of axially chiral biaryls. This strategy mainly relies on the usage of substrates bearing chiral auxiliaries. In 2013, Colobert reported the first example of atropodiastereoselective Pd(II)-catalyzed C−H olefination of biaryls employing an enantioenriched sulfoxide as both the directing group and chiral auxiliary (Scheme 91).[175] The reaction proceeded through the formation of an atropoenriched six-membered palladacycle

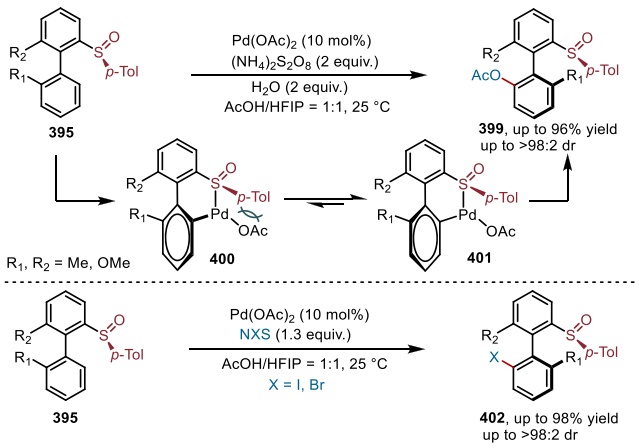
Scheme 91. Pd-Catalyzed Atropo-Diastereoselective C−H Olefination Using *p*-Tolylsulfinyl Group as the Chiral Auxiliary



intermediate **397**. In the presence of 10 mol % of $Pd(OAc)_2$, along with 6 equiv of AgOAc, and DCE solvent, a variety of axially chiral biaryls **396** were obtained in good to moderate yields and up to 82:18 dr. Later, in 2016, the same group disclosed that the HFIP solvent could significantly improve both the efficiency and diastereoselectivity of this reaction.[176]

Wencel-Delord and Colobert further extended this strategy to achieve atropo-diastereoselective C−H acetoxylation and halogenation through dynamic kinetic resolution using chiral *p*-tolyl sulfoxide auxiliary as the directing group (Scheme 92).[177] In the presence of 10 mol % of $Pd(OAc)_2$ as the

Scheme 92. Chiral Sulfoxide-Directed Atropo-Diastereoselective C−H Acetoxylation and Halogenation



catalyst, along with $(NH_4)_2S_2O_8$ as the oxidant, and AcOH as the acetoxylating reagent, a wide range of chiral acetoxylated biaryls **399** were obtained in excellent diastereoselectivities. By exchanging the above oxidant with NIS, the highly diastereoselecive (up to >98:2 dr) C−H iodination was also achieved. Importantly, the distereoselective brominated

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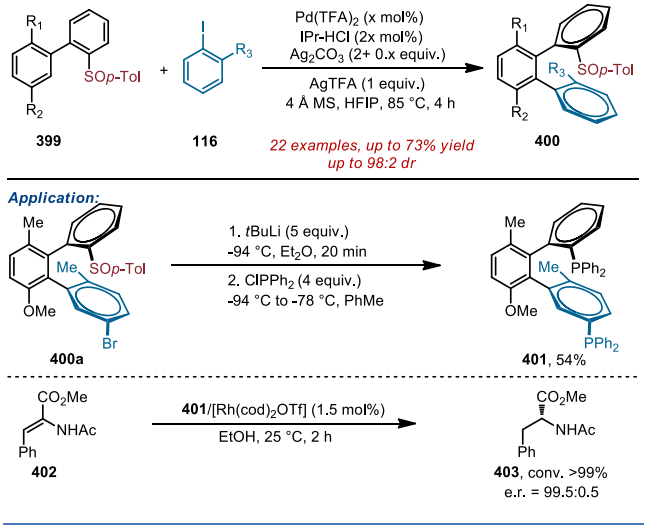
product could also be obtained by treating with NBS under otherwise identical conditions, although with a slight decrease in stereoselectivity.

