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Recent Advances on Transition-Metal-Catalyzed Asymmetric C–H Arylation Reactions

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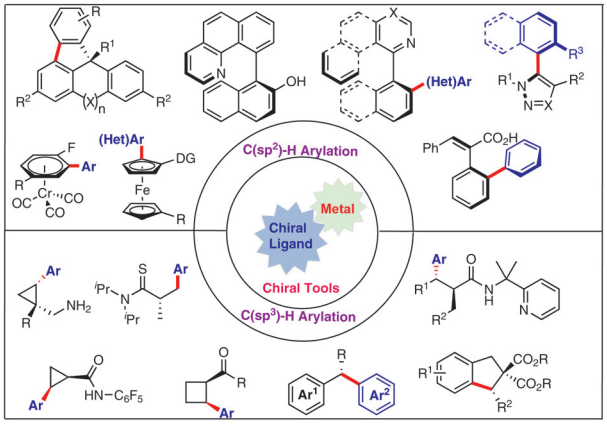

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Abstract Transition-metal-catalyzed asymmetric C–H functionalization has become a powerful strategy to synthesize complex chiral molecules. Recently, catalytic enantioselective C–H arylation has attracted great interest from organic chemists to construct aryl-substituted chiral compounds. In this short review, we highlight recent advances in asymmetric C–H arylation from 2019 to late 2021, including enantioselective C(sp^2)–H arylation to construct axial or planar chiral compounds, and enantioselective C(sp^3)–H arylation to introduce central chirality via desymmetrization of the methyl group or methylene C–H activation. These processes proceed with palladium, rhodium, iridium, nickel, or copper catalysts, and utilize aryl halides, boron, or diazo derivatives as arylation reagents.

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Key words C–H bond functionalization, transition-metal catalysis, asymmetric C–H activation, C(sp^2)–H arylation, C(sp^3)–H arylation, arylation, chiral ligands

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1 Introduction

Transition-metal-catalyzed C–H bond functionalization is a step-economic and environmentally benign approach to selectively construct C–C and C–heteroatom bonds at specific carbon site without the use of a distinct functional group.[1] More importantly, the strategy could provide convenience to discover or design drug molecules utilizing single step to deliver structurally diversified bioactive molecules.[2] However, catalytic site-selective C–H functionalization has a fundamental challenge due to the existence of multiple C–H bonds with similar electronic and steric properties.[3] Over the past two decades, organic chemists have made incessant efforts to successfully overcome the selectivity topic by regioselective metalation of proximal or remote C–H bonds with the assistance of directing effects or electronic biases of various functional groups.[4] Besides, late-stage functionalization of bioactive compounds has also been achieved by catalytic C–H functionalization.[5] With the development of C–H activation, transition-metal-catalyzed stereoselective C–H functionalization has become striking topic considering the paramount importance of chirality in pharmaceuticals and agrochemicals.[6]

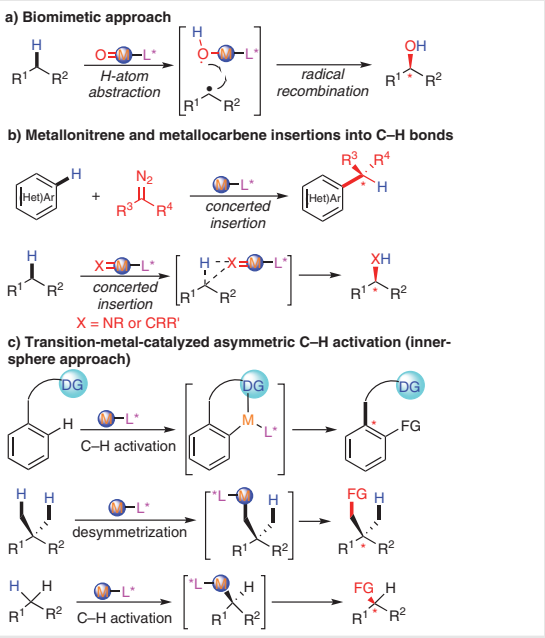


Figure 1 General mechanistic overview of transition-metal-catalyzed asymmetric C–H functionalization

Transition-metal-catalyzed asymmetric C–H functionalization always needs to tolerate harsh reaction conditions to activate and directly functionalize inert C–H bonds (BDE: 90–110 kcal mol^{-1}), which with difficultly discriminates the diastereomeric transition state. Despite the aforementioned obstruction, several different approaches have been used to accomplish the enantioselectively functionalize C–H bonds.[7] Two main mechanisms, including outer-sphere and inner-sphere, have been presented for the enantioselective functionalization of C–H bonds. In an outer-sphere mechanism, the C–H bond does not directly interact with the metal center, such as enzymatic C(sp^3)–H oxidation (Figure 1a)[8] and catalytic metallonitrene or metallocarbene insertion into C–H bonds (Figure 1b)[9]. In an inner-sphere mechanism, the transition-metal catalyst directly interacts with the C–H bond to provide an organometallic intermediate via C–H bond cleavage (Figure 1c). Catalytic asymmetric C–H arylation is an important part of transition-metal-catalyzed enantioselective C–H functionalization to deliver axial, planar, and central chiral molecules. For this reaction, the key point is to highly enantioselectively construct an organometallic intermediate by the interaction of the C–H bond with a chiral metal complex.

Recently, transition-metal-catalyzed enantioselective C–H functionalization reactions have been summarized in some reviews.[7c,10] In 2018, Yu summarized the recent developments in transition-metal-catalyzed (Pd, Ir, and Rh) enantioselective C(sp^3)–H bond functionalization with a chiral ligand scaffold to accelerate the metalation of C(sp^3)–H bonds.[10b] Cramer discussed approaches of using selective functionalization of C–H bonds to generate a remote heteroatom stereogenic center via an inner-sphere C–H activation mechanism in 2019.[10c] The You group reviewed the recent progress in transition-metal-catalyzed (Cu, Pd, Ir, Rh, Au, and Pt) asymmetric C–H bond functionalization to construct planar chiral ferrocenes in 2020.[10h] Also in 2020, Maiti reviewed the recent remarkable developments in the emerging area of enantioselective C(sp^2)–H bond functionalization.[10i] In this short review, we intend to highlight the recent advances in asymmetric C–H arylation from 2019 to late 2021, including enantioselective C(sp^2)–H arylation to construct axial or planar chiral compounds, and enantioselective C(sp^3)–H arylation to introduce central chirality via desymmetrization of methyl group or methylene C–H activation.

2 Transition-Metal-Catalyzed Asymmetric C(sp^2)–H Arylation

Transition-metal-catalyzed asymmetric C(sp^2)–H arylation was always used to construct atropisomer or planar chiral compounds.[10h,i] The stereochemistry generating step of these reactions is the formation of chiral organometallic intermediates by the interaction of a metal catalyst with the C(sp^2)–H bond. In this short review, we will discuss the recent progress in catalytic asymmetric C(sp^2)–H arylation reactions from various aspects: (i) chelation-assisted asymmetric C(sp^2)–H arylation for the construction of atropisomers, (ii) chelation-assisted asymmetric C(sp^2)–H arylation for the construction of planar chiral compounds, (iii) chelation-assisted asymmetric C(sp^2)–H arylation and axial-to-

central chirality transfer for the construction of spirocycles, and (iv) other asymmetric C(sp^2)–H arylation reactions.

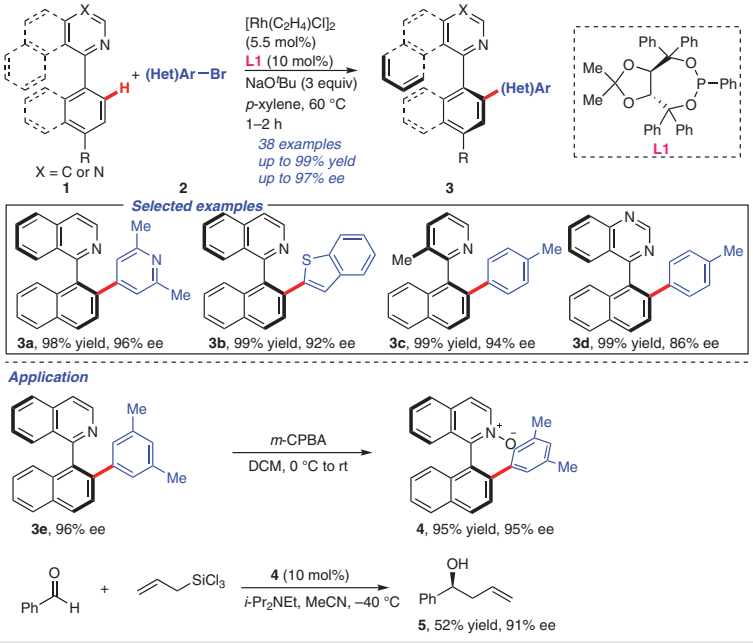
2.1 Chelation-Assisted Asymmetric C(sp^2)–H Arylation for the Construction of Atropisomers

In 2019, the You group developed a Rh(I)-catalyzed atroposelective C–H arylation of heterobiaryls catalyzed by $[Rh(C_2H_4)_2Cl]_2$ and a TADDOL-derived monodentate phosphonite ligand **L1** (Scheme 1).[11] A series of pyridine and isoquinoline derivatives were transformed into axially chiral heterobiaryls **3** in excellent yields and enantioselectivities. Aryl or heteroaryl bromides were all compatible with the reaction conditions. Furthermore, a one-step reaction of the heterobiaryl product delivered a chiral *N*-oxide **4** that acts as an efficient catalyst for asymmetric allylation of benzaldehyde with allyltrichlorosilane.

