12.05 C—C Bond Formation Through C-H Activation

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12.05.1 Introduction

Carbon-carbon bond forming reactions represent a class of fundamental transformations in synthetic organic chemistry. These transformations play a vital role in organic synthesis, medicinal chemistry, and materials. The 2010 Nobel Prize in chemistry was awarded to Heck, Negishi and Suzuki for their contributions on transition-metal catalyzed carbon-carbon bond formations. Typically, these reactions involve the coupling of an aryl halide or pseudo halide with an organometallic reagent. The requirement for installing a functional group prior to the desired C—C bond formation largely increases the synthetic steps and labor cost. As such, circumventing these issues will not only improve atom economy but also increase the overall efficiency of multistep synthetic sequences.

C—H bonds are ubiquitous in organic molecules. However, C—H bonds are not generally viewed as the viable functional groups owing to their inertness with high bond dissociation energies (BDEs) (>96 kcal/mol).[1] If carbon-carbon bonds could be forged directly by transformation of C—H bonds, similar to these activated C—X (or C—M) bonds, it would represent one of the most valuable and straightforward methods for the synthesis of complex molecules, and offer a distinct retrosynthetic approach (Fig. 1). Compared with conventional coupling reactions, where the reactive organometallic intermediate was generated via C-H activation, this provides a more step-economic and eco-friendly alternative. Therefore, direct catalytic functionalization of C—H bonds has been a highly intriguing research subject for a long time. In recent decades, intensive research efforts have witnessed the development of various transition-metal catalyzed C—H bond functionalizations.

Considering that palladium and rhodium are the most-investigated transition metals in this field, this chapter aims to outline recent representative advances on Pd- and Rh- catalyzed C—C bond formations via C-H direct functionalization. This chapter mainly details the development of C(sp^2)-H and C(sp^3)-H functionalizations according to the types of reactions including C-H arylation, alkenylation, alkylation, alkynylation and annulation. Asymmetric C-H functionalization via a transient carbon–metal species and the applications of C-H functionalization towards the synthesis of structurally complex molecules will also be introduced. However, C—H bond functionalizations through carbene insertion reactions are not included.[2]

Early works on this topic before 2005 have been discussed in the chapter titled "Synthetic Reactions via C—H Bond Activation: C—C and C—E Bond Formation" contributed by Pfeffer and Spencer in Comprehensive Organometallic Chemistry III.[3] Therefore,

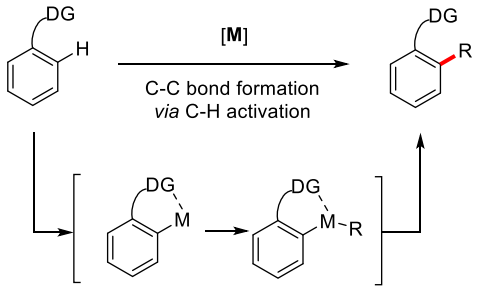


Fig. 1 Carbon-carbon bond formation by C-H activation.

only selected literatures after 2005 will be covered in this chapter. Unfortunately, many important contributions are not included in this chapter for which the authors would like to apologize due to limited space.

12.05.2 Pd-catalyzed C—H bond functionalization

Pd-catalyzed C—H bond functionalization has witnessed significant progress over the past decades. In this field, there are mainly three accepted reaction cycles (Fig. 2): (1) Pd(0)/Pd(II) cycle; (2) Pd(II)/Pd(0) cycle; (3) Pd(II)/Pd(IV) cycle. The first strategy starts with oxidative addition of Pd(0) catalyst to aryl halide (or pseudo halide) to afford an arylpalladium(II) species. Then the C—H bond cleavage may occur via concerted metallation deprotonation (CMD) to generate the Pd(II) intermediate. After reductive elimination, Pd(0) catalyst is regenerated. The overall redox process does not require an external stoichiometric oxidant. In the second strategy, the C—H bond is initially cleaved with Pd(II) catalyst, then transmetallation with an organometallic reagent, and finally reductive elimination gave the C-C coupling product. The released Pd(0) is oxidized by an external oxidant to complete the catalytic cycle. The third strategy involves the generation of Pd(IV) intermediate at the expense of an oxidant after the C—H bond activation.

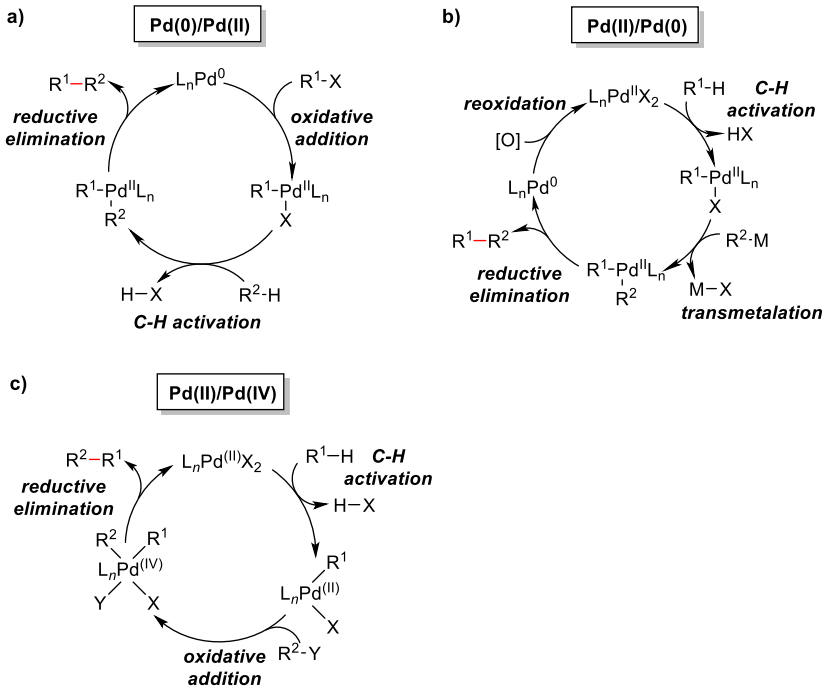
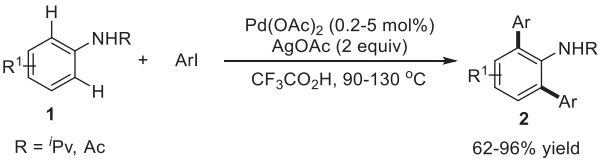


Fig. 2 Catalytic cycles for Pd-catalyzed C-H functionalization, (a) Pd(0)/Pd(II) catalytic cycle, (b) Pd(II)/Pd(0) catalytic cycle, (c) Pd(II)/Pd(IV) catalytic cycle.

12.05.2.1 C—H bond arylation

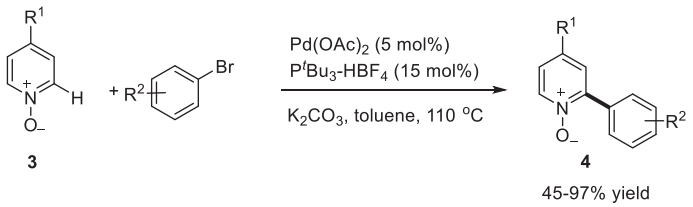
12.05.2.1.1 C(sp^2)—H bond arylation with aryl halides and aryl organometallic reagents

The biaryl subunit is an important structural motif found in a wide range of natural products, polymers, liquid crystals, etc. It is one of the most straightforward platforms to achieve aryl-aryl coupling via C-H direct functionalization. It has been known that specific aromatic compounds and heteroarenes can undergo the C-H arylations with high regioselectivity.[4] Following these pioneering works, significant progresses of C-H arylations have been achieved. In 2005, Daugulis and coworkers developed diarylations of anilides **1** via C-H activation catalyzed by $Pd(OAc)_2$ (0.2–5 mol%) with aryl iodide in the presence of 2 equivalents of AgOAc in CF_3COOH. This arylation reaction proceeded with very high functional group compatibility and tolerated halogens on the anilide and bromine on the aryl iodide (Scheme 1).[5]



Scheme 1 Pd-catalyzed C-H diarylation of anilides with aryl iodides.

Given the importance of 2-arylpyridines in material and medicinal chemistry, Fagnou and coworkers performed a direct arylation reaction of pyridine *N*-oxides with aryl bromides, providing a wide range of 2-arylpyridines in 45–97% yields with complete regioselectivity. The 2-arylated pyridines **4** could be readily obtained via Pd-catalyzed arylation of pyridine *N*-oxides **3**. This C-H arylation reaction not only improves the synthetic efficiency of 2-arylated pyridines but also avoids the use of unstable 2-pyridyl organometallics (Scheme 2).[6a] The detailed mechanistic studies were investigated by the Hartwig group. They found that

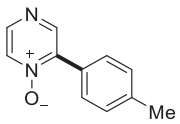
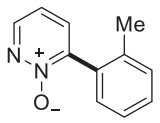
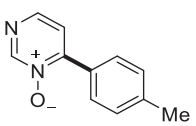


Scheme 2 Pd-catalyzed C-H arylation of pyridine *N*-oxides with aryl bromides.

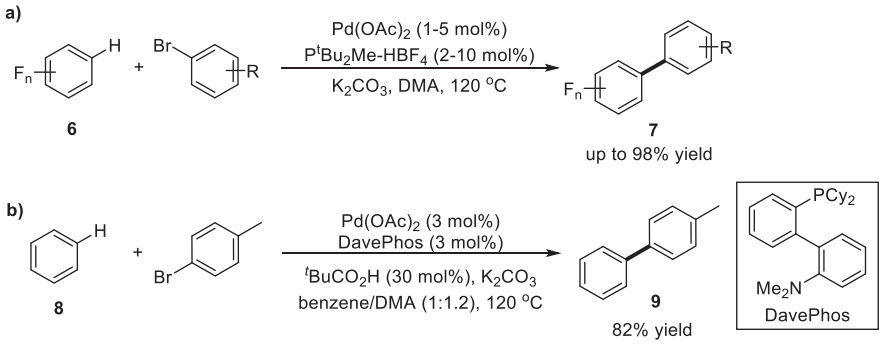
the cyclometalated complex $[Pd(OAc)(^tBu_2PCMe_2\text{-}CH_2)]_2$, generated from decomposition of $(P^tBu_3)Pd(Ar)(OAc)$, was the active catalytic species in this direct arylation of pyridine *N*-oxide.[6b]

This method could be extended to the C-H arylation of diazine *N*-oxides under slightly modified reaction conditions. By replacing toluene with dioxane, the arylations of pyrazine and pyridazine *N*-oxides gave the corresponding cross-coupled products **5** in 75% and 76% yield, respectively (Table 1, entries 1 and 2). Moreover, the addition of 10 mol% CuCN could allow the arylation of pyrimidine *N*-oxide in 61% yield (Table 1, entry 3). Notably, this reaction is compatible with aryl bromides, iodides and chlorides.[7]

Table 1 Pd-catalyzed C-H arylations of diazine *N*-oxides.