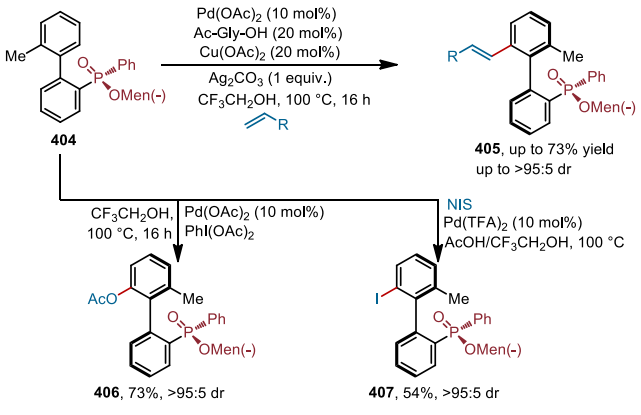
In 2018, the same group reported a Pd-catalyzed atroposelective C−H arylation for the synthesis of chiral terphenyl scaffolds bearing either one or two chiral axes (Scheme 93).[178] In the presence of $Pd(TFA)_2$, 1,3-bis(2,6-diisopropylphenyl) imidazolium chloride (IPr-HCl), Ag_2CO_3, AgTFA, and 4 Å MS, at 85 °C in HFIP, the reaction of biaryls containing a stereogenic sulfoxide moiety **399** as substrates with *ortho*-substituted aryl iodides **116** afforded the desired products **400** in good to moderate yields with high diastereoselectivities. Further, they also demonstrated the potential utility of these terphenyls with two chiral axes such as **401** as privileged chiral bidentate ligands in asymmetric catalysis.

Scheme 93. Chiral Sulfoxide-Directed Atropo-Diastereoselective C−H Arylation and Its Application



In 2015, Yang and co-workers reported a Pd(II)-catalyzed atropo-diastereoselective C−H alkenylation using an enantioenriched menthylphenylphate as chiral auxiliary (Scheme 94).[179] In the presence of $Pd(OAc)_2$ as the catalyst, along with *N*-Ac-glycine as the ligand, a wide variety of axially chiral biaryl phosphineoxides **405** were obtained in good yields with excellent diastereoselectivities. The diastereoselective C−H functionalization could also be extended to acetoxylation and iodination by employing similar substrates.

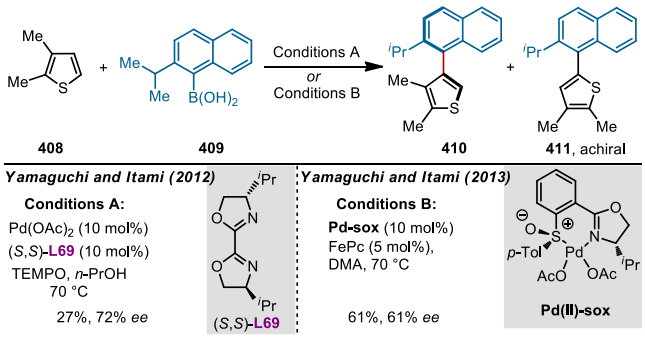
Scheme 94. Pd(II)-Catalyzed Menthylphenylphosphate-Directed C−H Activation for the Synthesis of Chiral Biaryl Phosphates via Dynamic Kinetic Resolution



5.2. The Creation of New Chiral Biaryl Axis via C−H Activation/Asymmetric Coupling. Over the past few years, transition metal catalyzed C−H arylation of arenes and heteroarenes has been recognized as the most straightforward strategy for the construction of biaryls.[1b,180] Despite these advances, the atroposelective synthesis of biaryls via asymmetric C−H activation remains a significant challenge.

In 2012, Yamaguchi and Itami first reported a Pd-catalyzed atropo-enantioselective coupling reaction for the construction of biaryls (Scheme 95 A).[181] In the presence of 10 mol % of $Pd(OAc)_2$ as the catalyst, 10 mol % of bisoxazoline **L69** as the chiral ligand, and TEMPO as the oxidant, the atroposelective C−H arylation of substituted thiophenes **408** with sterically hindered naphthylboronic acids **409** afforded the desired chiral biaryl **410** in 27% yield and 72% ee along with the formation of a achiral side product **411**. The reaction showed a drastic drop in enantioselectivity with increasing the reactivity of naphthylboronic acid coupling partner. In the next year, the same group disclosed a different catalytic systems for the similar reaction by employing chiral Pd(II)-**sox** complex as the catalyst and iron-phthalocyanine (FePc) as the cocatalyst (Scheme 95 B).[182] Although this dual catalytic system was able to increase the yield of the desired axially chiral product **410**, the enantioselectivity remains to be improved.

Scheme 95. Pd-Catalyzed Atropo-Enantioselective C−H Coupling of Thiophene with Naphthylboronic Acids



In 2017, Waldmann and Antonchick group described the development of chiral JasCp ligand derived Rh(III) catalysts to promote enantioselective C−H activation reactions (Scheme 96).[39] After several catalysts were evaluated, chiral [JasCpRh(III)] complex **Rh26** (exo) was proven as the optimal catalyst in the atroposelective C−H arylation of benzamides **77** with diazonaphthoquinones **78**. A broad variety of desired axially chiral biaryls (e.g., **79a−c**) were obtained in 37−93% yield and up to 90% *ee* under the optimized reaction conditions.