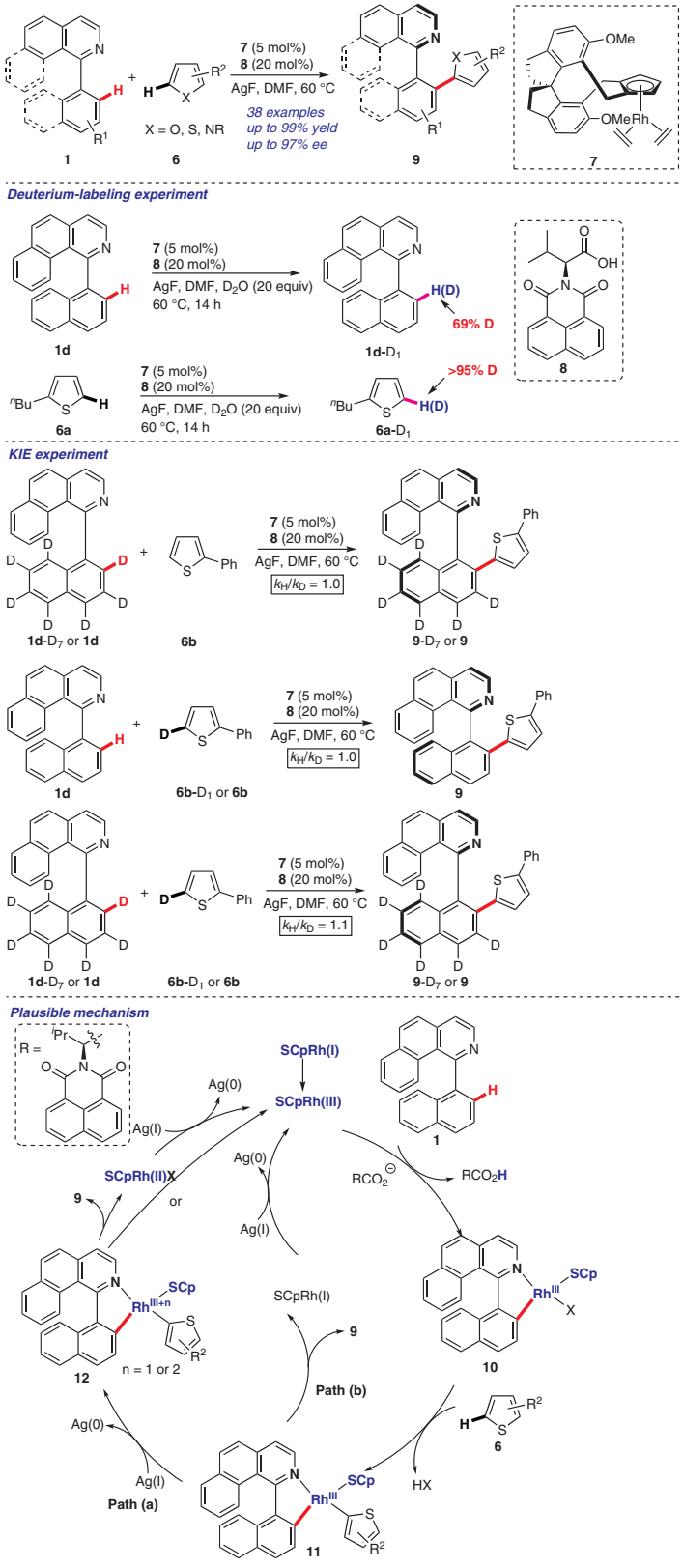
In 2020, the same group reported a Rh(III)-catalyzed enantioselective oxidative C–H/C–H cross-coupling reaction of 1-arylisoquinoline derivatives **1** with electron-rich heteroarenes such as thiophenes, furans, benzothiophenes, and benzofurans (Scheme 2).[12] A series of axially chiral isoquinolines **9** were obtained in excellent yields and enantioselectivities in the presence of a chiral CpRh(III) complex **7** and a chiral carboxylic acid additive **8**. This method first utilized electron-rich heteroarenes as the coupling partner to achieve asymmetric C(sp^2)–H arylation and involved a double C–H functionalization process. Deuterium-labeling experiments suggested that the C–H cleavage of two coupling partners were facile. KIE experiments indicated C–H bond cleavages of 1-arylisoquinolines **1** or electron-rich heteroarenes **6** might not be the turnover-limiting step. A plausible mechanism was proposed (Scheme 2). Initially, Rh(I) was oxidized to active Rh(III) catalyst, which affords rhodacycle intermediate **10** by the coordination with 1-arylisoquinolines **1** and subsequent enantioselective C–H activation with the assistance of the chiral carboxylic acid additive. Next, rhodacycle intermediate **10** undergoes electrophilic C–H substitution with thiophene derivative **6** to deliver Rh(III) intermediate **11**, which is oxidized by the Ag(I) salt to afford high-valent rhodacycle intermediate **12**. Finally, intermediate **12** undergoes reductive elimination to afford the corresponding cross-coupling product **9** and SCpRh(II) or SCpRh(III) to accomplish the catalytic cycle. Another pathway **b** through reductive elimination of Rh(III) intermediate **11** to provide product **9** and SCpRh(I) cannot be completely excluded.

Over the past few decades, the synthesis of axially chiral styrenes involving a chiral axis between the alkene moiety and the aryl substituent has been rarely reported due to the lower rotation barriers compared with atropisomeric biaryl derivatives.[13] In 2020, Shi and co-workers developed a revolutionary work on the enantioselective synthesis of axially chiral styrenes via Pd-catalyzed aryl C(sp^2)–H alkenylation and alkynylation in the presence of chiral carboxylic acid L-pGlu-OH (Scheme 3a).[14] Experimental and DFT calculations indicated that atroposelective C(sp^2)–H alkenylation proceeds by sequential C(sp^2)–H activation, alkene insertion, and pyridine-assisted β-hydride elimination.

In 2021, Wang and co-workers investigated the palladium-MPAA-catalyzed carboxyl-directed asymmetric C(sp^2)–H arylation of 2-arylcinnamic acid derivatives **18** with aryl-



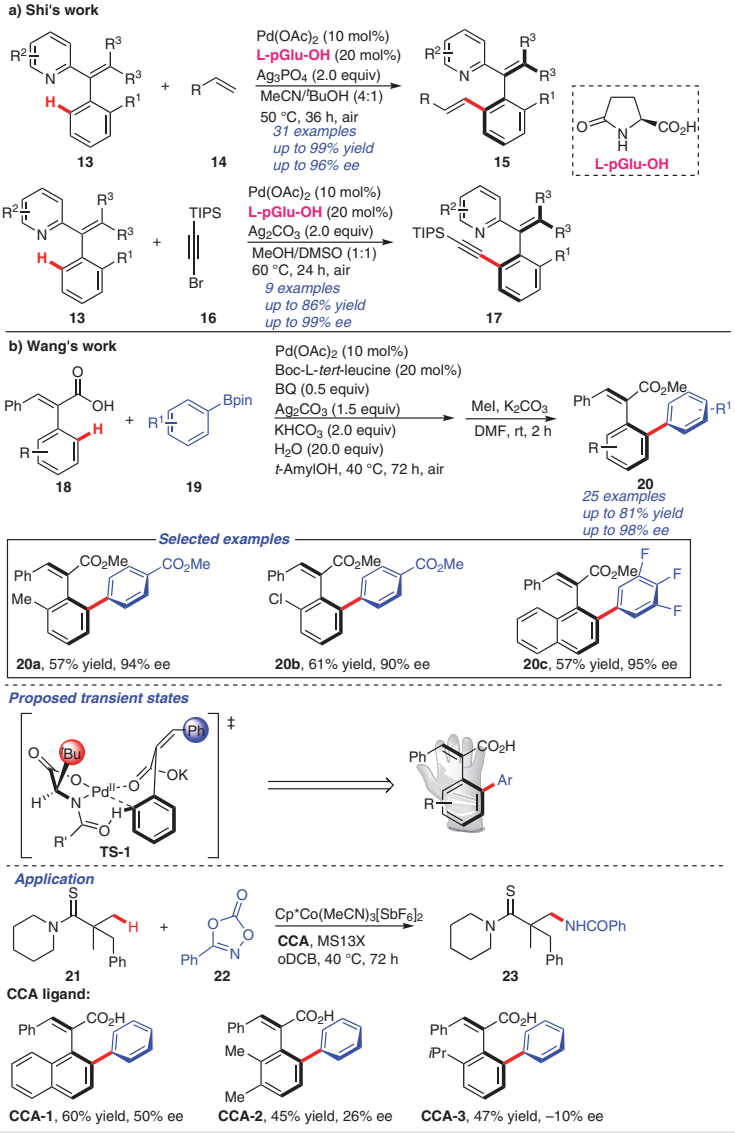
Scheme 1 Rh(I)-catalyzed atroposelective C–H arylation and its application



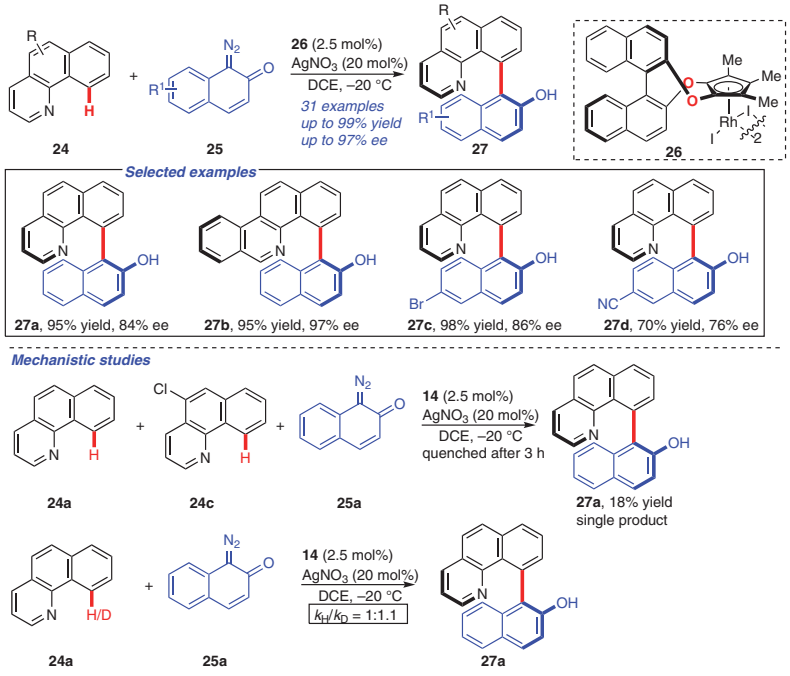
Scheme 2 Rh-catalyzed atroposelective C(sp²)–H arylation with electron-rich heteroarenes

boronic acid pinacol esters **19** (Scheme 3b).[15] This reaction transformed the axially chiral styrene-type carboxylic acids into the corresponding methyl esters **20** in moderate yields. A plausible stereo-model of the transition state **TS-1** was proposed, in which palladium is coordinated with the monoprotected amino acid (MPAA) ligand and the substrate in a square-planar coordination. The upward bulky side-chain of the amino acid pushes the alkenyl group away from the palladium coordination plane to avoid steric repulsion. When the axially chiral styrene-type carboxylic acids were used as chiral ligands for Co(III)-catalyzed asymmetric C–H activation reactions, the desired product was obtained with poor enantioselectivity.