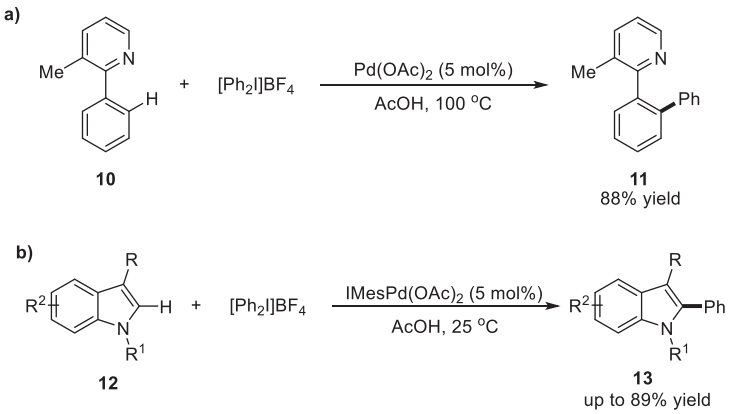
Entry	*Conditions*	*Product (**5**)*	*Yield*
1	Ar-Br $Pd(OAc)_2$ (5 mol%) P^tBu_3-HBF_4 (15 mol%) K_2CO_3 (2 equiv) dioxane, 110 °C		75%
2			76%
3	Ar-Br $Pd(OAc)_2$ (5 mol%) P^tBu_3-HBF_4 (15 mol%) K_2CO_3 (2 equiv) CuCN (10 mol%) dioxane, 110 °C		61%

Electron-deficient arenes were seldom employed for the catalytic C-H arylation until Fagnou and coworkers developed the intermolecular arylation reactions of fluorobenzenes **6** with aryl halides. The key C-H activation step occurs via a concerted metalation-deprotonation (CMD) mechanism, which largely relies on the acidity of the C—H bond (Scheme 3A).[8] Subsequently, the authors developed a direct arylation of benzene in the presence of $Pd(OAc)_2$ and pivalic acid (Scheme 3B). Mechanistic study indicates that the pivalate anion plays a key role in C—H bond cleaving step.[9]



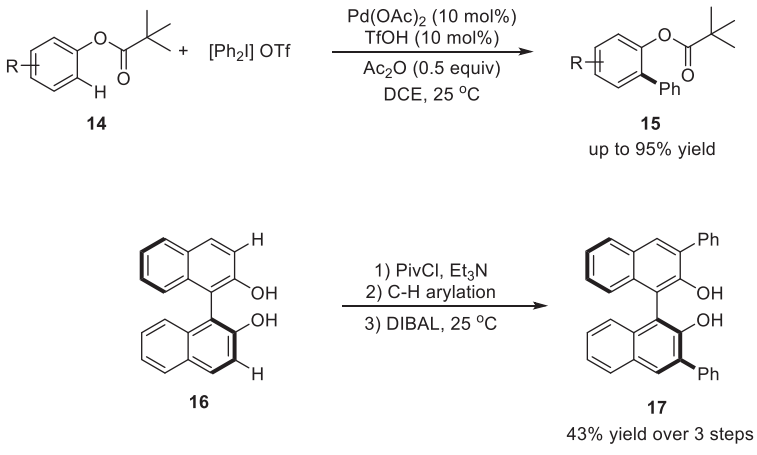
Scheme 3 Pd-catalyzed C-H arylation reactions of fluorobenzenes and benzene.

Sanford and coworkers reported an elegant C-H arylation reaction of 2-phenyl-3-methylpyridine (**10**) with $[Ph_2I]BF_4$, giving the phenylation product **11** in 88% yield. Besides pyridine, quinoline, pyrrolidinone and oxazolidinone are also effective directing groups in this transformation, providing diverse biaryl products. Notably, this reaction does not require the use of extra base or ligand. Preliminary mechanistic experiments more likely support a Pd(II)/(IV) catalytic cycle (Scheme 4A).[10] This method could be extended to C-H 2-arylation of indoles **12** in up to 89% yield. Remarkably, this reaction proceeds well at room temperature (Scheme 4B).[11]



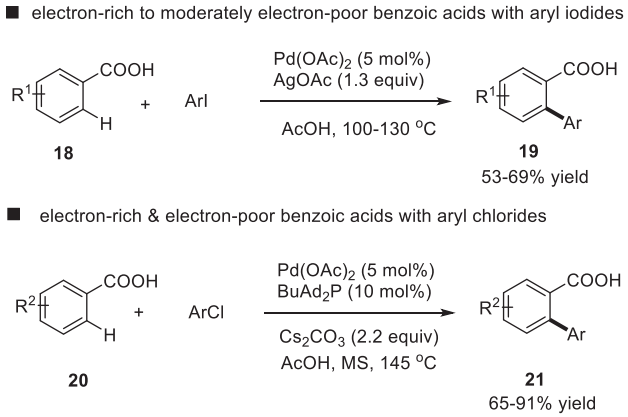
Scheme 4 Pd-catalyzed C-H arylation reactions with $[Ph_2I]BF_4$.

Remarkably, Fu, Liu and coworkers achieved the acyloxy-directed C-H arylation with $[Ph_2I]OTf$ at room temperature, affording *ortho*-arylated products **15** in up to 95% yield. The utility of the reaction was further demonstrated by the synthesis of 3,3′-bisarylated BINOL **17** in 43% yield over three steps (Scheme 5).[12]



Scheme 5 Acyloxy-directed C-H arylation with $[Ph_2I]OTf$.

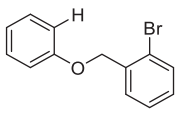
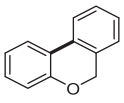
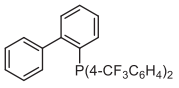
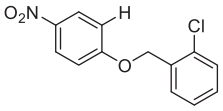
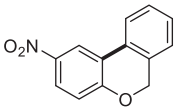
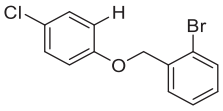
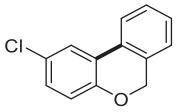
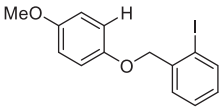
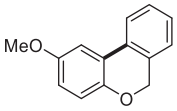
Aryl carboxylic acid is among the abundant chemical feedstocks. Accordingly, their C-H arylations would allow a one-step synthesis of 2-arylbenzoic acid derivatives. In addition, the carboxyl group could be conveniently removed or undergo diverse transformations. In 2007, two methods for direct *ortho*-arylation of benzoic acids were developed by Daugulis and coworkers. The first method for the arylation of electron-rich to moderately electron-poor benzoic acids **18** employed aryl iodide as the aryl reagent. Chloride and bromide substituents on both coupling partners were well tolerated. The second method relied on the use of aryl chloride, cesium carbonate and *n*-butyl-di-1-adamantylphosphine ligand. This reaction was compatible with both electron-rich and electron-poor benzoic acids **20** (Scheme 6).[13]



Scheme 6 Pd-catalyzed *ortho* C-H arylations of benzoic acids.

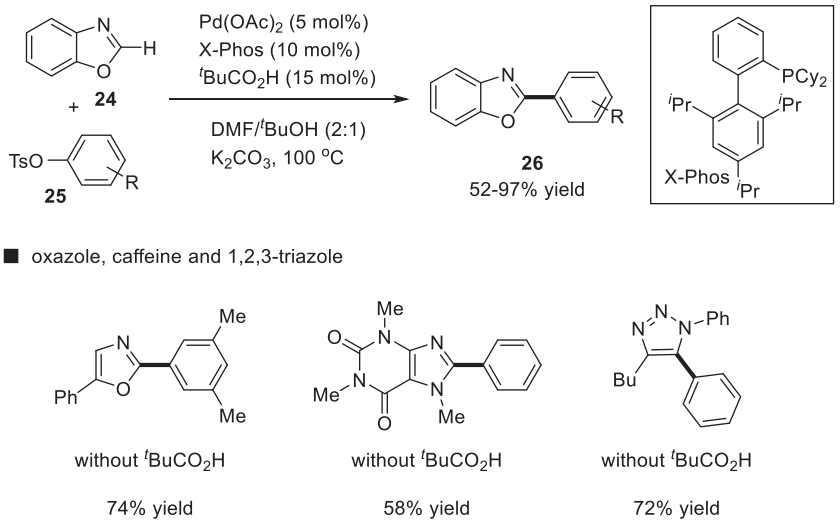
Intramolecular C-H arylations with unactivated arenes suffered from poor selectivity and low catalyst turnover number until Fagnou and coworkers developed a highly efficient catalytic system in 2004. They found that the combination of $Pd(OAc)_2$ and [1,1′-biphenyl]-2-ylbis(4-(trifluoromethyl)phenyl)phosphine could unprecedently enable the intramolecular C-H arylation of bromoarene **22a** with catalyst loading as low as 0.1 mol% (Table 2, entry 1).[14] While they achieved the C-H arylation with aryl

Table 2 Pd-catalyzed intramolecular C-H arylations.

Entry	*Substrate (**22**)*	*Product (**23**)*	*Conditions*	*Yield*	*References*
1	 **22a**	 **23a**	$Pd(OAc)_2$ (0.1 mol%)  (0.2 mol%) K_2CO_3 (2 equiv) DMA, 145 °C	96	13
2	 **22b**	 **23b**	$Pd(OAc)_2$ (1 mol%) PCy_3-HBF_4 (2 mol%) K_2CO_3 (2 equiv) DMA, 130 °C	97	14
3	 **22c**	 **23c**		90	14
4	 **22d**	 **23d**	$Pd(OAc)_2$ (5 mol%) PCy_3-HBF_4 (10 mol%) Ag_2CO_3 (0.5 equiv) K_2CO_3 (2 equiv) dioxane, 100 °C	93	14

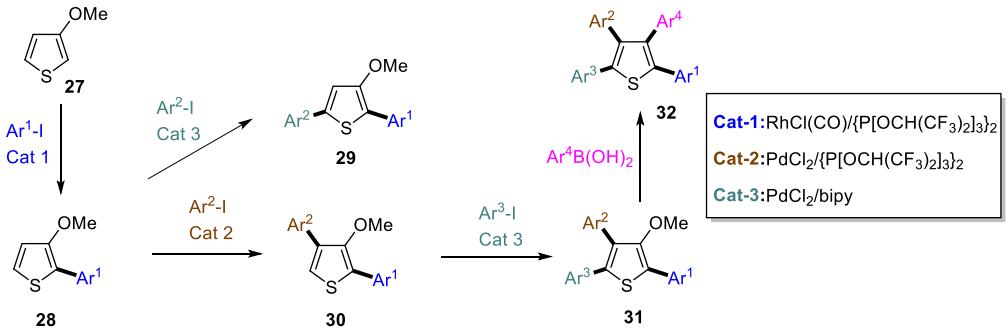
chlorides by using an *N*-heterocyclic carbene (NHC) as the ligand, the catalytic system exhibited low efficiency for sterically hindered substrates.[15] Finally, they identified that the combination of $Pd(OAc)_2$ and PCy_3-HBF_4 could efficiently enable the intramolecular direct arylation of arenes with aryl chloride, bromide, and iodide **22b-d** in 90–97% yields (Table 2, entries 2–4). The addition of Ag_2CO_3 was essential for the arylation with aryl iodides to prevent catalyst poisoning due to the facile accumulation of iodide anions.[16]

C-H arylation with aryl tosylates as the electrophile is highly desirable due to their ready availability and low cost. The pioneering Pd-catalyzed direct arylations using aryl tosylates **25** and mesylates as the electrophiles were reported by Ackermann and coworkers. A catalytic system comprising $Pd(OAc)_2$ and X-Phos enabled a broadly applicable C-H arylation of various heterocycles including benzoxazole (**24**), oxazole, caffeine and 1,2,3-triazole (Scheme 7).[17]



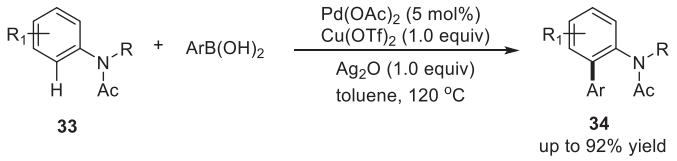
Scheme 7 Pd-catalyzed C-H arylation with aryl tosylate.