A year later, Cramer and co-workers reported an atropo-enantioselective C−H arylation of phosphine oxides **412** with *o*-quinone diazides **37** by using a combination of chiral iridium(III) complex **Ir1** as the catalyst and phthaloyl *tert*-leucine **L39** as the cocatalyst (Scheme 97).[183] A wide variety of axial and P-chiral biaryls **413** were obtained under the reaction protocol in 59−96% yield and up to 99% *ee*. In addition, the synthesis of purely axially chiral phosphine oxides were also achieved by using tris-3,5-dimethoxyphenylphosphine oxide as a substrate. Enantiospecific reduction of these chiral phosphine

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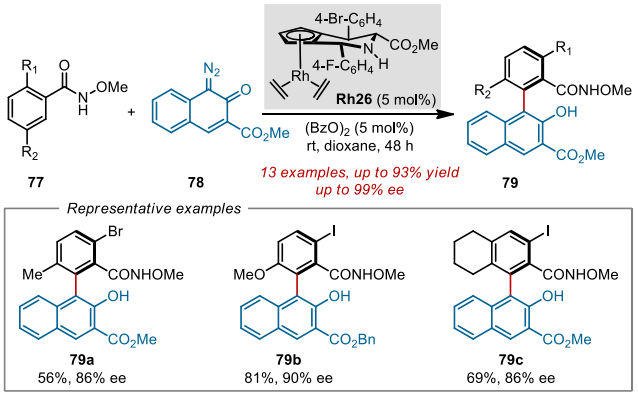
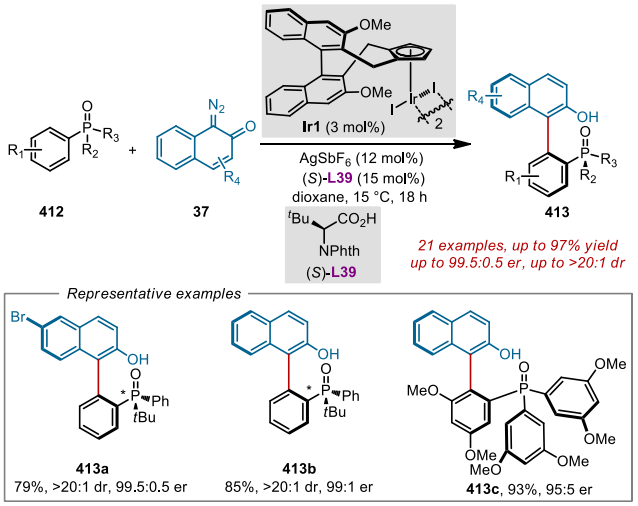
Scheme 96. Rh-Catalyzed Atropo-Enantioselective C−H Arylation



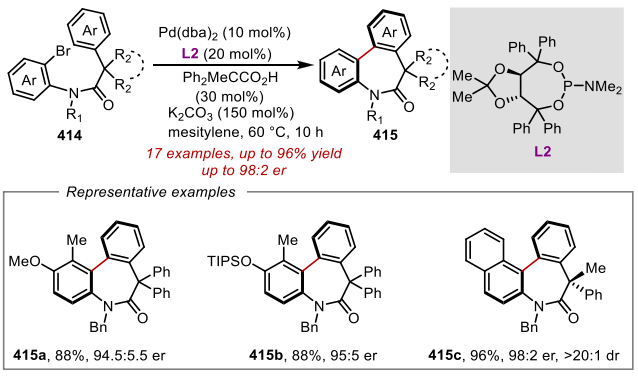
Scheme 97. Ir(III)-Catalyzed Atropo-Enantioselective C−H Arylation of Phosphine Oxides



oxides provided the valuable monodentate biaryl phosphorus compounds, which could be utilized as ligands in various important asymmetric reactions.