In 2021, the You group synthesized a new class of sterically and electronically tunable chiral cyclopentadienyl ligands (BOCps) bearing an oxygen linker from commercially available BINOL, which were efficient ligands in the Rh(III)-catalyzed chelation-assisted C(sp^2)–H arylation of benzo[*h*]quinolines **24** with 1-diazonaphthoquinone derivatives **25** (Scheme 4).[16] This method was used to construct a chiral axis between the substituted benzo[*h*]quinoline and the aromatic ring rather than functionalization of aryl-substituted heteroarenes. A series of axially chiral heterobiaryls **27** were obtained in excellent yields and enantioselectivity. When the competition reaction between benzo[*h*]quinolines **24a** and **24c** with 1-diazonaphthoquinone **25a** was carried out under the standard conditions, only desired product **27a** was obtained, which showed Cp^xRh^{III} cat-



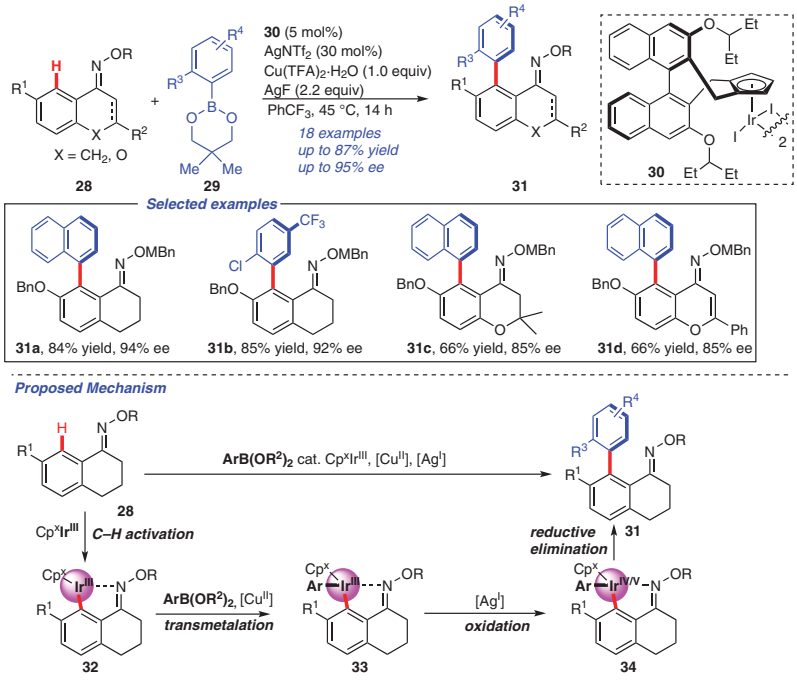
Scheme 3 Pd-catalyzed enantioselective synthesis of axially chiral styrenes



Scheme 4 BOCpRh(III)-catalyzed asymmetric C(sp^2)–H arylation of benzo[*h*]quinolines

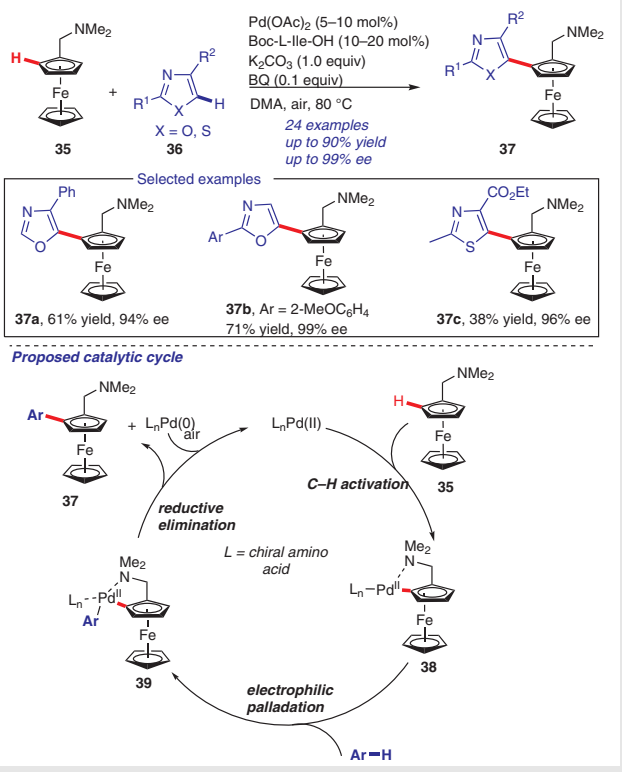
alyzed C(sp^2)–H activation of benzo[*h*]quinolines with 1-diazonaphthoquinones took place via an electrophilic process. Initial rate kinetic isotope studies (k_H/k_D = 1.1:1) indicated that C–H activation might not be involved in the rate-determining step.

In 2021, Cramer and Woźniak developed a highly atropo-enantioselective directing C(sp^2)–H arylation of oximes **28** derived from α-tetralones with arylboronic esters **29** in the presence of an Ir(III) catalyst with fine-tuned disubstituted chiral Cp^x ligands (Scheme 5).[17] A variety of aryl-



Scheme 5 Atropo-enantioselective oxidation-enabled Ir-catalyzed C(sp^2)–H arylation

boronic esters were smoothly converted into their corresponding products **31** in good yields and excellent enantioselectivities. This methodology provided an efficient access to unexplored axially chiral oxime-derived α-tetralones, as well as chromanone and flavone products. According to related reports, this Ir(III)-catalyzed C(sp^2)–H arylation is enabled by oxidatively promoted reductive elimination from high-valent cyclometalated Ir species **34**, which is afforded by C(sp^2)–H activation of the oxime, transmetalation with an arylboronic ester, and subsequent oxidation. Oxidation-induced reductive elimination would be an effective strategy for the transition-metal-catalyzed asymmetric C–H activation.



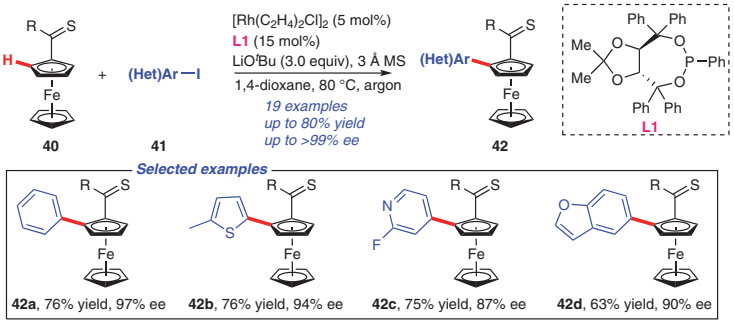
Scheme 6 Pd(II)-catalyzed enantioselective oxidative C–H/C–H cross-coupling reaction between ferrocenes and azole derivatives

2.2 Chelation-Assisted Asymmetric C(sp^2)–H Arylation for the Construction of Planar Chiral Compounds

In 2019, the You group achieved the Pd(II)-catalyzed amine-directed enantioselective oxidative C–H/C–H cross-coupling reactions of [(dialkylamino)methyl]ferrocenes **35** with oxazole or thiazole derivatives **36** (Scheme 6).[18] The reaction was carried out with a monoprotected chiral amino acid as a ligand and air as the oxidant. This method first used electron-deficient heteroarenes as coupling partners in asymmetric C(sp^2)–H activation and offered a powerful strategy for the highly enantioselective construction of planar chiral ferrocenes. A possible catalytic cycle was proposed (Scheme 6). A Pd(II) catalyst containing the chiral amino acid ligand undergoes an enantioselective C(sp^2)–H bond cleavage with ferrocene **35** to generate chiral Pd(II) intermediate **38**, which is converted into intermediate **39** via an electrophilic palladation of the electron-deficient azole derivative. Subsequently, reductive elimination affords planar chiral ferrocene products **37**. Meanwhile, the released Pd(0) is oxidized by air to generate Pd(II) species for the next catalytic cycle.

Also in 2019, the You group reported a Rh(I)-catalyzed thioketone-directed enantioselective C(sp^2)–H arylation of ferrocenes (Scheme 7).[19] The reaction of various aryl iodides with ferrocenyl thioketones **40** all proceeded well to provide the planar chiral ferrocenes **42** with excellent enantioselectivity in the presence of a Rh(I) catalyst derived from $[Rh(C_2H_4)_2Cl]_2$ and a TADDOL-based chiral phosphonite ligand. Heteroaryl iodides were also compatible with this catalytic system to afford heteroaryl-substituted ferrocenes in good yields with promising enantioselectivity.