Polyaryl-substituted thiophenes are privileged structures within many interesting functional molecules. Itami and coworkers reported an efficient method for the programmed synthesis of tetraarylthiophenes via the sequential C-H/C-H/C-H/C-O arylations of 3-methoxythiophene (**27**). The regioselective C-H arylations were composed of C2-arylation by $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (**Cat-1**), C4-arylation by $PdCl_2$/$P[OCH(CF_3)_2]_3$ (**Cat-2**), and C5-arylation by $PdCl_2$/2,2′-bipyridine (**Cat-3**) (Scheme 8).[18]



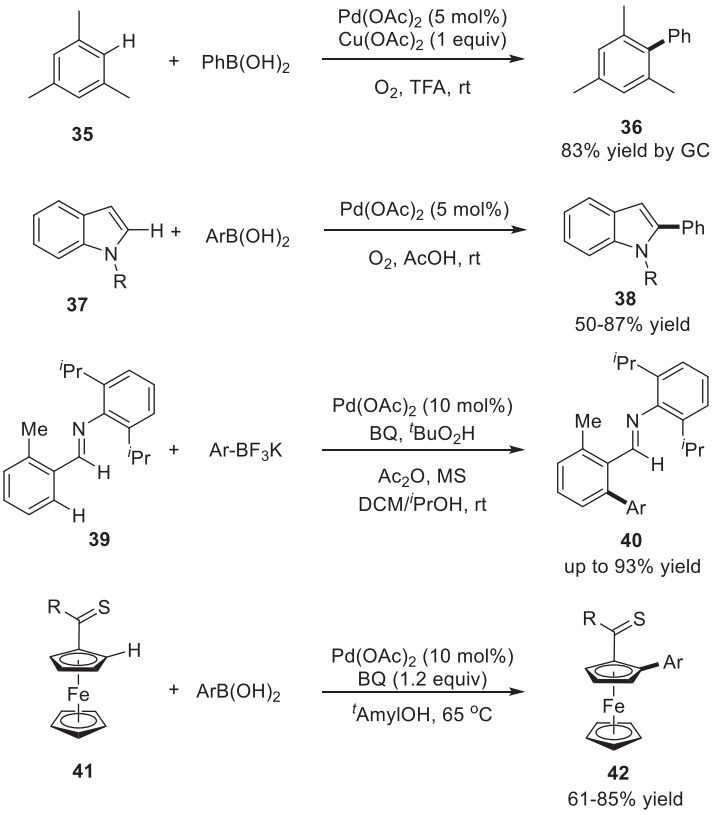
Scheme 8 Sequential C-H/C-H/C-H/C-O arylations of 3-methoxythiophene.

Compared with redox neutral Pd-catalyzed C-H activations, the oxidative Pd-catalyzed C-H arylations rely on the reoxidation of Pd(0) and suffer from facile homocoupling side reactions. The pioneering example of Pd-catalyzed alkylation of aryl C—H bonds with a variety of primary-alkyl tin reagents was reported by Yu and coworkers in 2006.[79] Shi and coworkers then developed Pd(II)-catalyzed oxidative C-H arylation of *N*-alkyl acetanilides **33** with aryl boronic acids in a Suzuki-Miyaura-type coupling reaction (Scheme 9). A plausible pathway for this transformation involves generation of a palladacyclo intermediate via C-H activation, transmetalation with aryl boronic acid and reductive elimination.[19] In addition, they also developed Hiyama-type coupling reaction of acetanilides with trialkoxyarylsilanes via C-H activation, affording *ortho* arylation products in up to 92% yield.[20]



Scheme 9 Pd(II)-catalyzed C-H arylation of *N*-alkyl acetanilides with aryl boronic acids.

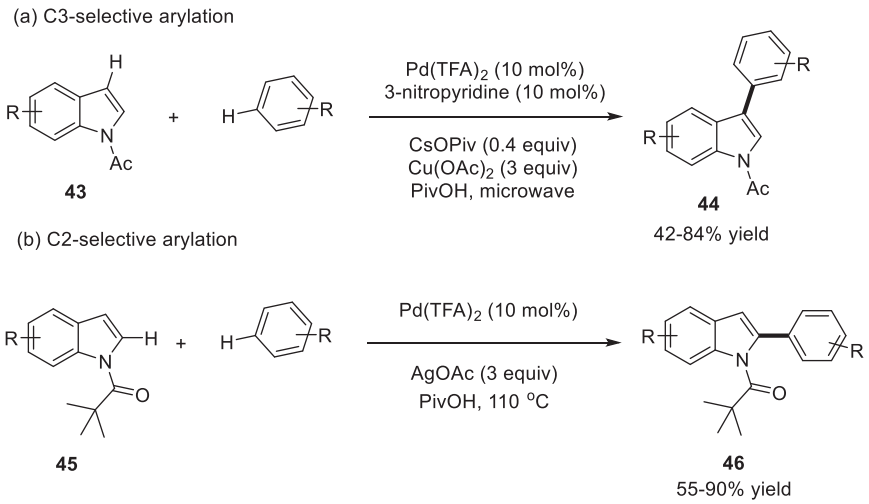
Soon afterwards, Pd(II)-catalyzed C-H arylations of electron-rich (hetero)arenes (**35**, **37**) with aryl boronic acids, benzaldimines (**39**) with aryl-BF_3K salts, and ferrocenes (**41**) with aryl boronic acids were developed successively (Scheme 10).[21]



Scheme 10 Pd(II)-catalyzed C-H arylations.

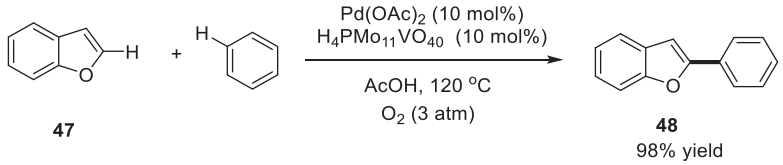
12.05.2.1.2 C(sp^2)—H bond arylation with simple aromatic ring

From the viewpoint of atom and step economy, C-H/C-H cross-coupling reaction of two unfunctionalized arenes undoubtedly is the most straightforward approach for C-C formation.[22] As early as in 2006, Lu and coworkers pioneeringly reported an intermolecular cross-coupling of simple arenes via double C-H activation with a catalytic system of $Pd(OAc)_2/CF_3CO_2H/K_2S_2O_8$, albeit with moderate efficiency and selectivity.[23] Breakthroughs were achieved by Fagnou and co-workers, who discovered Pd-catalyzed cross-coupling reactions of *N*-acetylindoles **43** with simple arenes. This transformation afforded highly C3-selective arylation product **44** in 42–84% yields (Scheme 11A).[24a] Interestingly, the C2-selective arylation of indole **45** was also accomplished when $Cu(OAc)_2$ was replaced by AgOAc (Scheme 11B).[24b]



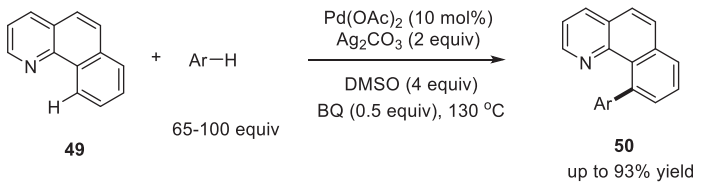
Scheme 11 Pd(II)-catalyzed C-H/C-H cross-coupling reactions.

Shortly thereafter, the cross-coupling of benzofuran (**47**) with benzene catalyzed by $Pd(OAc)_2$ with oxygen as the terminal oxidant was developed by DeBoef and coworkers, giving the C2-selecitve phenylation product **48** in 98% yield (Scheme 12).[25] Subsequently, they extended this double C-H functionalization method to the oxidative cross-coupling of indoles with simple aromatics. Mechanistic studies indicated that the acidity of the medium had effect on the regioselectivity for this cross-coupling reaction.[26]



Scheme 12 Pd(II)-catalyzed cross-coupling of benzofuran with benzene.

The directing group on arene can suppress the undesired C-H/C-H homocoupling in the direct cross-coupling reaction of two unfunctionalized arenes. Sanford and coworkers described a Pd-catalyzed coupling of benzo[*h*]quinoline (**49**) with simple arenes, and high chemo- and regioselectivity were obtained by using Ag_2CO_3 as the oxidant. The site selectivity is predominantly controlled by the directing group for the first C-H activation and by the steric environment around the simple arene C—H bond for the second C-H activation. Mechanistic studies suggest that BQ (benzoquinone) is bound to the Pd center during the arene C-H activation process and affects the regioselectivity of arene C-H activation as well (Scheme 13).[27]



Scheme 13 Pd(II)-catalyzed coupling of benzo[*h*]quinoline with simple arenes.

Subsequently, Shi and Buchwald also achieved Pd-catalyzed C-H/C-H cross-arylation of *N*-acetyl-1,2,3,4-tetrahydroquinoline or anilides by using O_2 as the terminal oxidant, respectively (Fig. 3A and B).[28] In 2010, the cross-coupling of *O*-phenylcarbamates with simple arenes was achieved by Dong and coworkers using sodium persulfate ($Na_2S_2O_8$), an inexpensive and easy-to-handle oxidant (Fig. 3C). Trifluoroacetic acid (TFA) plays a critical role for the cyclopalladation of *O*-phenylcarbamate. Two discrete C—H bond activations including directing-group assisted cyclopalladation and electrophilic metalation were proposed.[29] When a simple monosubstituted arene was employed as the arylation partner, a mixture of regioisomers was always encountered in these C-H/C-H coupling reactions. In the presence of *N*-fluorobenzenesulfonimide (NFSI), high *para*-selectivity for the C-H/C-H coupling of benzamides with monosubstituted arenes was achieved by Yu and coworkers. NFSI as an oxidant is crucial for this high *para*-selectivity (Fig. 3D).[30]

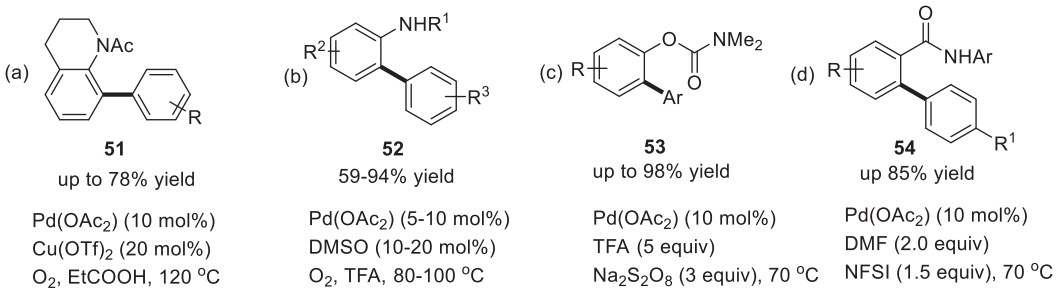
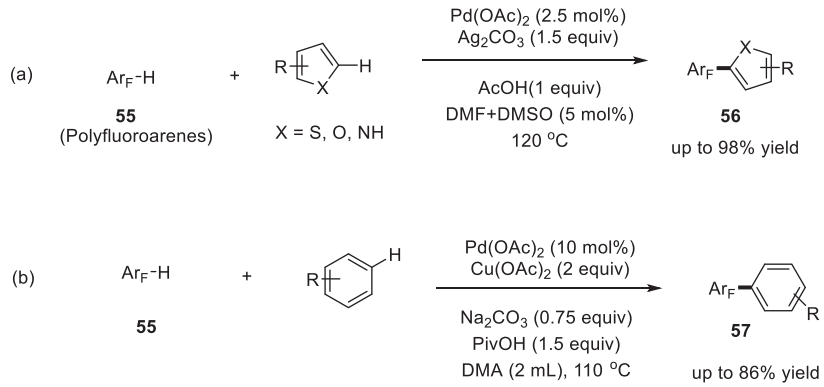


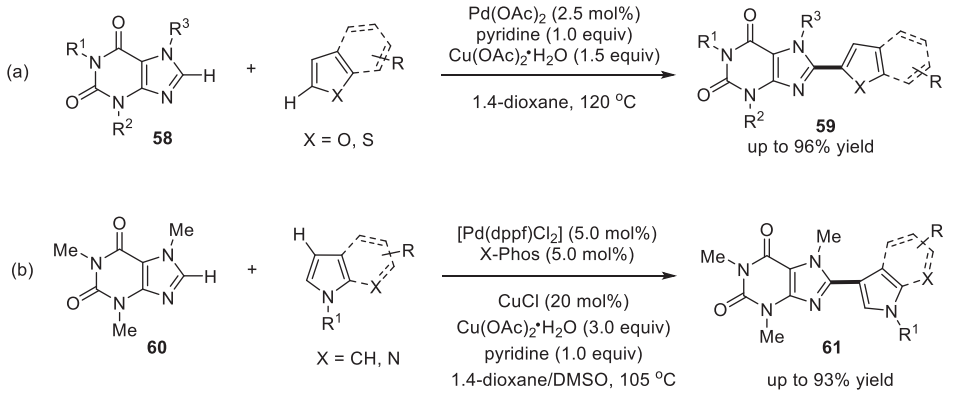
Fig. 3 Pd-catalyzed C-H/C-H cross-coupling products, (a) C-H arylation of 1,2,3,4-tetrahydroquinolines, (b) C-H arylation of anilides, (c) C-H arylation of *o*-phenylcarbamates, (d) C-H arylation of benzamides.