In 2018, the same research group described Pd(0)-catalyzed atropo-enantioselective intramolecular C−H arylation for the synthesis of axially chiral dibenzazepinones using TADDOL-based phosphoramidite **L2** as the chiral ligand (Scheme 98).[184]

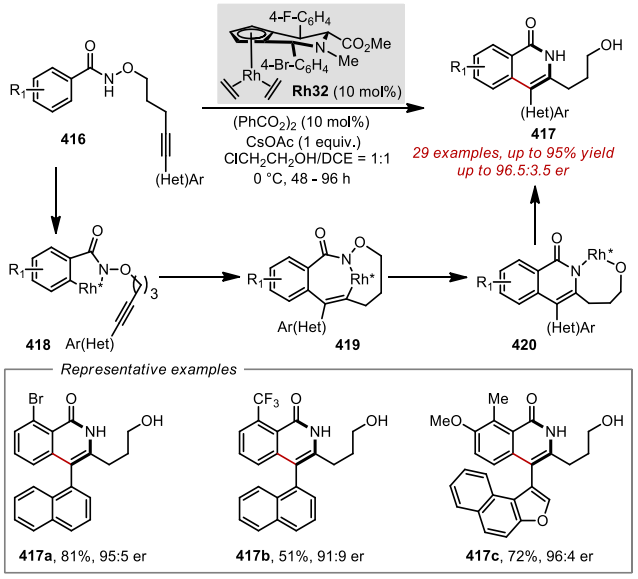
Scheme 98. Pd(0)-Catalyzed Atropo-Enantioselective Intramolecular C−H Arylation



In this reaction, acid additive played a crucial role in achieving excellent reactivity and stereocontrol. A wide range of axially chiral dibenzazepinones **415** were synthesized under the reaction conditions in good yields with high enantioselectivities.

In 2018, Waldmann and Antonchick group reported a Rh(III)-catalyzed cascade sequence of C−H bond activation and intramolecular annulation for the atropo-enantioselective synthesis of axially chiral 4-arylisoquinolones (Scheme 99).[185]

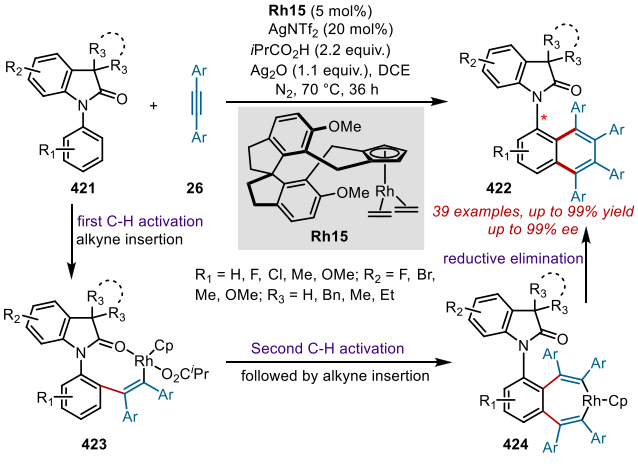
Scheme 99. Rh(III)-Catalyzed Atroposelective Synthesis of 4-Arylisoquinolones



The piperidine-fused chiral cyclopentadienyl ligand derived Rh(III)-catalyst **Rh32** was proven as the optimal ligand and afforded the desired products **417** in good yields with high enantioselectivities. Furthermore, they also investigated the biological activity of the 4-arylisoquinolones in different cellular assays, resulting in the discovery of novel non-SMO (SMO = smoothened) binding Hedgehog pathway inhibitors.

In 2019, Wang and co-workers described the first example of enantioselective Satoh-Miura type reaction (Scheme 100).[186]

Scheme 100. Rh-Catalyzed Enantioselective Synthesis of C−N Axially Chiral *N*-Aryloxindoles



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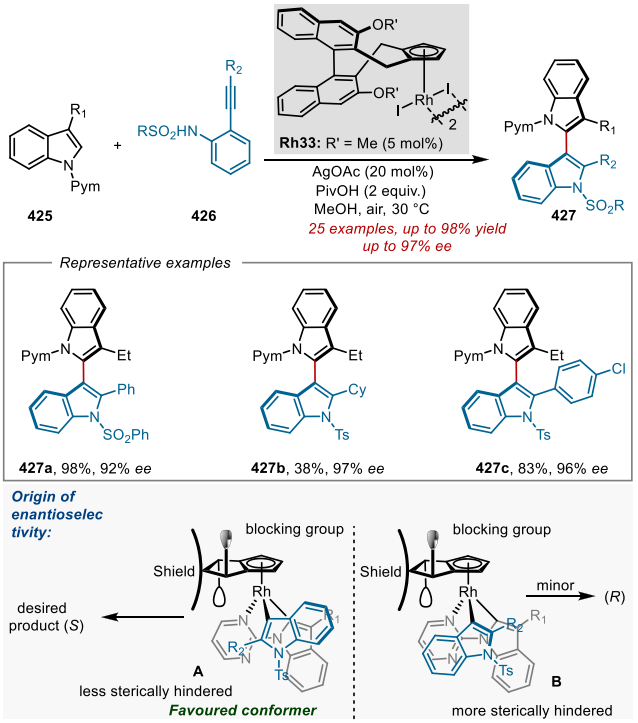
In the presence of 5 mol % of chiral Rh-catalyst **Rh15**, along with 20 mol % $AgNTf_2$, a combination of $^tPrCO_2H$ (2.2 equiv) and Ag_2O (1.1 equiv) as the additive, the reaction of *N*-aryloxindoles **421** with alkynes **26** afforded the desired C−N axially chiral *N*-aryloxindoles **422** in high yields and enantioselectivities (up to 99% yield and up to 99% ee) via dual C−H activation. The kinetic isotope effect (K_H/K_D) was found to be 1.07, suggesting that the C−H activation step is not rate-determining. Mechanistically, the reaction proceeded through the formation of intermediate **423**. Then, the second C−H activation followed by insertion of a second molecule of alkyne led to the formation of intermediate **424**. Finally, this intermediate underwent reductive elimination to furnish the desired products **422**.