In 2020, the You group reported a Rh(I)-catalyzed pyridine-assisted asymmetric C(sp^2)–H arylation of ferrocenes **43** with readily available aryl halides (Scheme 8).[20] This methodology showed excellent levels of monoarylation selectivity and enantioselectivity and high catalytic efficien-

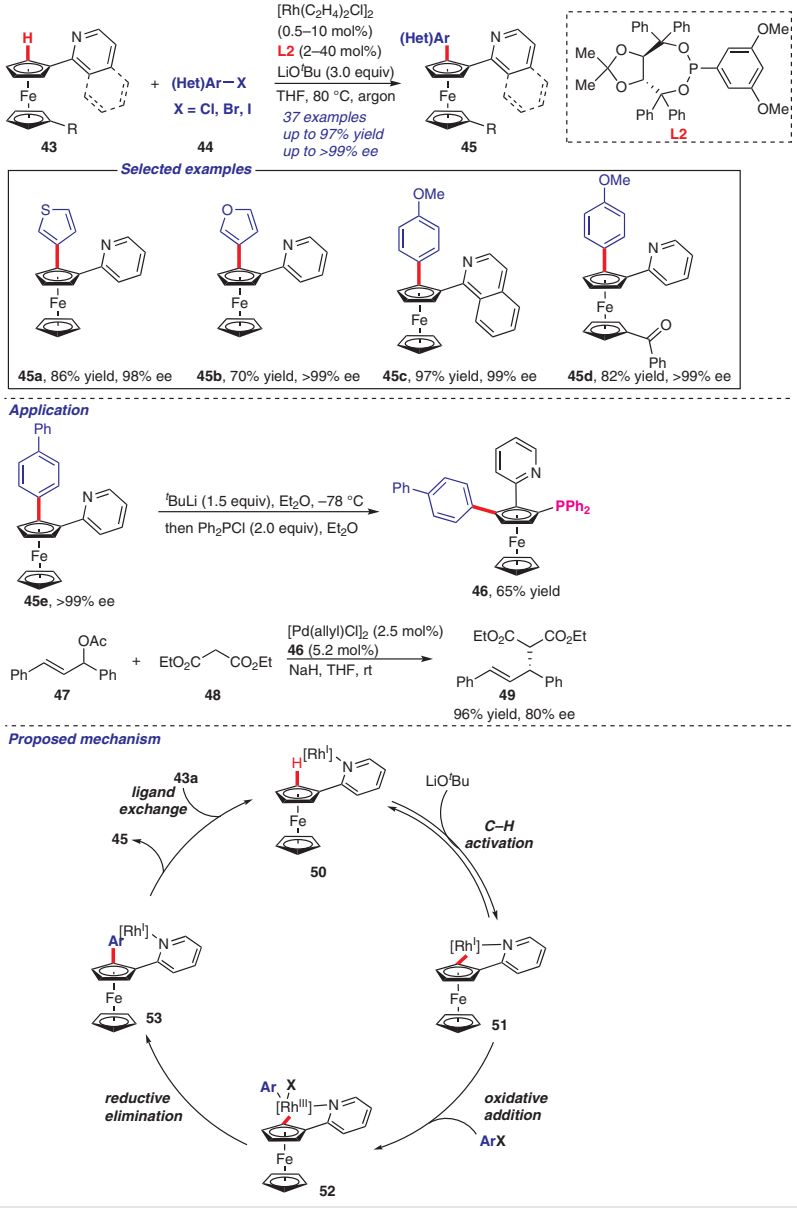


Scheme 7 Thioketone-directed Rh(I)-catalyzed enantioselective C(sp^2)–H arylation of ferrocenes

cy. The low catalyst loading (down to 1 mol% based on [Rh]) greatly improved the practicality of the reaction. Regrettably, the directing group could not be removed and only used the nitrogen atom of pyridine ring to coordinate with metal catalyst. Product **45e** underwent a one-step reaction to afford a chiral bidentate *P,N*-ligand **46** that was utilized as an efficient ligand in a Pd-catalyzed allylic alkylation reaction. A possible catalytic cycle was proposed (Scheme 8). Initially, Rh(I) catalyst and chiral ligand coordinate to the N atom of the pyridine directing group moiety in ferrocene **43a** to afford complex **50**, which undergoes a reversible cyclometalation through a *tert*-butoxide-assisted deprotonation to deliver cyclometalated Rh(I) intermediate **51**. Then, the oxidative addition of aryl halide to intermediate **51** forms Rh(III) species **52**. Subsequently, reductive elimination provides the desired planar chiral ferrocene product **45**. Meanwhile, the Rh(I) catalyst is released via ligand exchange with substrate **43a** to accomplish the catalytic cycle.

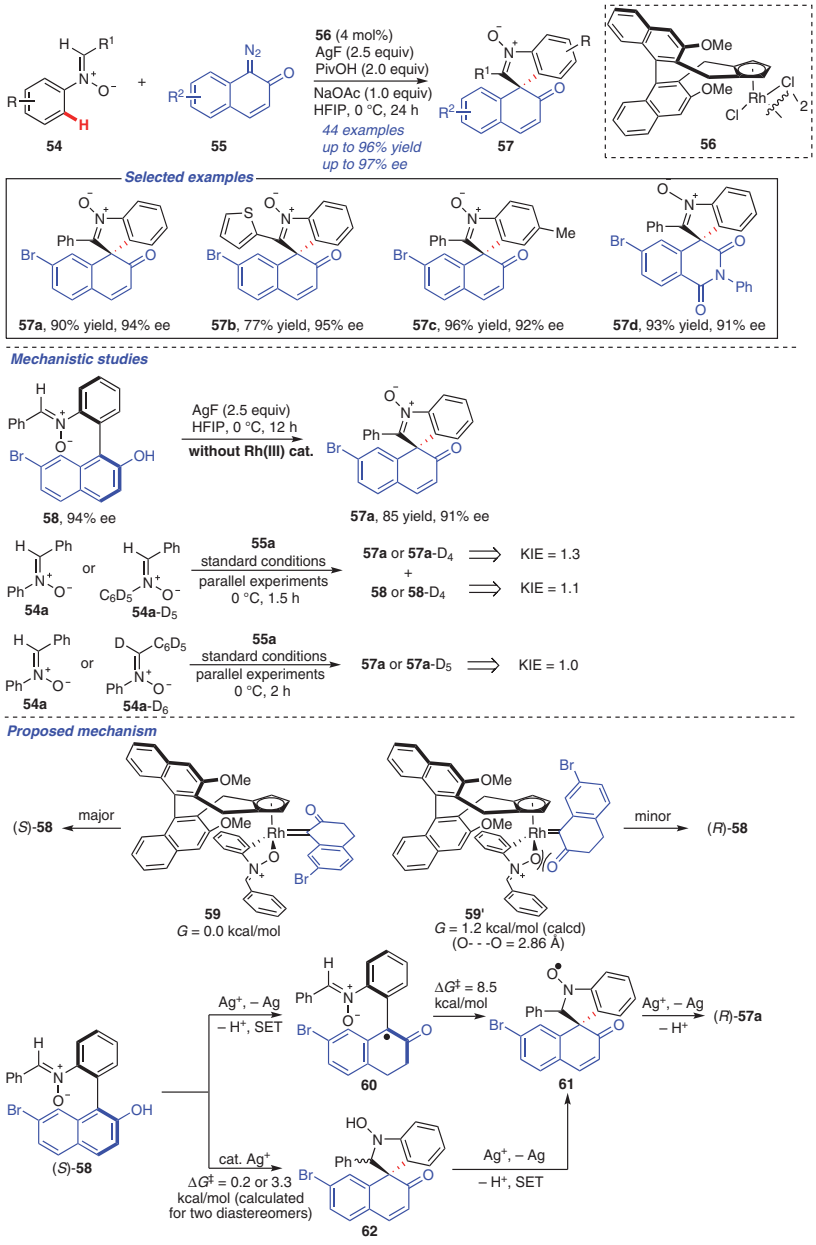
2.3 Chelation-Assisted Asymmetric C(sp²)–H Arylation and Axial-to-Central Chirality Transfer for the Construction of Spirocycles

In 2020, Li and co-workers described a Rh(III)-catalyzed enantioselective spiroannulative synthesis of nitrones **57** bearing an all-carbon quaternary center (Scheme 9).[21] A se-



Scheme 8 Rh-catalyzed pyridine-assisted C(sp²)–H arylation of ferrocenes

ries of nitrones and 1-diazonaphthoquinones (quinone diazides) were transformed into the desired chiral spirocycles in excellent yields and high enantioselectivities. The coupling reaction proceeded via C(sp^2)–H arylation to give an atropomerically metastable biaryl, followed by intramolecular dearomative trapping under oxidative conditions with high chiral controlling. The strategy of axial-to-central chirality transfer provided a novel thinking to construct a chiral carbon center. Several kinetic isotope effects were measured by parallel reactions. KIE values with respect to the biaryl intermediate (1.1) and the final spirocyclic products (1.3) both suggest C(aryl)–H activation is not the rate-determining step. In addition, a mechanism for the coupling was proposed (Scheme 9). Nitrone **54a** undergoes cyclorhodation to afford a rhodacyclic intermediate, in which the *N*-arene ring (less hindered) is oriented backward to minimize steric interactions. The diazo reagent approaches with the C=O group of the nitrone distal to the nitrone functionality (**59**), affording the major (*S*)-**58** intermediate. Otherwise, the C=O···O repulsion in **59′** raises the ground-state energy. Intermediate **58** may go through SET oxidation to deliver a radical intermediate **60**, which readily generates a stable