Perfluorinated aromatic rings are a prominent structural motif found in numerous functional materials. In 2010, Zhang and coworkers developed a Pd-catalyzed C-H/C-H cross-coupling of perfluoroarenes **55** with heteroarenes including (benzo)thiophenes, (benzo)furans, and indoles by using Ag_2CO_3 as the oxidant (Scheme 14A).[31] Almost at the same time, Wei and Su described a Pd-catalyzed cross-coupling of perfluoroarenes with simple arenes via twofold C-H functionalization by using $Cu(OAc)_2$ as the oxidant (Scheme 14B).[32]



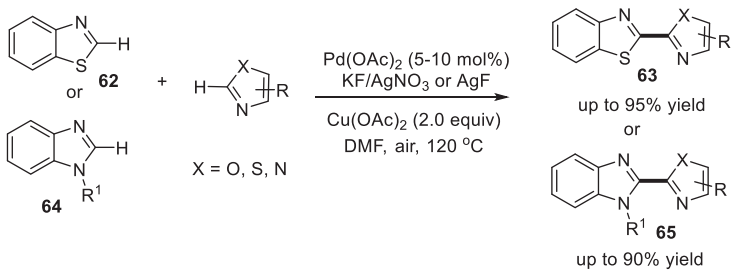
Scheme 14 Pd-catalyzed cross-coupling of perfluoroarenes with arenes.

The heteroaryl-heteroaryl fragment is widely distributed in many electronic materials, natural products and pharmaceuticals. It has been a challenge to avoid the homo-coupling side reaction in these C-H/C-H cross-coupling reactions. Hu, You and coworkers developed Pd(II)-catalyzed oxidative cross-coupling of heteroarenes with high regioselectivity via double C-H functionalization. The success was probably ascribed to the instability of intermediate in the process of homo-coupling product formation. This catalytic system works for a wide range of substrates, allowing the C-H/C-H hetero-coupling of diverse *N*-containing heteroarenes (e.g., caffeines, imidazoles, azoles, quinolines and pyridine *N*-oxides) with (benzo)thiophene, (benzo)furan (Scheme 15A). In addition, this strategy could be further extended to the C-H/C-H cross-coupling of caffeine (**60**) with indoles and pyrroles (Scheme 15B).[33]



Scheme 15 Pd-catalyzed C-H/C-H cross-coupling of heteroarenes.

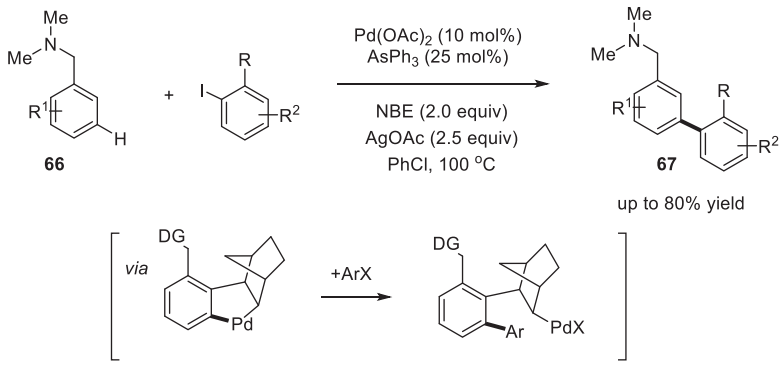
The C-H/C-H cross-coupling reactions of heteroarenes with similar electronic properties are quite challenging because of their tendency to undergo homo-coupling side reaction. In 2011, Ofial and coworkers accomplished an efficient Pd-catalyzed C-H/C-H cross-coupling of benzothiazoles (**62**) or benzimidazoles (**64**) with *N*-, *O*-, and *S*-containing azoles. Silver salts effectively suppressed the formation of homo-coupling products by facilitating the cleavage of the second C—H bond selectively at the other azole (Scheme 16).[34]



Scheme 16 Pd-catalyzed cross-coupling of benzothiazoles with azoles.

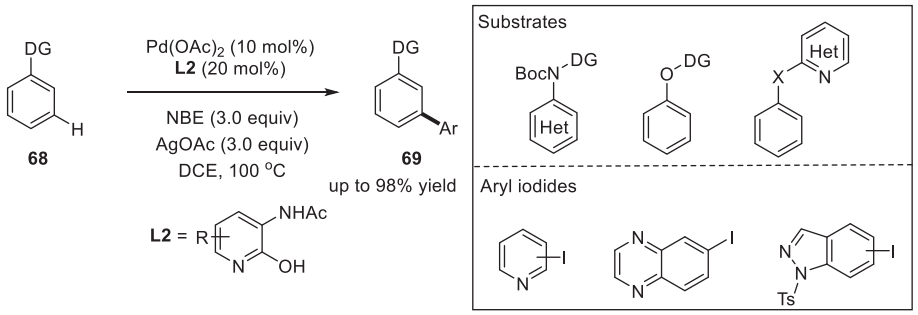
12.05.2.1.3 meta-*C(sp²)-H arylation*

While numerous *ortho* C-H arylations of arenes have been extensively developed, *meta*-selective C-H arylation of electronically unbiased arenes remains a difficult task. Dong and coworkers reported *meta*-selective C-H arylations by using Pd/norbornene catalysis in 2015. The key NBE (norbornene)-bridged five-membered palladacycle, generated via C-H activation, reacts with an aryl halide through a Pd(IV) intermediate to generate a *meta*-substituted complex. The resulting Pd intermediate then undergoes β-carbon elimination followed by reprotonation at the *ortho* position to furnish the desired *meta* product (Scheme 17). This *meta* C-H arylation with aryl iodides bearing an *ortho* electron-withdrawing group (ester, acyl, and nitro group etc.) could give reasonable yields (up to 80%).[35]



Scheme 17 *meta*-Selective C-H arylation by Pd/norbornene catalysis.

Soon after, Yu and coworkers identified a class of 3-acetylamino-2-hydroxypyridine ligands (**L2**), which could promote the *meta*-C-H arylations of a wide range of arenes **68** including anilines, heterocyclic aromatic amines, phenols, and 2-benzyl heterocycles using norbornene as a transient mediator (Scheme 18). A variety of aryl iodides and heteroaryl iodides could be used as effective coupling partners.[36]

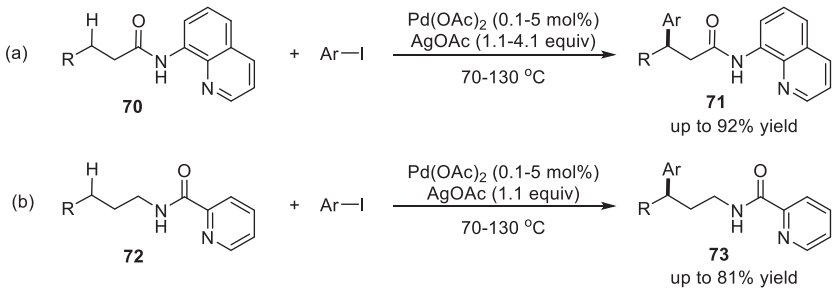


Scheme 18 3-Acetylamino-2-hydroxypyridine promoted *meta*-C-H arylation.

12.05.2.1.4 C(sp^3)-H arylation

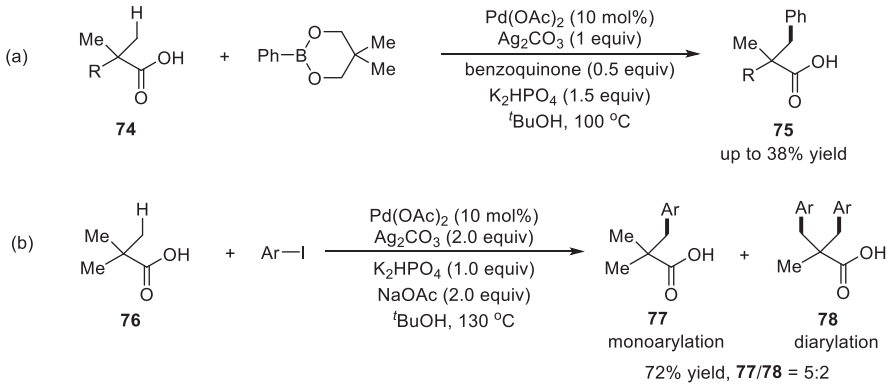
To date, a wide variety of C(sp^2)–H arylations have been well developed. Meanwhile, much attention has also been paid on more challenging C(sp^3)—H bond functionalization. Significant progress has been made despite of inherent difficulties such as low acidity, and unreactive molecular orbital profiles.

Daugulis and coworkers pioneeringly developed a regioselective Pd-catalyzed C(sp^3)–H arylation of aliphatic carboxylic amides **70** at the β-position by utilizing the aminoquinoline (AQ) directing group (Scheme 19A). Notably, extremely high efficiency was observed, and the arylation of propionamide with *p*-iodoanisole was complete in less than 5 min. This approach could also be applicable to C(sp^3)–H arylation of amine derivatives **72** at the γ-position (Scheme 19B).[37] In addition, C(sp^3)–H monoarylation of primary C(sp^3)—H bonds can be achieved by employing 2-methylthioaniline auxiliary.[38]



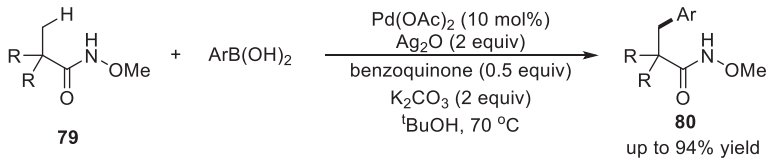
Scheme 19 Secondary β-and γ-C-H arylations of aliphatic acids and amines.

The use of the carboxyl group to facilitate C-H activation/C-C coupling processes proved of great value in developing C—C bond forming reactions. Yu and coworkers reported the first catalytic protocol for the coupling of β-C(sp^3)—H bonds in aliphatic acids **74** with an organoboron reagent via Pd(II)/Pd(0) catalysis, albeit with moderate yield (up to 38% yield) (Scheme 20A). This C(sp^3)—H bond arylation reaction with ArI as the arylating reagent was also feasible, leading to mono- (**77**) and diarylation (**78**) of aliphatic acid **76** in 72% combined yield (mono/di = 5:2) (Scheme 20B). It likely involves a COOH directed C—H bond activation and subsequent formation of Pd(IV) intermediate oxidized by ArI.[39]



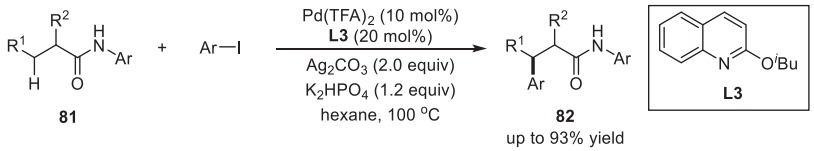
Scheme 20 Primary β-C-H arylation of aliphatic acids.

To further improve the versatility and efficiency of C(sp^3)—H bond arylation reactions of aliphatic acid derivatives, the more strongly binding directing group *O*-methyl hydroxamic acid was introduced. The arylation reaction with various aryl boronic acids in the presence of $Pd(OAc)_2$ proceeded smoothly to afford arylation products **80** in up to 94% yield, which could be readily converted to esters and amides (Scheme 21).[40]



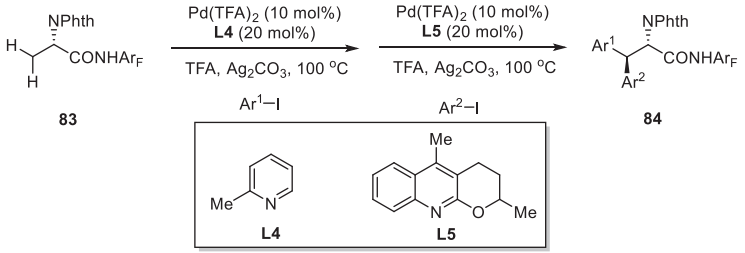
Scheme 21 Primary β-C-H arylation of aliphatic acids.