Achieving high enantiomeric excess in synthesizing pentatomic biaryls is a formidable challenge due to their low rotational barrier. To overcome this problem, in 2019 Li and co-workers developed a chiral Rh(III)-catalyst based strategy for the synthesis of atropoenantioselective 2,3′-biindolyls by integrating C−H activation with nucleophilic alkyne cyclization (Scheme 101).[187] In the presence of 5 mol % of **Rh33** as

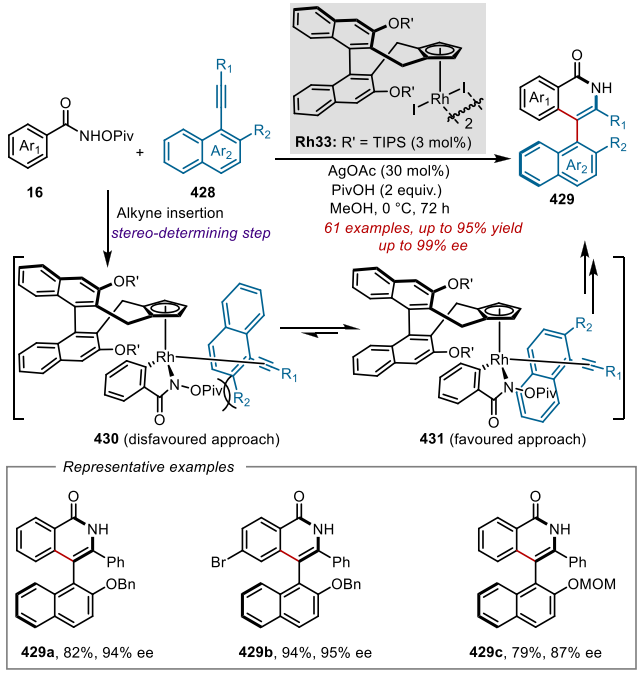
Scheme 101. Rh(III)-Catalyzed Atroposelective Synthesis of Axially Chiral 2,3′-Biindolyls



the chiral catalyst, along with 20 mol % of AgOAc, and 2 equiv of PivOH as the additive, a broad range of axially chiral desired biindolyls were obtained in good to excellent yields and up to 97% *ee*. Mechanistically, this reaction proceeded via cyclometalation followed by alkyne cyclization to generate Rh(III)-diaryl intermediate **A** and **B**. Finally, the reductive elimination occurs from intermediate **A** due to minimized steric hindrance, affording the desired (*S*)-2,3′-biindolyl.

In 2020, Li and co-workers disclosed a Rh(III)-catalyzed atroposelective synthesis of biaryl NH isoquinolones **429** via C−H bond activation of benzamides **16** followed by intermolecular [4 + 2] annulations of 2-substituted 1-alkynylnaphthalenes **428**, as well as sterically hindered, symmetric diarylacetylenes (Scheme 102).[188] In the presence

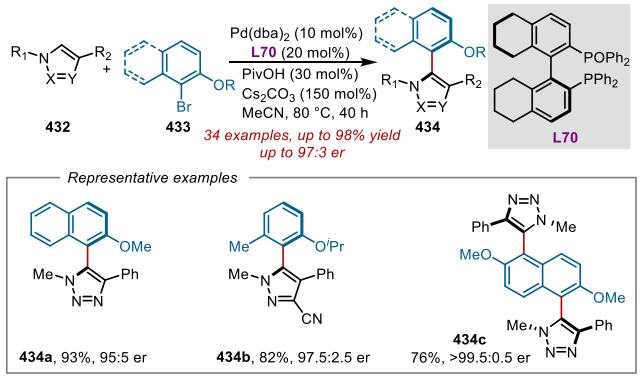
Scheme 102. Rh(III)-Catalyzed Atroposelective Intermolecular Annulation



of 3 mol % of chiral cyclopentadienyl ligand derived Rh-catalyst **Rh33**, along with 0.3 equiv of AgOAc, and 2 equiv of PivOH, a variety of desired axially chiral biaryls **429** were obtained in 38−95% yield and up to 99% *ee*. In this transformation, the alkyne insertion step was found to be stereodetermining.