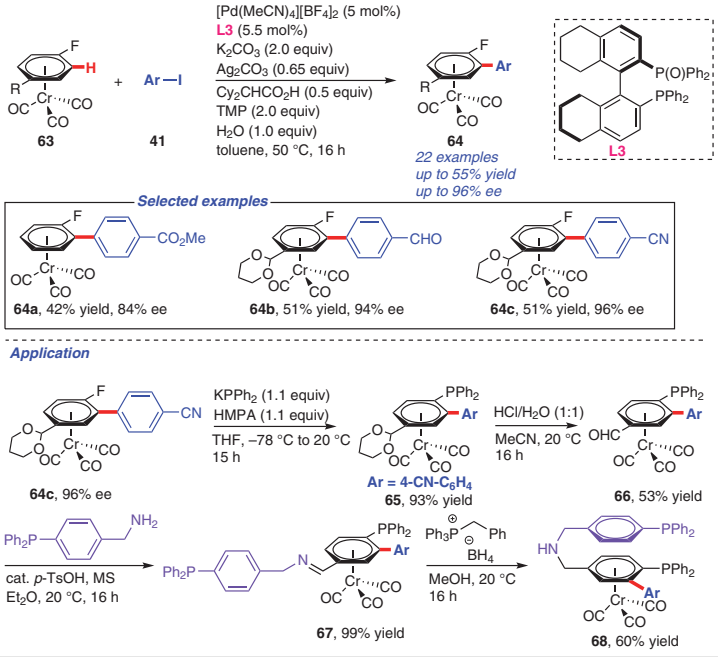


Scheme 9 Rh(III)-catalyzed asymmetric access to spirocycles through C(sp^2)–H activation and axial-to-central chirality transfer

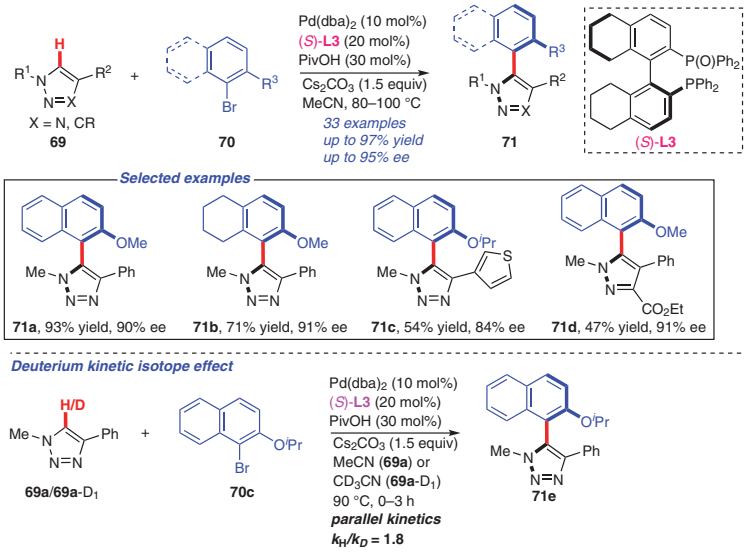
nitroxide radical **61** via radical cyclization with the nitrone. Subsequent, further SET oxidation steps furnish the final spirocyclic nitrone with dearomatization of the naphthol species. However, the pathway of cyclization-SET oxidation cannot be ruled out considering that the cyclization of **58** to **62** is calculated to be slightly uphill (0.2 and 3.3 kcal mol^{-1} for two diastereomers).

2.4 Other Asymmetric C(sp^2)–H Arylation Reactions

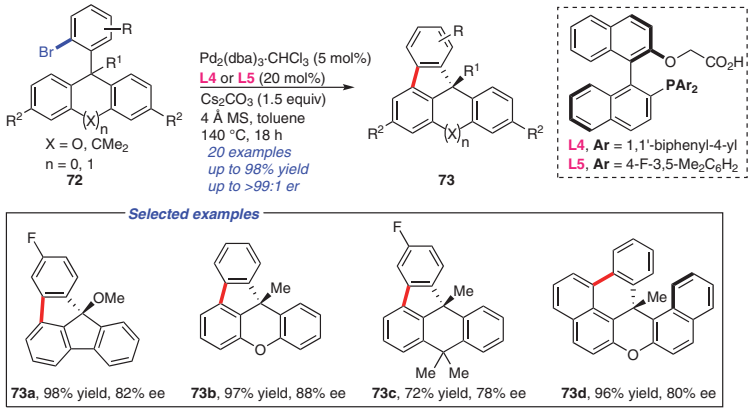
In 2019, Larrosa and co-workers developed a Pd(II)/Ag(I)-catalyzed enantioselective C(sp^2)–H arylation of (η^6-arene)chromiumtricarbonyl complexes **63** in the presence of H_8-BINAP(O) ligand **L3** (Scheme 10).[22] Under the optimized catalytic conditions, a series of iodoarenes



Scheme 10 Pd(II)/Ag(I)-catalyzed asymmetric C(sp^2)–H arylation of (η^6-arene)chromium complexes and its application



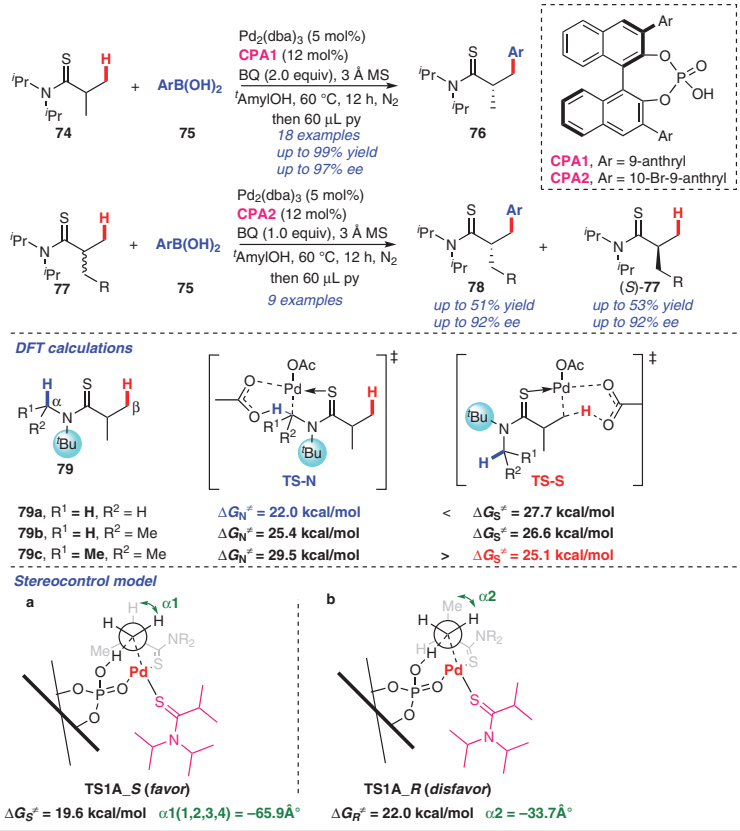
Scheme 11 Pd(0)-catalyzed atropo-enantioselective C(sp^2)–H arylation of heteroarenes



Scheme 12 Enantioselective Pd(0)-catalyzed C(sp^2)–H arylation for the synthesis of chiral warped molecules

and (fluoroarene)$Cr(CO)_3$ complexes were converted into enantioenriched planar chiral products **64** in moderate yields and excellent enantioselectivity. This methodology achieved regioselective arylation of the fluorinated arene moiety in chromium complex **63** without using a directing group. Mechanistic studies suggested that the C(sp^2)–H activation is carried out by the silver catalyst. In addition, the enantioenriched aryl complexes **64c** were transformed into a new class of chiral planar bidentate phosphines **68** in four steps.

In 2020, Baudoin, Cramer, and co-workers reported a Pd-catalyzed atropo-enantioselective C(sp^2)–H arylation of heteroarenes **69** with aryl bromides **70** (Scheme 11).[23] The Pd(0) catalyst equipped with H_8-BINAPO (*S*)-**L3** as a chiral ligand enabled the arylation of a broad range of 1,2,3-triazoles and pyrazoles in excellent yields and enantioselectiv-



Scheme 13 Pd-catalyzed enantioselective β-C(sp^3)–H arylation of thioamides

ity. This method utilized catalytic C–H/C–X cross-coupling to construct a chiral axis between the naphthalene ring and substituted heteroarene. Independent experiments provided a k_H/k_D value of 1.8, which indicates that the C–H bond cleavage of the heteroarene is the rate-limiting step. Moreover, the effect of the ligand dihedral angle on the enantioselectivity tended to show that reductive elimination is the enantiodetermining step of the reaction.

In 2021, Baudoin and Savary reported an enantioselective intramolecular Pd-catalyzed C(sp^2)–H arylation protocol for the synthesis of chiral fluoradenes and other warped molecules (Scheme 12).[24] Chiral bifunctional phosphine-carboxylate ligands played an important role in the enantiodetermining C(sp^2)–H activation step. A series of chiral polycyclic compounds **73** were afforded in high yields and with good to excellent enantioselectivities. This methodology provided an effective route to synthesize chiral fluoradenes and other warped molecules.

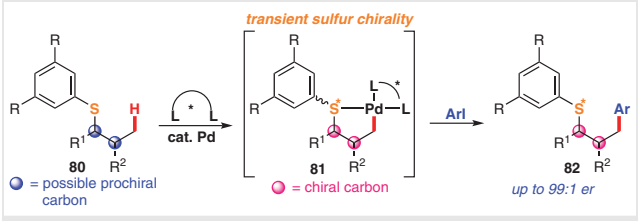
3 Transition-Metal-Catalyzed Asymmetric C(sp^3)–H Arylation

Recently, transition-metal-catalyzed asymmetric C(sp^3)–H functionalization has been widely developed to construct chiral carbon centers.[10b,d] These reactions are achieved by two main strategies including desymmetrizing C(sp^3)–H activation and transition-metal-complex recognition of enantiotopic methylene C(sp^3)–H bonds. In this short review, we will discuss the recent progress on catalytic asymmetric C(sp^3)–H arylation reactions from three aspects involving (i) chelation-assisted enantioselective C(sp^3)–H arylation through desymmetrization, (ii) chelation-assisted enantioselective methylene C(sp^3)–H arylation, and (iii) other asymmetric C(sp^3)–H arylation reactions.