Activation of methylene C—H bonds is more challenging than primary C—H bonds mainly due to their steric hinderance. Previous studies showed that Pd-catalyzed C–H activation of methylene C—H bonds usually requires strongly coordinating pyridine auxiliaries.[37,38] Encouraged by their ligand acceleration in a number of Pd(II)-catalyzed C(sp^2)-H functionalizations, Yu and coworkers achieved Pd(II)-catalyzed arylation of acyclic β-methylene C(sp^3)—H bonds (**81**) enabled by a 2-isobutoxyquinoline ligand (**L3**) (Scheme 22). This catalytic system was also compatible for cyclic β-methylene C—H bonds, giving the monoarylated product as a single *cis*-substituted diastereomer.[41]



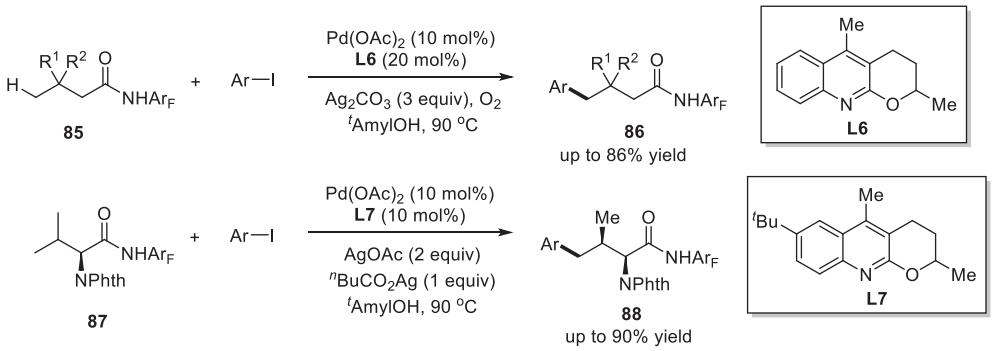
Scheme 22 Secondary β-C-H arylation of aliphatic acids.

The synthesis of unnatural amino acids via direct C(sp^3)-H functionalization has been an area of extensive research. Yu and coworkers developed an unprecedented ligand-controlled sequential β-C(sp^3)–H arylation of alanine derivatives **83** using pyridine and quinoline derivatives as the ligands (Scheme 23). The pyridine ligand (**L4**) enabled primary C(sp^3)–H monoarylation exclusively and subsequently the quinoline ligand (**L5**) enabled secondary C(sp^3)–H arylation in one pot. A wide range of β-Ar-β-Ar′-α–amino acids **84** with excellent diastereoselectivity could be efficiently prepared by using two different aryl iodides.[42] The *N*-methoxyamide (CONHOMe) directing group displayed excellent efficiency. Moreover, it can be conveniently installed and removed. Yu then realized Pd-catalyzed C(sp^3)–H mono- and diarylation of a broad range of carboxylic acids using the CONHOMe auxiliary promoted by pyridine-type ligands. 2-Picoline ligand promoted the selective monoarylation of primary C(sp^3)—H bonds, and 2,6-lutidine ligand enabled the subsequent arylation of secondary C(sp^3)—H bonds in one pot. The utility of this efficient method was further demonstrated by gram-scale synthesis of various unnatural amino acids.[43]



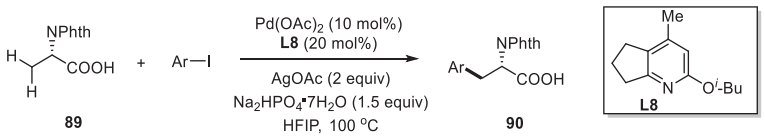
Scheme 23 Sequential β-C-H arylations of amino acid derivatives.

Significant achievements have been made toward directed β-C(sp^3)-H arylations of carboxylic acids and their derivatives through five-membered palladium intermediate. Development of γ-C-H activation at more distal carbon center through six-membered palladacycle greatly expanded the synthetic utility of C(sp^3)-H functionalization reactions. In 2016, Yu and coworkers realized a γ-C(sp^3)-H arylation of aliphatic acid-derived amides **85** promoted by a tricyclic quinoline ligand (**L6**) (Scheme 24).[44] Importantly, the γ-C(sp^3)-H arylation of amino acids including valine (**87**), isoleucine, and *tert*-leucine was also achieved by employing a modified quinoline ligand (**L7**).



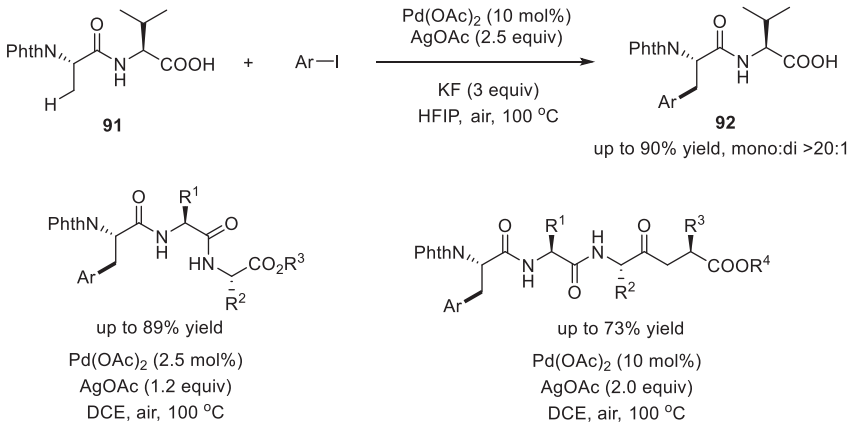
Scheme 24 γ-C-H arylations of aliphatic acid-derived amide and amino acid derivatives.

The C(sp^3)-H arylations of amino acids bearing CONHAr$_F$ or CONHOMe as a directing group have been well-developed by ligand-accelerated Pd catalysis. C-H activation directed by the carboxyl group is more practical due to its ready availability and diverse transformations. Yu and coworkers developed β-(sp^3)-H arylation of α-amino acids **89** promoted by a pyridine-based ligand **L8**. No requirement of an exogenous directing group further enhances the synthetic utility of this method (Scheme 25).[45]



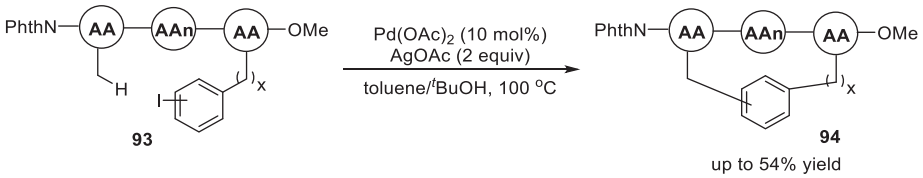
Scheme 25 Sequential β-C-H arylation of amino acids.

Site-selective functionalization of C(sp^3)—H bonds in a peptide side chain will improve the efficiency and step economy of peptide syntheses and allow for postsynthetic modification of peptides. Yu and coworkers pioneeringly accomplished C(sp^3) – H arylations of various dipeptides **91** directed by native amino acid embedded in the peptide backbone (Scheme 26).[46] A wide range of arylated dipeptides at the *N*-terminus were obtained in up to 90% yield. Importantly, this arylation method is also suitable for esterified tripeptides and tetrapeptides under slightly modified reaction conditions.



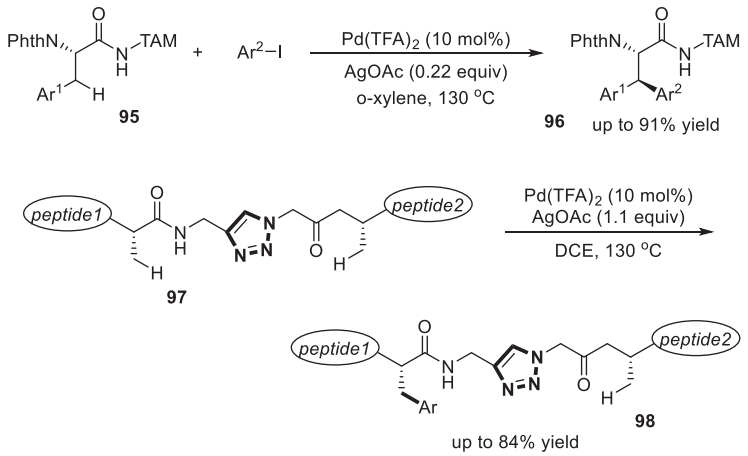
Scheme 26 Pd-catalyzed C(sp^3) – H arylation of dipeptides.

Inspired by Yu's C(sp^3) – H arylation of peptides, Noisier, Albericio and co-workers reported an elegant C(sp^3)-H peptide macrocyclization. Pd-catalyzed intramolecular C-H cross-coupling between an alanine (Ala) and a phenylalanine (Phe) residue proceeded smoothly to afford a novel class of stapled peptides **94** in up to 54% yield (Scheme 27).[47]



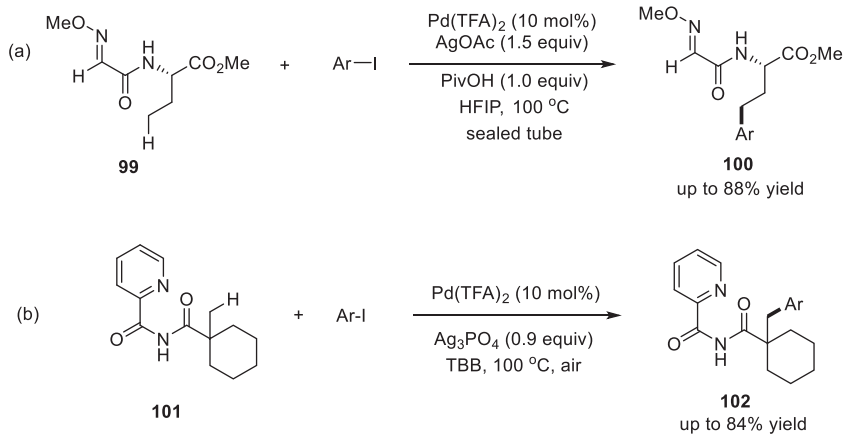
Scheme 27 Pd-catalyzed intramolecular C-H arylation between alanine (Ala) and phenylalanine (Phe) residue.

Based on Pd-catalyzed secondary C(sp^3)-H arylation of triazolyldimethylmethyl (TAM) amide, Ackermann and coworkers extended this method to an intermolecular reaction of peptides bearing two viable sites of potential reactivity. Surprisingly, the unprecedented positional selective C(sp^3)-H arylations of the internal peptide position were realized with the aid of the peptide-bond-isosteric triazole (Scheme 28).[48]



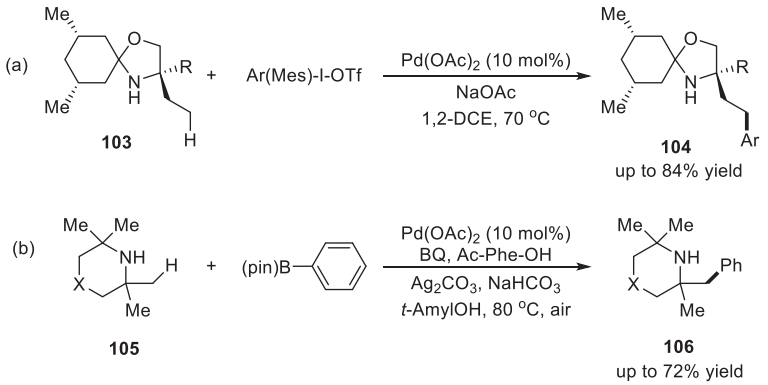
Scheme 28 Pd-catalyzed C(sp^3)-H arylation of peptides.