In 2020, Baudoin and Cramer described a Pd(0)-catalyzed intermolecular atropo-enantioselective C−H arylation of heteroarenes **432** using H_8-BINAPO **L69** as the chiral ligand (Scheme 103).[189] A wide variety of aryl bromides were amenable under the reaction conditions, affording the desired axially chiral (hetero)biaryls **434** in good to excellent yields with high enantioselectivities. Moreover, double intermolecular atroposelective C−H arylation could also be achieved by utilizing this method, allowing the access of two stereogenic

Scheme 103. Pd(0)-Catalyzed Atropo-Enantioselective Intermolecular C−H Arylation of Heteroarenes



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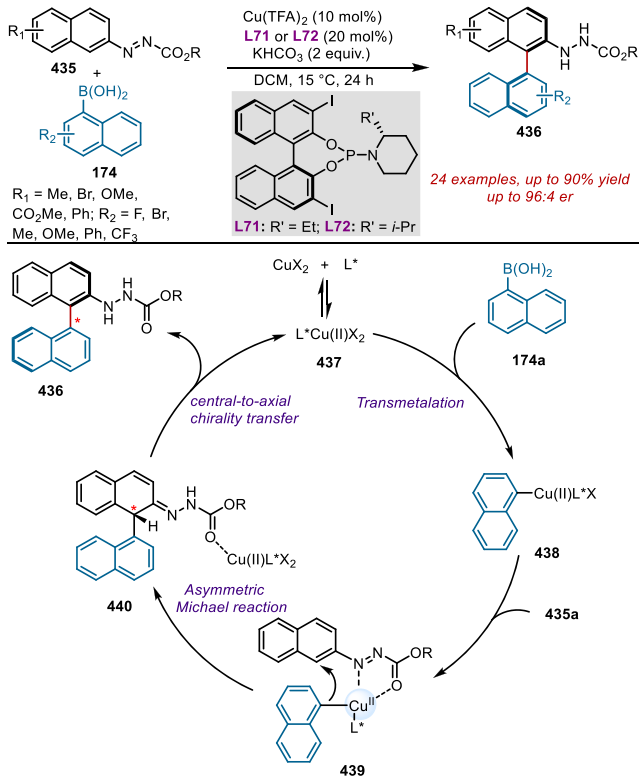
axes **434c** in 76% yield and >99.5:0.5 er. Mechanistic studies suggested C−H activation as the rate-determining (K_H/K_D = 1.8) but not enantio-determining step.

Very recently, Tan and Song reported the first example of Cu-catalyzed atropo-enantioselective arylation of azonaphthalenes **435** with arylboronic acids **174** (Scheme 104).[190] In the