3.1 Chelation-Assisted Enantioselective C(sp^3)–H Arylation through Desymmetrization

In 2020, Gong, Zhang, and co-workers developed an efficiently enantioselective β-C(sp^3)–H arylation of thioamides with a chiral phosphoric acid as a chiral auxiliary (Scheme 13).[25] Besides, the kinetic resolution of unsymmetrical thioamides **77** via intermolecular C(sp^3)–H arylation was achieved. Density-functional theory (DFT) calculations suggested that an increase in steric hindrance at the α-position of the amide nitrogen (**79a–c**) led to considerably higher activation barrier ($\Delta G_N^{\neq}$) of α-nitrogen C(sp^3)–H activation, via **TS-N**, and a comparable C(sp^3)–H activation barrier at the β-position of the thioamide, via **TS-S** ($\Delta G_S^{\neq}$). The regioselective C(sp^3)–H cleavage was accomplished by the employment of a bulky diisopropylamine auxiliary in the thioamide to get more favorable transition state **TS-S**. This methodology provided an effective way to elucidate the regioselectivity of C(sp^3)–H activation. To explore the origin of the enantioselectivity, they calculated diastereomers of the transition states, which revealed that **TS1A_S** delivering the *S*-configured product is 2.4 kcal mol^{-1} lower in energy than **TS1A_R** yielding the *R*-configured product. These studies indicated that stereocontrol was achieved by embedding the substrate in a robust chiral cavity defined by the bulky CPA and a neutral thioamide ligand.

In 2021, the Yu group reported a mechanistic study of the enantioselective Pd(II)-catalyzed C(sp^3)–H arylation of aryl alkyl (pentan-3-yl or isobutyl) thioethers for the construction of α- and β-chiral centers (Scheme 14).[26] A mechanistic quantitative structure-selectivity relationship study described disparate responses for α- and β-desymmetrization processes to the influence of the size of ligand and directing group substitution. This method illustrated the utility of an unconventional transient chirality of sulfur(II) in enantioselective catalysis.



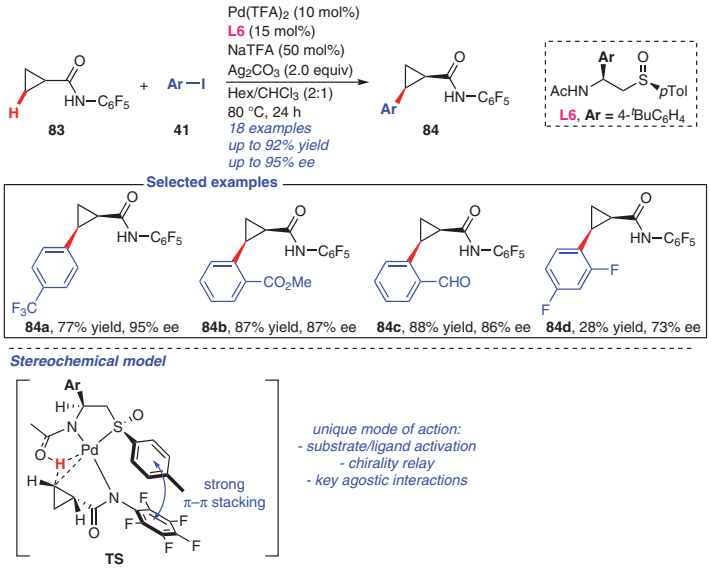
Scheme 14 Pd-catalyzed enantioselective C(sp^3)–H arylation of aryl alkyl thioethers

3.2 Chelation-Assisted Enantioselective Methylene C(sp^3)–H Arylation

Transition-metal-catalyzed asymmetric methylene C(sp^3)–H activation is a synthetic challenge due to the much lower reactivity compared with the methyl C(sp^3)–H bond, and is always achieved with the assistance of a chiral auxiliary to lower activation energy.[10b] In this part, we will discuss the recent progress on chelation-assisted enantioselective methyl C(sp^3)–H arylation involving traditional directing group assisted and chiral transient directing group assisted strategies.

3.2.1 Traditional Directing Group Assisted Enantioselective Methylene C(sp^3)–H Arylation

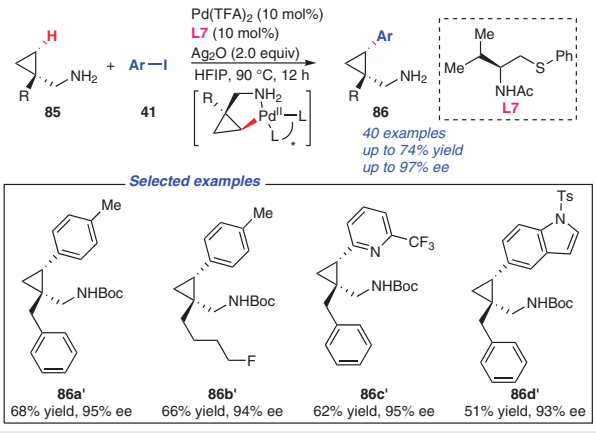
In 2019, Wencel-Delord, Colobert, and co-workers described a Pd(II)-catalyzed asymmetric C(sp^3)–H arylation of cyclopropanecarboxylic acid derivatives **83** with easily-accessible *N*-protected amino sulfoxides **L6** as a new chiral ligand (Scheme 15).[27] A variety of aryl iodides proceeded well to afford the desired products in good yields and enantioselectivities. This method developed a new chiral amino sulfoxide ligand to accomplish C(sp^3)–H arylation of continually explored cyclopropane derivatives. Preliminary mechanistic studies revealed a unique action mode for this reac-



Scheme 15 Pd/amino sulfoxide-catalyzed asymmetric C(sp^3)–H arylation of cyclopropanecarboxylic acid derivatives

tion, including key noncovalent interactions between the chiral Pd(II) complex and the substrate to stabilize agostic M–H–C interactions and π-stacking ligand-substrate bonding. DFT investigations suggested that this unusual ligand/substrate activation made the cleavage of the C(sp^3)–H bond to be virtually barrier-less.

In 2020, the Yu group reported a Pd(II)-catalyzed asymmetric C(sp^3)–H arylation of free aliphatic amines, cyclopropylmethylamines, **85** enabled by a chiral bidentate thioether ligand **L7** (Scheme 16).[28] The reaction utilized the free amine as a directing group rather than an in situ formed transient directing group. The privileged bidentate coordination and thioether motif of this ligand favored the formation of the requisite mono(amine)–Pd(II) intermediate to achieve the enantioselective C(sp^3)–H arylation. A series of

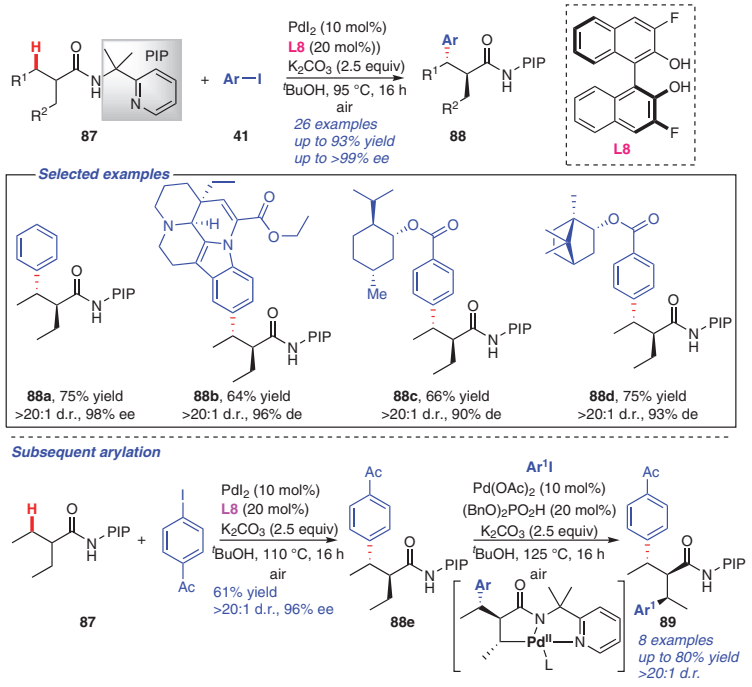


Scheme 16 Pd(II)-catalyzed asymmetric C(sp^3)–H arylation of cyclopropylmethylamines

cyclopropylmethylamines and aryl iodides were converted into the desired arylation products **86** in moderate to good yields and excellent enantioselectivity. This method provided a convenient route to chiral γ-(hetero)aryl-free amines without installing exogenous directing groups.

Also in 2020, the Shi group described a protocol for the construction of acyclic aliphatic amides with α,β-contiguous stereogenic centers by Pd(II)-catalyzed enantioselective methylene C(sp^3)–H arylation in good yields and with high levels of enantio-, chemo-, and diastereoselectivity (Scheme 17).[29] This method utilized the readily available 3,3′-F_2-BINOL ligand **L8** to effectively distinguish four chemically identical β-methylene C(sp^3)–H groups and control selective monoarylation. Chiral aliphatic amides bearing three contiguous stereogenic centers could be provided by sequential arylation using two distinct procedures. Chiral β-arylation product **88e** reacted well with $Pd(OAc)_2$ to deliver a chiral palladacycle intermediate without the addition of a chiral ligand. This methodology provided a versatile platform for constructing α,β-chiral centers in asymmetric synthesis.