The use of directing groups has proven to be a powerful, common, and practical strategy to directly functionalize C—H bond. An ideal directing group should be readily available, easily introduced and removed. Ma and coworkers developed 2-methoxyiminoacetyl (MIA) assisted γ-C(sp^3)-H arylation of aminobutanoic acid derivatives **99** (Scheme 29A).[49] The MIA auxiliary could be conveniently removed with KOH at room temperature. Shi and coworkers disclosed the commercially available 2-picolinamide to be a novel directing group for Pd-catalyzed C(sp^3)-H arylations. Sequential primary and secondary C(sp^3)-H arylations could also be realized with different aryl iodides. Notably, this directing group can be removed at room temperature (Scheme 29B).[50]



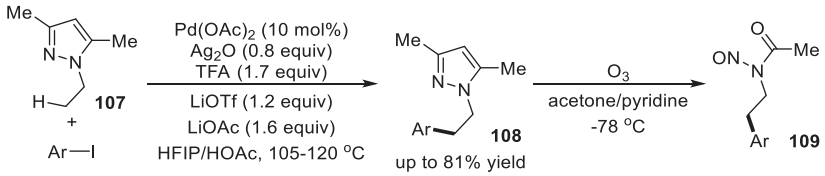
Scheme 29 2-Methoxyiminoacetyl (MIA) and 2-picolinamide assisted C(sp^3)-H arylations.

While Pd-catalyzed aliphatic C-H arylations directed by imine generated in situ and oxime have been well investigated, the use of amine as a directing group for C-H activation is less investigated but attractive. In 2015, Gaunt and coworkers described a general Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic amino alcohols. With a hindered *N*,*O*-ketal motif derived from *cis*-3,5-dimethyl cyclohexanone as an efficient directing group, Pd-catalyzed arylations with hypervalent iodine reagent (Ph_2IOTf) afforded a variety of arylation products **104** in up to 84% yield (Scheme 30A).[51] The hindered environment around the Pd center promotes the formation of the active mono ligated Pd species by destabilizing the unreactive Pd/bis(amine) complex. In addition, a hydrogen bond between the acetate ligand on the palladium and the N–H of amine substrate are also responsible for this facile C–H arylation. Subsequently, they reported Pd-catalyzed C-H arylations of hindered secondary aliphatic amines **105** with arylboronic esters through an uncommon four-membered-ring cyclopalladation pathway. The addition of amino acid ligand significantly improved the reaction efficiency (Scheme 30B).[52]



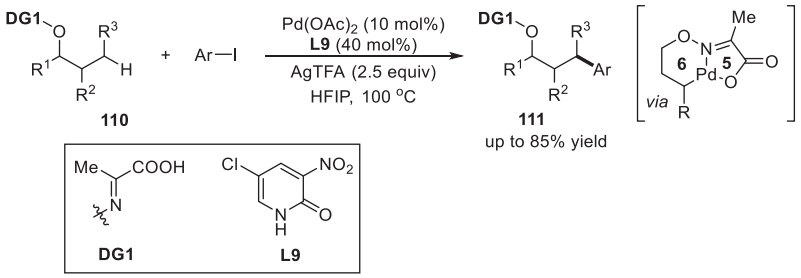
Scheme 30 Pd-catalyzed C(sp^3)-H arylations of aliphatic amino alcohols and aliphatic amines.

C-H functionalization of aliphatic amines by employing a directing-group strategy always occurred at the γ-position owing to the formation of five-membered metallacycle preferentially. Gulia and Daugulis developed a Pd-catalyzed pyrazole-directed C(sp^3)-H arylation with aryl iodides, which tolerated a wide range of functional groups (Scheme 31).[53] β-Phenethylamine derivatives **109** were afforded by ozonolysis of the pyrazole moiety.



Scheme 31 Pd-catalyzed pyrazole-directed C(sp^3)-H arylation.

Regioselective Pd-catalyzed C(sp^3)–H activation reactions were developed generally through a five-membered cyclopalladation pathway, which is kinetically and thermodynamically favorable over its six-membered counterparts. In 2019, Gaunt and coworkers achieved γ-C(sp^3)-H arylation of aliphatic alcohols **110** via six-membered cyclopalladation by a pyruvic acid-derived directing group in combination with 3-nitro-5-chloro-2-pyridone ligand **L9** (Scheme 32).[54] The 5,5-fused ring is more strained than the 5,6-fused ring due to the existence of double bond in the bicyclic palladacycle, and thus favors the six-membered cyclopalladation.

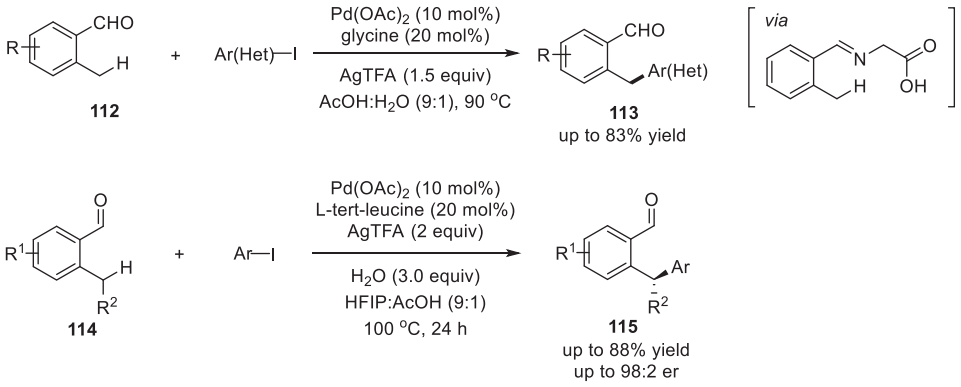


Scheme 32 Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic alcohols.

12.05.2.1.5 C-H arylation using transient directing group

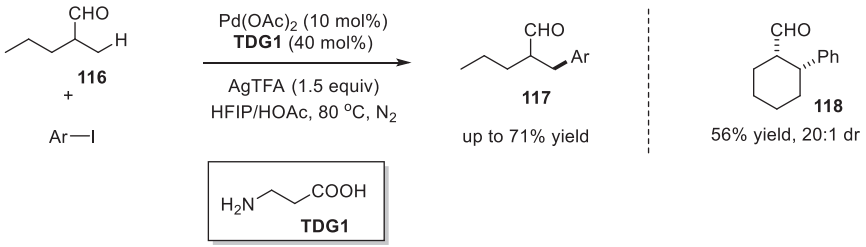
While great progresses on C-H functionalization assisted by covalent directing groups have been made, the requirement of installing and removing the directing group diminishes the synthetic efficiency and functional group compatibility. The strategy of using a temporary directing group that reversibly reacts with the substrate and binds to the metal center can well address these disadvantages. The condensation of benzaldehyde with amino acid gives imine reversibly, which serves as a transient directing group. The imine moiety and the carboxyl group act as a bidentate directing group. In 2016, Yu and coworkers accomplished Pd-catalyzed C(sp^3)–H arylations of 2-methylbenzaldehyde (**112**) by employing such a transient directing group strategy (Scheme 33).[55] This method can also be applicable to aliphatic ketone substrates by using 50 mol% glycine and a mixture of HFIP:AcOH as the

co-solvent. Importantly, the enantioselective C–H arylation of benzaldehydes **114** bearing a methylene C(sp^3)—H bond using L-*tert*-leucine as a transient directing group is also feasible. More works on Pd-catalyzed asymmetric C—H bond functionalizations will be described in Section 12.05.2.5.



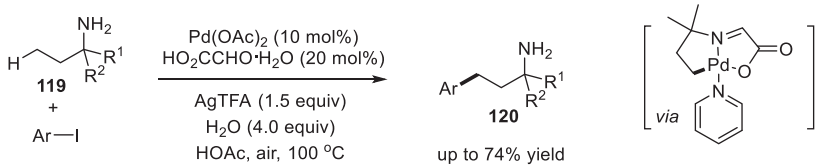
Scheme 33 Pd-catalyzed C(sp^3)–H arylations by employing transient directing group.

Aliphatic aldehydes are ubiquitous structural units in biologically active natural products and pharmaceuticals, and the key intermediates in organic synthesis. Therefore, functionalization of aliphatic aldehydes has attracted much attention in organic chemistry community. Ge and coworkers discovered β-C(sp^3)-H arylation reaction of aliphatic aldehydes **116** with aryl iodides by using 3-aminopropanoic acid (**TDG1**) as a novel transient directing group (Scheme 34).[56] Notably, this highly site-selective arylation occurred preferentially at the primary β-C(sp^3)–H position over the secondary β-methylene, γ- or δ-terminal C – H positions. The C-H arylation was also compatible with cyclic aldehyde, affording the desired *cis* product **118** with 20:1 dr.



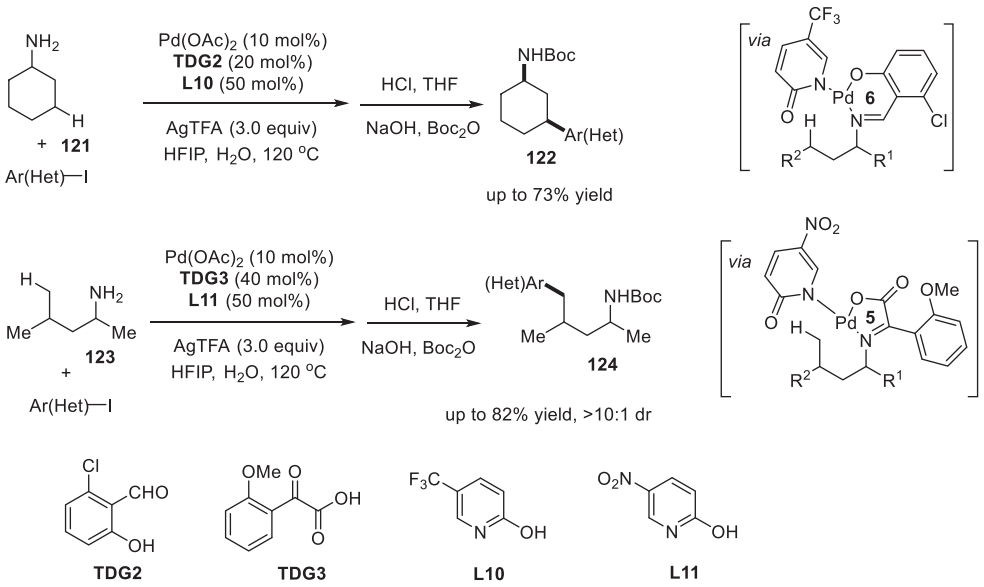
Scheme 34 β-C(sp^3)-H arylation reaction of aliphatic aldehydes.

The development of Pd-catalyzed C(sp^3)-H functionalization of aliphatic amines is of great interest due to their popularity and importance in organic synthesis and medicinal chemistry. Ge and coworkers reported a Pd-catalyzed direct γ-arylation of primary amines **119** (Scheme 35).[57] With glyoxylic acid as a transient directing group, a wide range of primary γ-arylation alkylamines **120** were prepared in up to 74% yield without any additional protection or deprotection manipulations. Moreover, the key cyclopalladated intermediate was obtained from the reaction of glyoxylic acid, *tert*-amylamine and $Pd(OAc)_2$ in the presence of stoichiometric amounts of pyridine.



Scheme 35 Pd-catalyzed γ-arylation of primary amines.