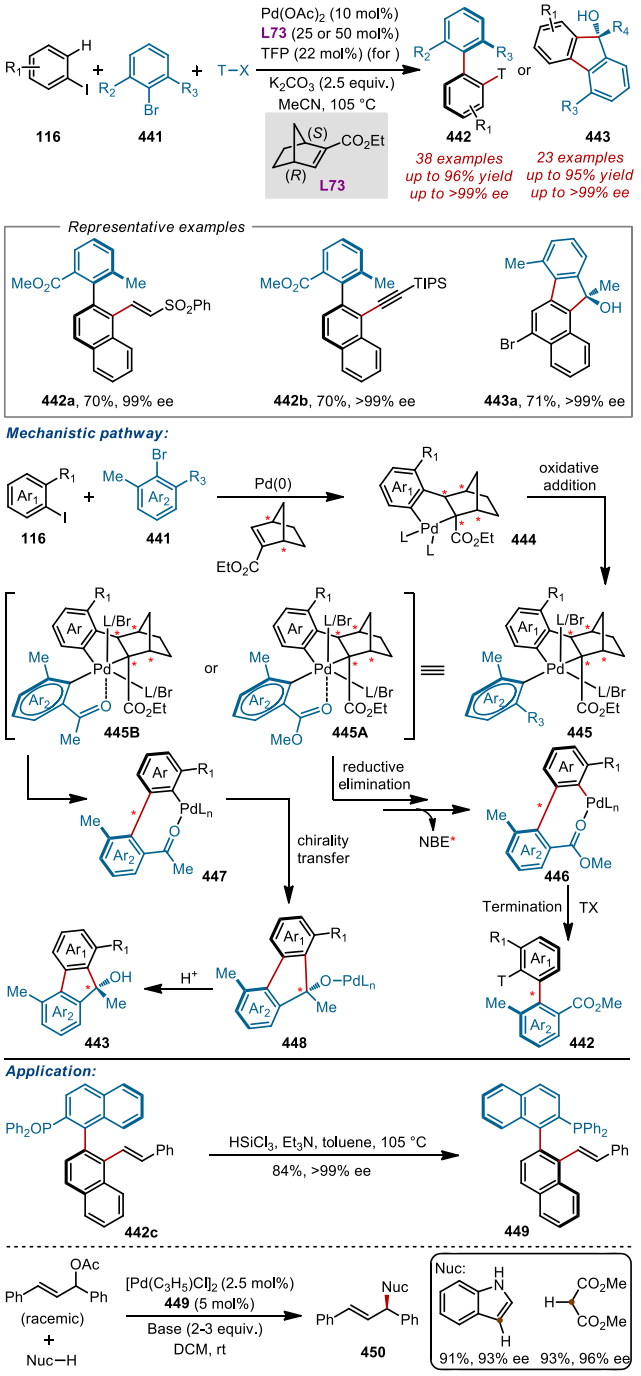
Scheme 104. Michael Reaction Inspired Cu-Catalyzed Atroposelective Synthesis of Axially Chiral Biaryls



presence of 15 mol % of $Cu(TFA)_2$ as the catalyst, along with 20 mol % of BINOL-derived phosphoramidite **L71** or **L72** as the chiral ligand, and 2 equiv of $KHCO_3$ as the base, a broad range of axially chiral biaryls **436** were obtained in 44−90% yield and up to 96:4 er. The reaction proceeded with transmetalation between arylboronic acid **174a** and the chiral Cu-species **437** to afford intermediate **438**. Subsequently, the coordination of azonaphthalene with this aryl copper species furnished intermediate **439**. Then, this intermediate underwent an asymmetric Michael-type reaction to provide intermediate **440** containing central chirality. Eventually, rapid central-to-axial chirality transfer afforded the desired biaryl atropisomer **436** along with the regeneration of Cu-phosphoramidite complex **437**.

Recently, Zhou and co-workers described a palladium/chiral norbornene cooperative catalysis strategy for the construction of axially chiral biaryls (Scheme 105).[191] This modular platform is basically a three-component cascade process, which involves a broad variety of aryl iodides **116**, 2,6-substituted aryl bromides **441**, and terminating reagents including olefins, alkyne, boronic acids, cyanide, and ketone. In addition, this strategy is also effective for the synthesis of chiral fluorenols in an intramolecular termination manner via axial-to-central chirality transfer. Mechanistically, the reaction proceeded with the oxidative addition of aryl iodide to Pd(0)

Scheme 105. Pd/Chiral Norbornene Cooperative Catalysis Strategy for the Synthesis of Axially Chiral Biaryls



and followed by chiral norbornene **L73** insertion to generate aryl-norbornyl-palladacycle intermediate **444**. Then, this intermediate undergoes oxidative addition reaction with 2,6-disubstituted aryl bromide to form a chiral Pd(IV) complex **445**. A subsequent cascade sequence of reductive elimination and norbornene extrusion via β-carbon elimination leads to the formation of axially chiral Pd(II) complexes **446** and **447**. Finally, these chiral complexes could be either coupled with appropriate terminating reagents or terminated via intramolecular processes. It is worth noting here that the proposed intermediates adopt a planar orientation to minimize the steric constraints. Notably, the electron-withdrawing group of the