In 2021, the Shi group developed a Pd(II)-catalyzed chelation-assisted asymmetric intramolecular methylene C(sp^3)–H arylation to construct chiral benzo-ring containing compounds in good yields and high ee values (Scheme 18a).[30] The choice of non-C_2-symmetric chiral phosphoric acid (CPA) ligand was crucial for the reaction to obtain high reactivity and enantioselectivity. Also in 2021, the same group reported an enantioselective β-C(sp^3)–H arylation of acyclic aliphatic amides using the aforementioned palladium system but with chiral 3,3′-F_2-BINOL ligand **L8** (Scheme 18b).[31] A range of aliphatic amides and aryl iodides were

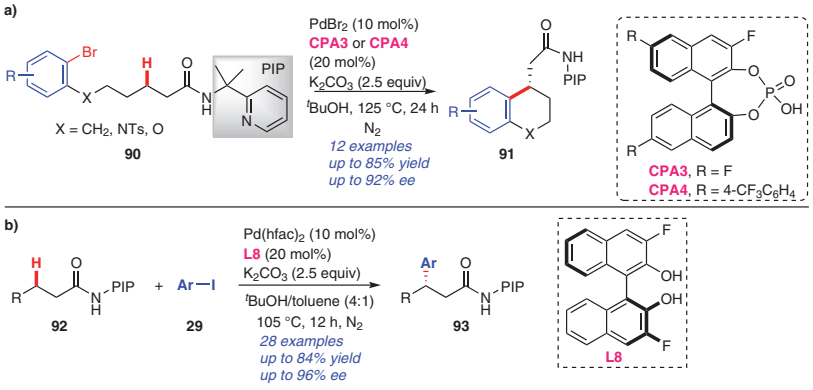


Scheme 17 Pd(II)-catalyzed asymmetric methylene C(sp^3)–H arylation of acyclic aliphatic amides

compatible with the reaction conditions to deliver the desired arylated products in high enantioselectivities.

3.2.2 Chiral Transient Directing Group Assisted Enantioselective Methylene C(sp^3)–H Arylation

In 2020, the Yu group developed a Pd(II)-catalyzed enantioselective β-C(sp^3)–H arylation of aliphatic ketones **94** using an α-amino acid derivative as a chiral transient directing group (Scheme 19).[32] This method utilized electron-deficient 3-nitro-5-(trifluoromethyl)-2-pyridone (**L9**) as an effective ligand and acetate surrogate to enable C(sp^3)–H bond cleavage in the transient directing strategy. Deuterium incorporation experiments with **94a** under the standard conditions with different silver salts in the presence of TFA-*d* and HFIP-ol-*d* suggested the irreversible C–H cleavage was the rate-limiting step with AgTFA, and reversible C–H cleavage was not the rate-limiting step with Ag_3PO_4. The abstraction of iodide might be rate-limiting step for the reaction with Ag_3PO_4 as base. It means that the combination of an electron-deficient 2-pyridone ligand with the silver salts provided an efficient controlling on the rate-limiting steps, which afforded the high yield and enantioselectivity for this reaction. Investigating the effect of the anion on the reaction mechanism could facilitate the exploration and optimization of other asymmetric C(sp^3)–H activations.



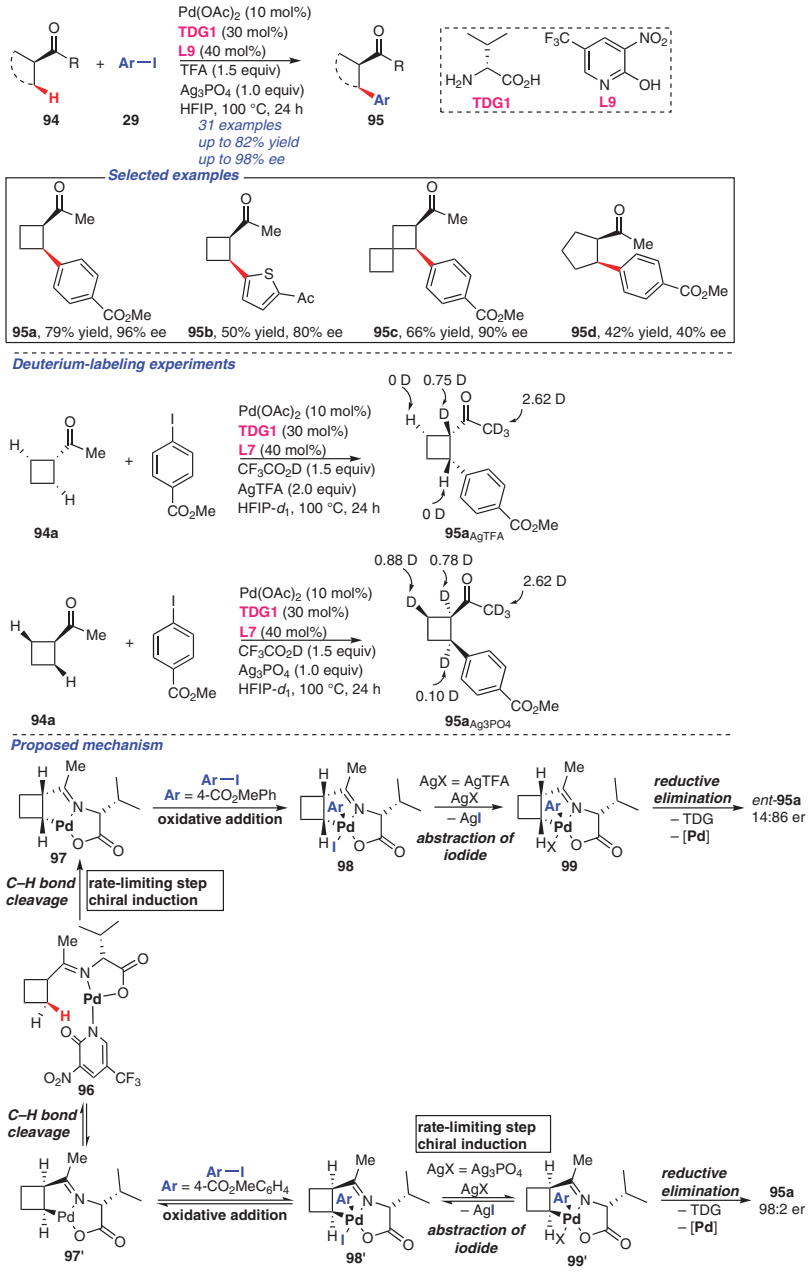
Scheme 18 Pd(II)-catalyzed asymmetric methylene C(sp^3)–H arylation

3.3 Other Asymmetric C(sp³)–H Arylations

Except for the aforementioned transition-metal-catalyzed chelation-assisted asymmetric methyl or methylene C(sp³)–H arylation, radical-type and intramolecular enantioselective C(sp³)–H arylation can also be used to construct chiral carbon centers. So far, there are rare examples on catalytic radical-type asymmetric C(sp³)–H arylation reactions, which were accomplished by key radical addition of chiral aryl metal intermediates with an alkyl radical. In this part, we will discuss catalytic radical-type and intramolecular asymmetric C(sp³)–H arylation.

3.3.1 Catalytic Radical-Type Asymmetric C(sp³)–H Arylation

In 2019, Liu and co-workers reported a copper/bisoxazoline (Box)-catalyzed asymmetric benzylic C(sp³)–H arylation by radical relay using alkylarenes **100** as limiting reagents (Scheme 20).[33] The introduction of a benzyl ester



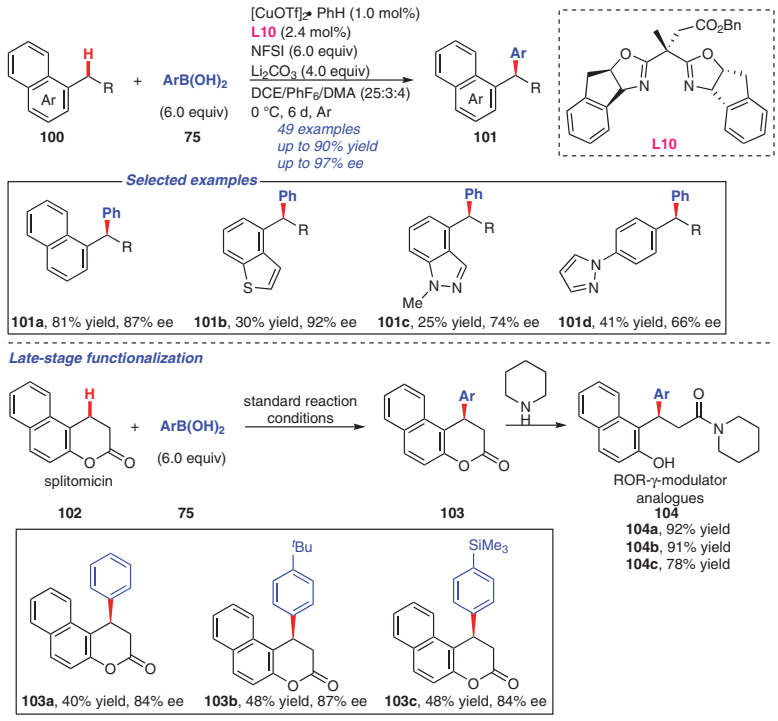
Scheme 19 Pd-catalyzed asymmetric C(sp³)–H arylation of cyclobutyl ketones

moiety onto the bisoxazoline ligands **L10** favored the enhancement of chemo- and enantioselectivity for enantioselective arylation. This method provided an efficient and straightforward approach to construct a series of chiral 1,1-diarylalkanes **101** with good to excellent enantioselectivities. The late-stage asymmetric arylation of splitomicin was successfully achieved by using this methodology to deliver various arylated products in moderate yields with good enantioselectivities. Regrettably, the reaction needed to use large loading of arylboronic acid (6.0 equiv) and long reaction times (6 days). This methodology still opened an access to explore radical-type asymmetric C(sp^3)–H activation.