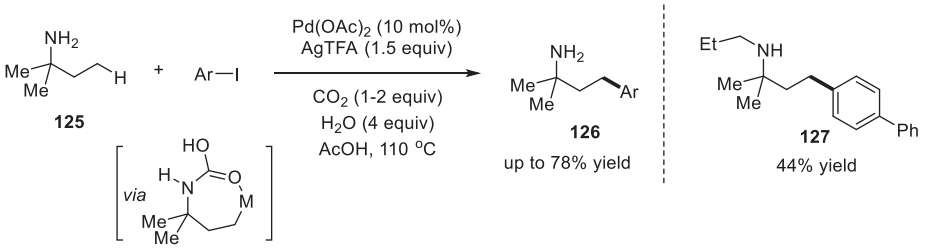
Encouraged by their previous outstanding findings that pyridone ligands can accelerate both C(sp^2) – H and C(sp^3) – H activations, Yu and coworkers further developed pyridine enabled γ-methylene C(sp^3) – H arylation and δ-C(sp^3) – H arylation of aliphatic amines using two different transient directing groups, respectively (Scheme 36).[58] The combination of 5-trifluoromethyl pyridine **L10** and phenol-based **TDG2** coordinate with Pd via a six-membered chelate that favors γ-C – H



Scheme 36 Pyridone promoted γ- and δ-C(sp^3)-H arylations of aliphatic amines.

arylation, whereas 5-nitro pyridine **L11** together with 2-oxo-2-phenylacetic acid **TDG3** coordinates with Pd via a five membered chelate that favors δ-C – H arylation. A cooperative effect between the transient directing group and the pyridone ligand plays an important role in the regioselectivity.

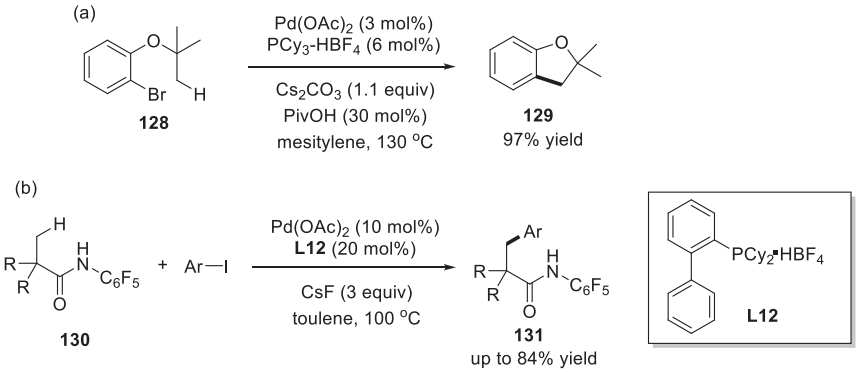
Young and coworkers reported the first example of CO_2-mediated C-H arylation of aliphatic amines **125**. In this reaction, the carbamate moiety as a transient directing group was generated by the reversible reaction of amine with CO_2 (Scheme 37).[59] Both primary and secondary aliphatic amines (**127**) can be arylated selectively at the γ-C-H position. Mechanistic studies suggest that CO_2 acts as a transient DG through a rare seven-membered palladacycle.



Scheme 37 CO_2-Mediated C-H arylation of aliphatic amines.

12.05.2.1.6 Pd(0)-initiated C-H arylation

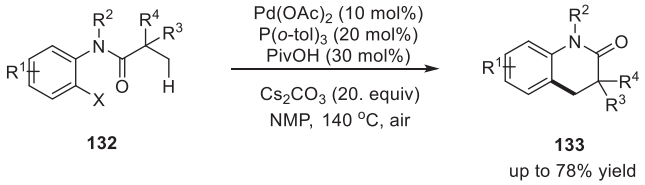
In Pd(II)-initiated C(sp^3)-H arylation reactions, the stoichiometric amount of metal salts as external oxidants is always required, impeding the practical utility of these methods. Therefore, Pd(0)-catalysis allowing redox neutral reaction conditions has attracted much attention. Generally speaking, Pd(0) is produced by reducing Pd(II) with a reducing agent such as phosphine ligand in the system. In 2007, Fagnou and coworkers reported a Pd(0)-initiated intramolecular C(sp^3)-H arylation in the presence of $Pd(OAc)_2$ and PCy_3-HBF_4 with pivalic acid affording 2,2-dialkyldihydrobenzofurans (**129** in 97% yield) (Scheme 38A).[60] Later,



Scheme 38 Pd(0)-initiated C(sp^3)-H arylation reactions.

Yu and coworkers described Pd(0)-catalyzed intermolecular C(sp^3)-H arylation with aryl iodide by using a CONH-C_6F_5 directing group and cyclohexyl JohnPhos ligand (**L12**). Notably, both reactions can be performed with stable phosphine-HBF_4 salt (Scheme 38B).[61]

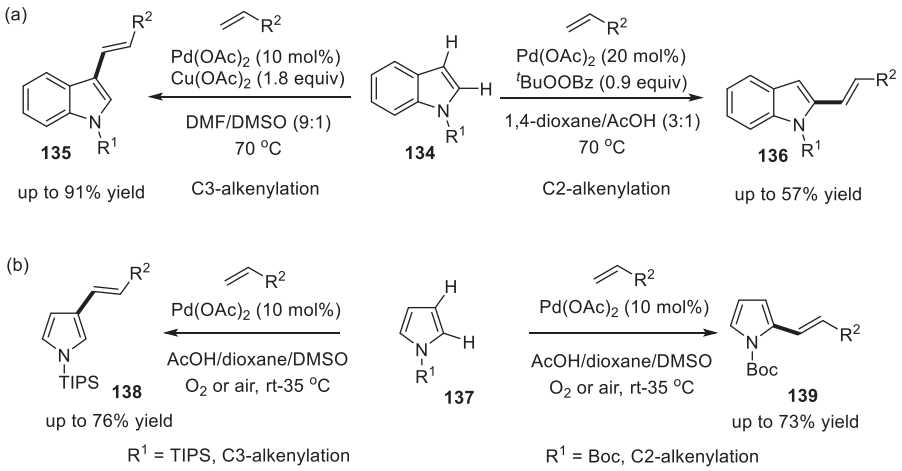
The intramolecular C(sp^3)-H arylations usually afforded five-membered ring products. In this context, the synthesis of six-membered or larger rings is relatively challenging. In 2014, Shi and coworkers developed a Pd(0)-catalyzed intramolecular C(sp^3)-H arylation through a seven-membered palladacycle intermediate, providing a wide range of 3,4-dihydroquinolinones **133** in up to 78% yield (Scheme 39).[62] The intramolecular KIE ($k_H/k_D = 6.2$) indicated that the C(sp^3)—H bond cleavage is involved in the rate-determining step.



Scheme 39 Pd(0)-catalyzed intramolecular C(sp^3)-H arylation for six-member ring synthesis.

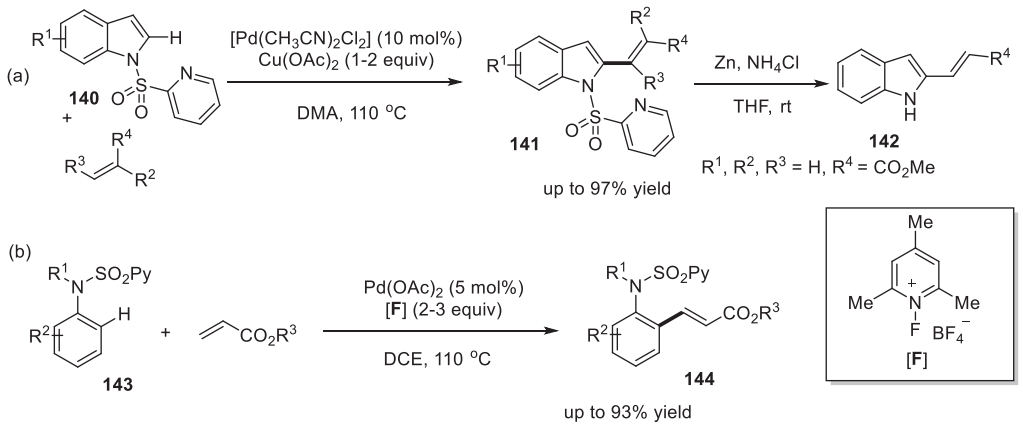
12.05.2.2 C—H bond alkenylation

Over the past decades, the direct oxidative Heck reaction has become one of the most fundamental C—C bond formation methods, in which preactivated reaction partners are not needed. In this aspect, pioneering works on Pd-catalyzed oxidative coupling of arenes and activated alkenes were developed by Fujiwara and Moritani.[63] In 2005, Gaunt and coworkers developed a Pd-catalyzed intermolecular oxidative Heck reaction of indoles at either the C2- or the C3-position by varying the solvent and additives. The alkenylation reaction took place preferentially at the C3-position (**135**) in a mixed solvent of DMSO and DMF. When the reactions were performed in dioxane/AcOH, the regioselectivity was switched in favor of C2-position (**136**) (Scheme 40A).[64a] Furthermore, the regio-divergent oxidative Heck reactions of pyrroles were realized by sterically and electronically tuned *N*-pyrrole protecting groups, affording either the C2 or C3 alkenylated products (**138**, **139**) (Scheme 40B).[64b]



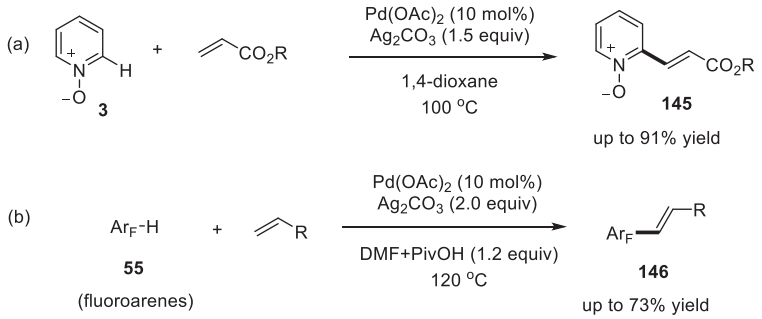
Scheme 40 Pd-catalyzed oxidative Heck reaction of indoles and pyrroles.

Arrayás, Carretero and coworkers reported a Pd-catalyzed regioselective direct C2 alkenylation of indoles **140** directed by a *N*-(2-pyridyl)sulfonyl group. Multi-substituted alkenes are also suitable substrates in this reaction. The 2-pyridylsulfonyl group could be removed conveniently to generate the unprotected C2 alkenylative indoles **142** (Scheme 41A).[65] Furthermore, this general and reliable strategy could be applied in the C-H olefination of *N*-alkyl aniline **143**, benzylamine, and phenethylamine derivatives by using *N*-fluoro-2,4,6-trimethylpyridinium triflate [**F**] as an oxidant (Scheme 41B).[66]



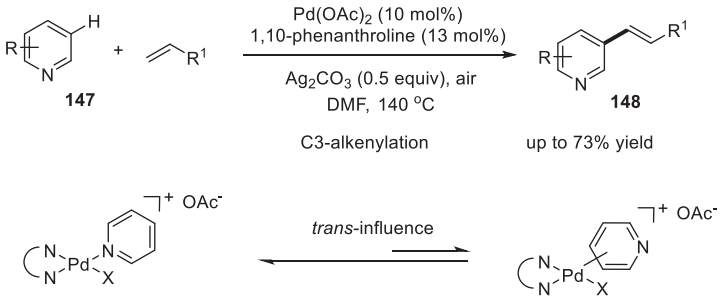
Scheme 41 Pd-catalyzed alkenylation reaction directed by the *N*-(2-pyridyl)sulfonyl group.

Both pyridine *N*-oxides and perfluoroarenes are suitable substrates for C-H functionalization (e.g., C-H arylations) as described above. In 2008, Chang and coworkers achieved a Pd-catalyzed C-H alkenylation of pyridine *N*-oxide (**3**), which exhibited highly high site-selectivity at the 2-position, generating (*E*)-products **145** exclusively in up to 91% yield (Scheme 42A).[67] Zhang and coworkers reported a $Pd(OAc)_2$ catalyzed direct olefination of electron-deficient perfluoroarenes **55** with a broad range of alkenes in up to 73% yield (Scheme 42B).[68]



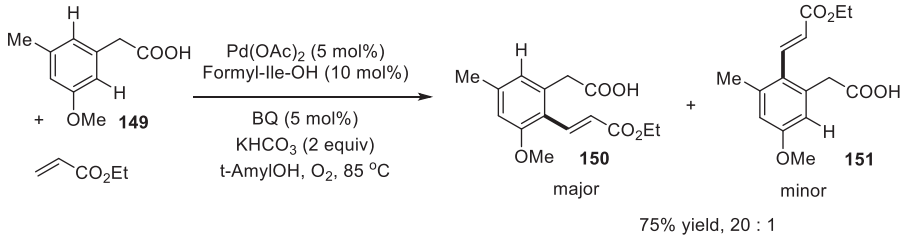
Scheme 42 Pd-catalyzed alkenylation of pyridine *N*-oxide and perfluoroarenes.