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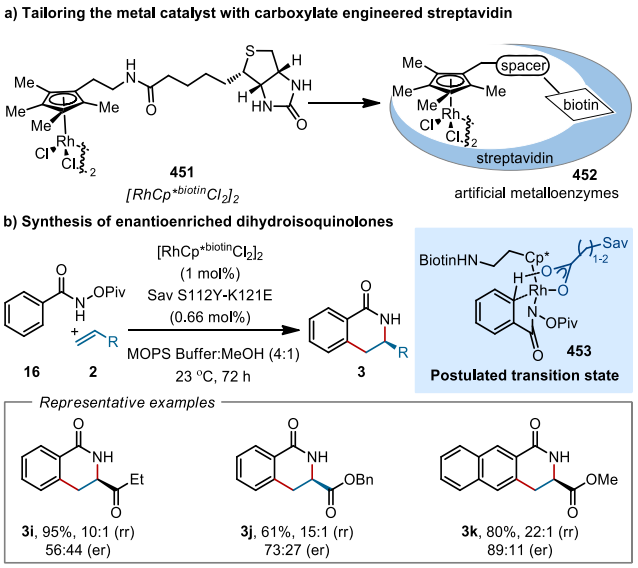
intermediates (**446** and **447**) would assist to fix this orientation by coordinating with the Pd-center. Further, they demonstrated the potential utility of this transformation by synthesizing an axially chiral phosphine-olefin ligand **449**, which could act as an efficient chiral ligand in Pd-catalyzed asymmetric allylation reactions.

6. ARTIFICIAL METALLOENZYMES

In the same time of Cramer's first report on chiral Cp^{x}Rh catalyzed enantioselective C(sp^2)−H functionalizations,[20] Ward and Rovis disclosed a conceptually distinct approach toward chiral Cp facilitated enantioselective C(sp^2)−H bond functionalizations.[40] Utilizing a supramolecular concept, a chiral environment was generated by introducing Cp* biotin derivative (**451**) into an engineered streptavidine protein, which binds in a host−guest complexation manner. This metalloenzyme (**452**) contains two different mutations, S112Y and K121E, which are key components for reactive and selective annulation reactions of hydroxamic acid derivatives and electron-deficient alkenes (Scheme 106). The chiral

Scheme 106. Engineered Streptavidin/Biotin−Rhodium-Catalyzed Benzannulation through C−H Activation



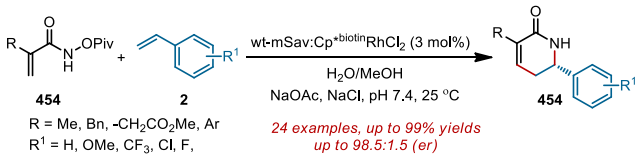
pocket around the active metal-catalyst was provided by the S112Y mutation, at the same time as the K121E mutation-assisted C−H activation step through a carboxylate-assisted CMD pathway. The metalloenzyme approach provided promising reactivity and selectivity in annulation reaction (Scheme 106b).

Recently, Rovis and co-workers significantly expanded the scope of this approach to enantioselective olefinic C(sp^2)-H bond functionalization reactions (Scheme 107).[192] Without additional mutations around the binding pocket, [biot-Cp*RhCl$_2$(H$_2$O)].WT mSav catalyzed the annulation between acrylamide hydroxamate esters (**454**) and styrenes (**2**) to achieve δ-lactums (**454**) with both high yields of up to 99% and selectivity up to 97% ee.

7. SUMMARY AND OUTLOOK

In this review, we have emphasized recent developments regarding the various techniques and their implementation in

Scheme 107. Enantioselective Synthesis of Dihydropyridinones by Monomeric Streptavidin/Biotin−Rhodium Catalyst



asymmetric C(sp^2)−H functionalization reactions. In the current scenario, enantioselective C(sp^2)−H functionalization is emerging as a new avenue for developing asymmetric transformations and thereby holds interest in both academia and industry. The appropriate combination of transition metal and chiral ligand systems provide a candid way to afford numerously important enantio-enriched C−H functionalized products. Initial development of chiral Cp^x ligands by Cramer's group is a significant step forward to open up new directions in Rh-catalyzed asymmetric C(sp^2)−H bond functionalization. Thereafter, various elegant enantioselective transformations have been developed in terms of new ligand and catalyst systems. However, still enantioselective C−H functionalization is not a wide-ranging topic in the synthetic community because of the presence of several formidable challenges. In order to achieve a higher degree of stereoselectivity in asymmetric C−H functionalization, the efficiency of catalysts must need to be improved. Special attention needs to be paid in designing of suitable ligand systems that can activate any kind of C−H bond with the assistance of metal catalysts and transform them into different functionalities in high yields with excellent enantioselectivities. Similarly, enhanced operational simplicity of the catalysis could bring out methodology from the laboratory to the industrial application. Herein, we have discussed the overall growth and underscore this promising field in a systematic way to enrich the synthetic disconnection process and expedite the chemist's effort to synthesize chiral molecules from simple chemical feedstock. We assume this review will provide a comprehensive understanding of this emerging area of asymmetric catalysis to the readers and inspire them to discover more innovative strategies in transition metal catalyzed asymmetric C−H functionalization reactions.

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Notes

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