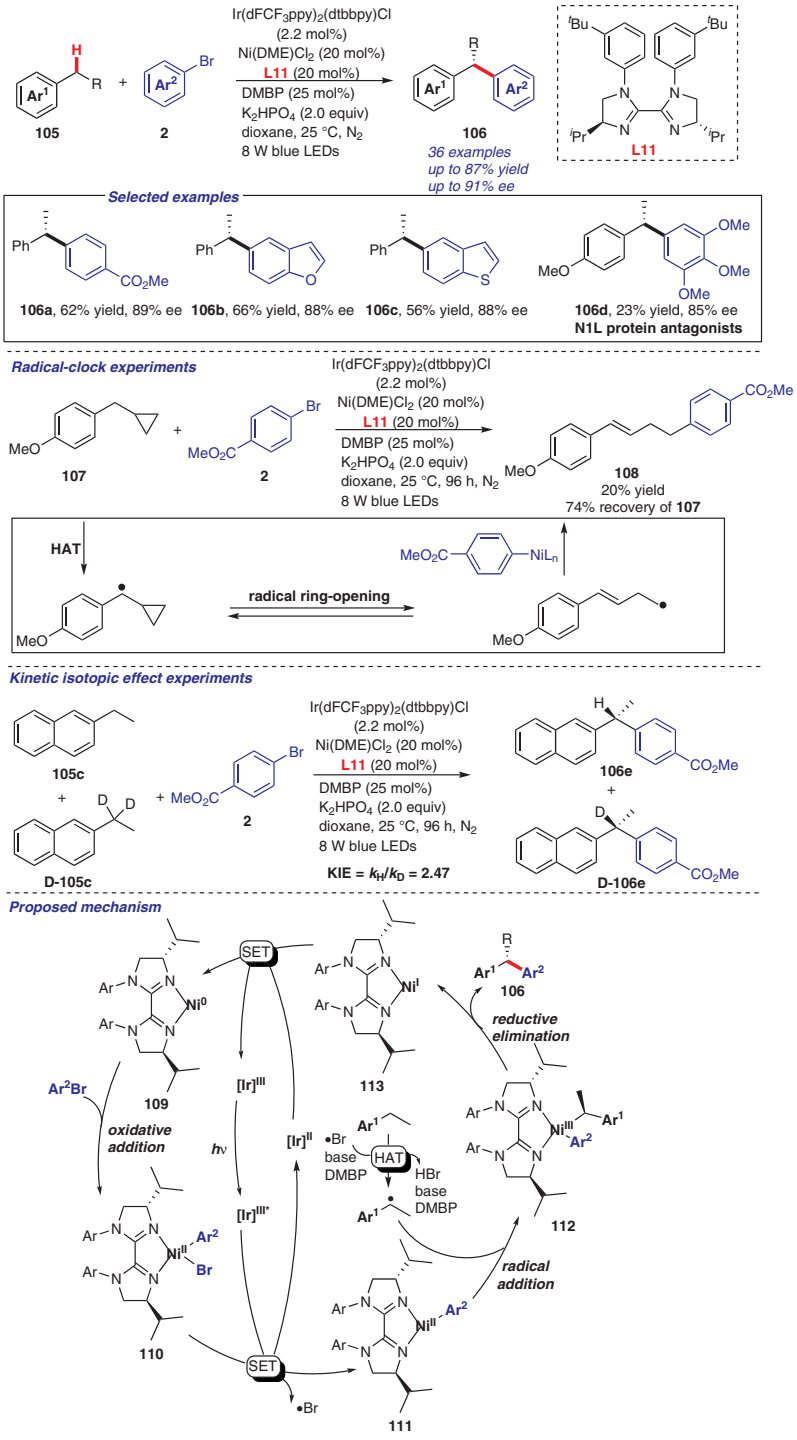
Also in 2019, the Lu group developed an enantioselective benzylic C(sp^3)–H arylation of alkylarenes with aryl bromides via photoredox/nickel dual catalysis (Scheme 21).[34] A series of chiral 1,1-diarylalkanes were obtained with a good level of enantioselectivity using novel chiral biimidazoline (BiIM) ligand **L11**. The utilization of photoredox conditions avoided the use of any additional single-electron oxidant or reductant. A radical-clock experiment was carried out with 1-(cyclopropylmethyl)-4-methoxybenzene (**107**) and methyl 4-bromobenzoate to afford the desired product **108** in 20% yield via a radical ring-opening process followed by an irreversible capture by nickel species, which strengthened the possibility of a radical pathway. Kinetic isotope effect (KIE) experiments indicated that H-atom abstraction might be the turnover limiting step. The proposed mechanism is shown in Scheme 21. Oxidative addition of nickel(0) catalyst **109** with chiral BiIM ligand with aryl bromide occurs to afford aryl-Ni(II) bromide species **110**, which undergoes visible-light-induced single-electron oxidation to deliver aryl-Ni(II) intermediate **111** and an active bromine radical. Then radical addition of intermediate **111** with a benzylic radical, formed by the bromine free radical, DMBP, and alkylbenzene, provides Ni(III) complex **112**. Finally, the reductive elimination of intermediate **112** affords the chiral 1,1-diarylalkane **106** and Ni(I) complex **113**, which undergoes single-electron reduction by Ir(II) species to regenerate Ni(0) species **109** and photocatalyst Ir(III) complex. The combination of transition-metal catalysis and photoredox catalysis afforded an effective pathway to achieve radical-type asymmetric C(sp^3)–H activation.

3.3.2 Catalytic Intramolecular Asymmetric C(sp^3)–H Arylation

In 2020, Duan and co-workers reported a Pd-catalyzed asymmetric intramolecular C(sp^3)–H arylation of *N*-(*o*-Br-aryl)anilides **114** to construct quaternary α-nitro amides **115** (Scheme 22).[35] This method was significantly affected by the electronic properties of α-substituent groups. Only α-nitro amides could deliver the corresponding products in good yields and excellent enantioselectivity. In 2021, Baudoin and co-workers described a palladium-catalyzed enantioselective intramolecular arylation of enantiotopic

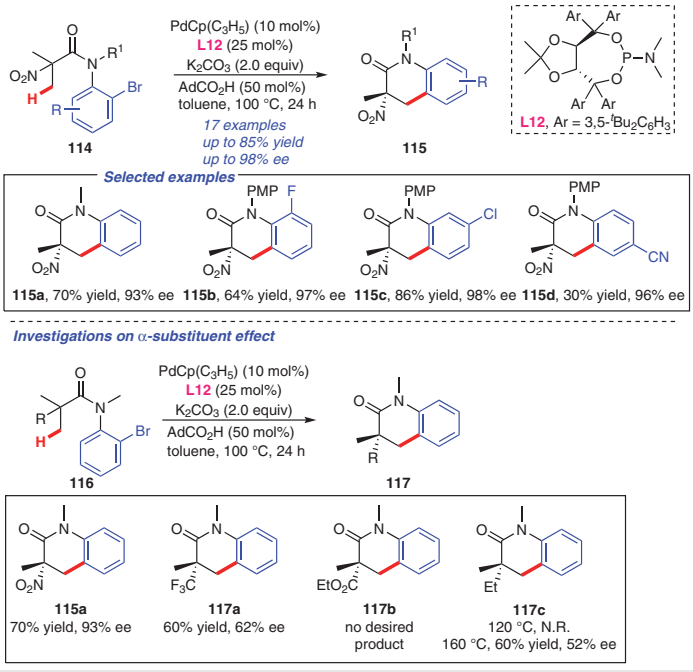


Scheme 20 Cu-catalyzed enantioselective arylation of benzylic C(sp^3)–H bonds



Scheme 21 Nickel/photoredox-catalyzed asymmetric benzylic C(sp^3)–H arylation

secondary C–H bonds in the presence of the IBiox family of NHC ligands (Scheme 23).[36] This intramolecular asymmetric C(sp^3)–H arylation only explored the reactivity and enantioselectivity of malonic esters. Analysis of the steric maps of the IBiox ligands indicated chiral C_2-symmetric IBiox ligands having the difference between the two most occupied and the two less occupied space quadrants, led to indane products containing a tertiary stereocenter with

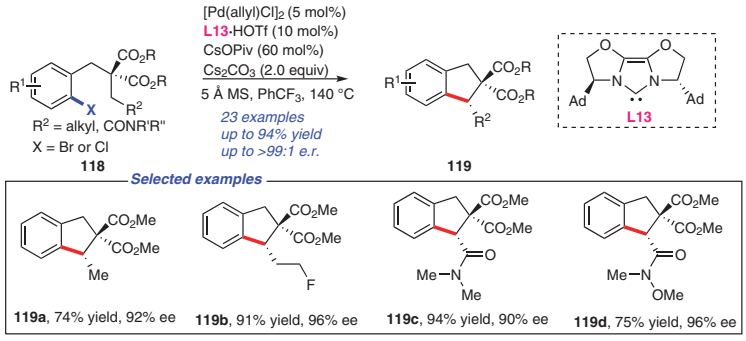


Scheme 22 Pd-catalyzed asymmetric intramolecular C(sp^3)–H arylation

high enantioselectivities. Parallel kinetic experiments suggested that the C(sp^3)–H activation was the turnover-limiting step.

4 Conclusion and Outlook

In this short review, we have described recent advances in transition-metal-catalyzed asymmetric C(sp^2)–H and C(sp^3)–H arylation reactions. The appropriate combination of chiral ligand and transition metal provide a candid way to construct numerously important enantioenriched aryl-substituted atropisomer, planar chiral, and central chiral molecules. However, these catalytic enantioselective C–H arylation reactions heavily rely on using palladium or rhodium catalysts with aryl halides, boron, or diazo derivatives as arylation reagents. Therefore, there are still a series of unsettled scientific issues regarding the transition-metal-catalyzed asymmetric C–H arylation reactions that need to be explored from the following aspects, including (i) developing novel catalyst system with low-cost and earth-abundant metals and suitable chiral ligands to achieve enantioselective C–H arylation utilizing other arylation reagents such as phenol derivatives, (ii) exploring effective strategies to accomplish transition-metal-catalyzed asymmetric C–H arylation via a radical mechanism, and (iii) bringing out the developed methodology from the laboratory to industrial applications. It is strongly believed that significant research efforts with innovative strategies in transition-metal-catalyzed asymmetric C–H arylation will continue to be reported in the future.



Scheme 23 Pd-catalyzed enantioselective intramolecular arylation of enantiotopic secondary C–H bonds

Conflict of Interest

The authors declare no conflict of interest.

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