The utilization of pyridyl *N*-oxide substrates has allowed for C-H olefination and arylation reactions at the C-2 position.[6,67] Interestingly, the Pd-catalyzed C-3 selective alkenylation of pyridines **147** was achieved by introducing a bidentate ligand (1,10-phenanthroline), which weakens the coordination between Pd center and the pyridyl *N* atom through the *trans*-influence (Scheme 43).[69] A small amount of Pd(II)/π-ring complex was sufficient to initiate this catalytic reaction. A significant isotope effect ($k_H/k_D = 4.0$) suggested that this reaction undergoes via a Pd-catalyzed C-H activation rather than a Lewis acid mediated Friedel-Crafts pathway.



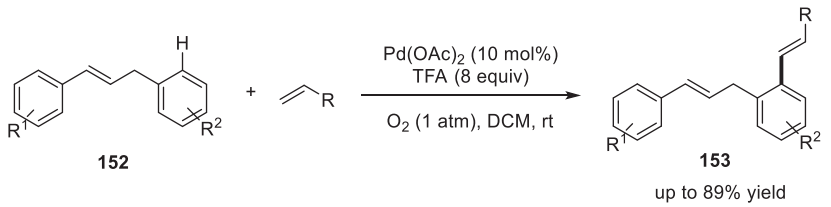
Scheme 43 Pd-catalyzed C-3 selective alkenylation of pyridines.

The previous examples of Pd-catalyzed C–H olefination are restricted to specific cases, generally including electron-rich heterocycles, such as indoles and pyrroles, or electron-deficient arenes such as pyridine *N*-oxides and perfluoroarenes. Breakthrough was made by Yu and co-workers in 2010, and they succeeded in ligand-controlled, position-selective C–H olefination through carboxyl group directed C—H bond activation (Scheme 44).[70] In this elegant study, amino acids were able to increase the reactivity significantly and the regioselectivity for multi-substituted phenylacetic acids **149**. Mechanistic studies suggest that the increased reaction rates stem from the acceleration in the C-H cleavage step.



Scheme 44 Amino acid promoted C–H olefination reaction.

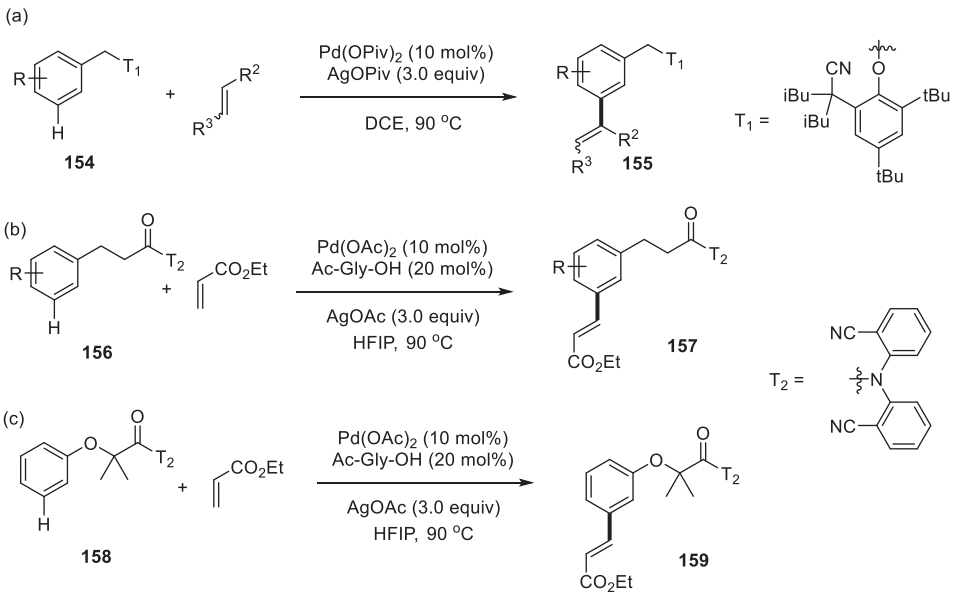
Generally, the *N*- or *O*-containing directing groups are usually installed in the substrates in order to control the regioselectivity and assist C-H activation. Gandeepan and Cheng reported a Pd-catalyzed *ortho* C-H olefination of arenes **152** with excellent regioselectivity at ambient temperature by utilizing an allylic alkenyl double bond as a directing group for the first time (Scheme 45).[71] Mechanistic studies supported the existence of coordination of C=C to Pd(II) and an electrophilic C-H functionalization process.



Scheme 45 Pd-catalyzed *ortho* C-H olefination directed by the double bond.

ortho-Directed metalation of C—H bond has been used as a powerful approach for achieving *ortho*-selective functionalizations of aromatic compounds. On the other hand, a generally applicable approach for remote *meta*-C–H activation is challenging mainly due to the difficulty in forming a macrocyclic *pre*-transition state.

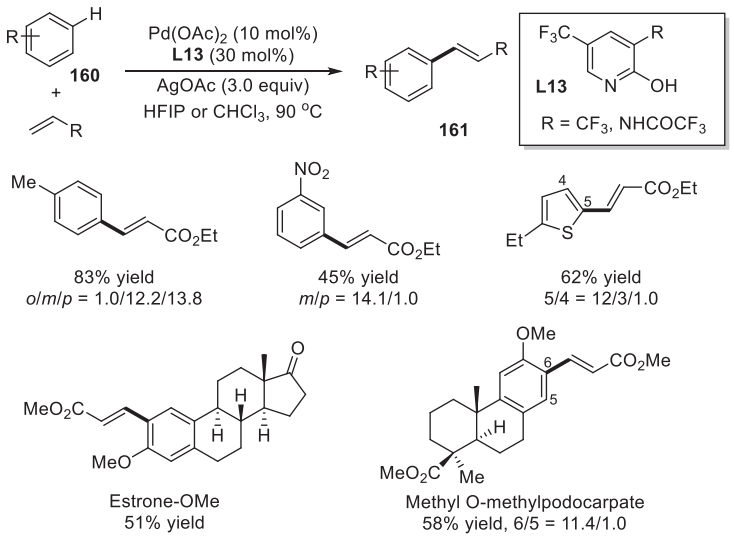
In 2012, *meta* C—H bond olefination of benzyl alcohols was accomplished by using a nitrile-containing template (**T1**). In this reaction, a series of di- or tri-substituted olefins were also found to be suitable substrates. The authors proposed that the nitrile group in the template was weakly coordinated to the [Pd(II)–Ar] intermediate and thus could be effectively coordinated with disubstituted olefins (Scheme 46A). Having established this nitrile-containing end-on template to activate *meta*-C—H bond, this



Scheme 46 Pd-catalyzed *meta*-C—H bond olefination directed by a nitrile-containing template.

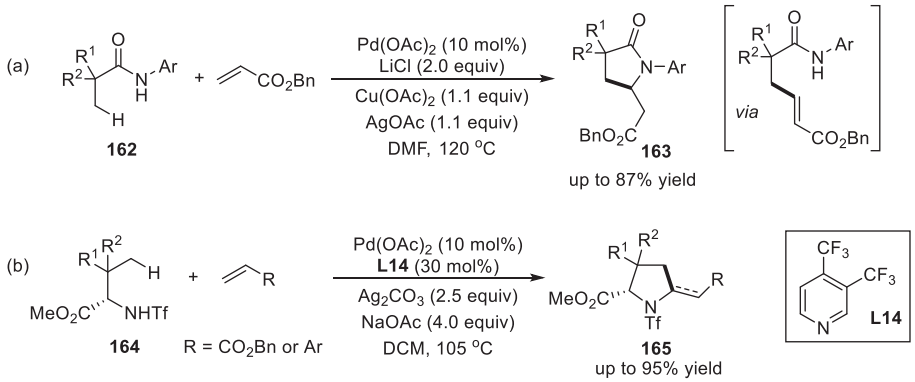
approach could further be applied to *meta* C—H bond olefination of hydrocinnamic acids **156**. Mono-*N*-protected amino acid ligands such as *N*-acetyl-protected glycine were found to be essential to accelerate C–H olefinations (Scheme 46B).[72] The nitrile template **T2** could also efficiently direct *meta* C – H olefination of α-phenoxyacetic acids **158** (Scheme 46C).[73]

Nondirected C-H functionalization is highly attractive, as it allows the functionalization of more distant sites and enable further useful reactions without the directing group. In 2017, Yu and coworkers discovered an electron-deficient 2-pyridone ligand **L13**, which could enable Pd-catalyzed non-directed C–H olefination of both electron-deficient and electron-rich arenes (**160**) as the limiting reagent (Scheme 47).[74] These ligands not only accelerate the reaction but also prevent the catalyst from forming a stable and less reactive palladium complex. Importantly, this non-directed C-H olefination allows late-stage functionalization of C—H bonds that are not accessible by directing group strategy.



Scheme 47 Pd-catalyzed non-directed C-H olefination promoted by 2-pyridone ligand.

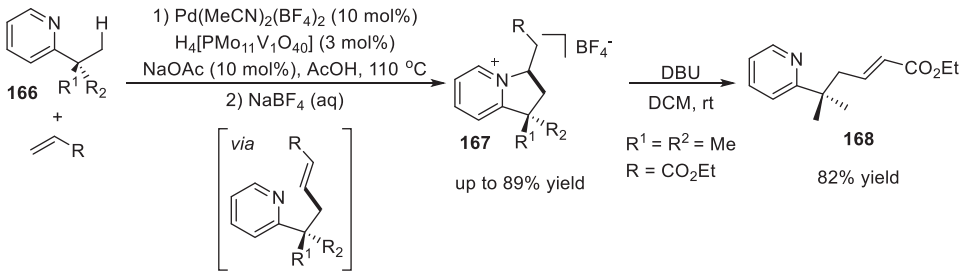
While C(sp^2)-H olefination has been extensively explored, Pd-catalyzed olefination of unactivated C(sp^3)—H bonds remains a challenge since it is mechanistically distinct from that of aryl C-H olefination. Encouraged by Fu's pioneering work concerning intramolecular olefination of alkyl halides,[75a] Yu and coworkers developed a Pd(II)-catalyzed direct olefination of C(sp^3)—H bond assisted by an *N*-arylamide (CONHAr) directing group in 2010 (Scheme 48A).[75b] After C-H olefination, the amide products underwent 1,4-conjugate aza-addition to give the corresponding lactams **163** in up to 87% yield. They also reported Pd-catalyzed γ-C(sp^3)-H olefination of Tf-protected amines enabled by pyridine-based ligand **L14**. This protocol was also compatible with styrenes besides acrylates. A variety of C-2 alkylated pyrrolidines **165** were accessed after subsequent aza-Wacker oxidative cyclization or conjugate addition of the olefinated intermediates (Scheme 48B).[76]



Scheme 48 Pd-catalyzed C(sp^3)-H olefination reactions.

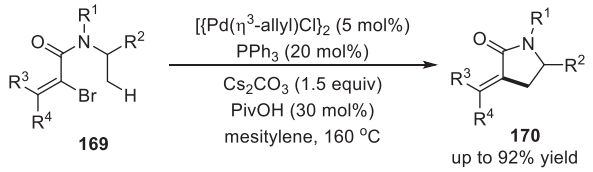
Sanford and coworkers reported Pd/polyoxometalate-catalyzed olefination of unactivated C(sp^3)—H bonds with pyridine or quinoline as a directing group and air as the terminal oxidant. The products underwent reversible intramolecular Michael addition,

affording pyridinium salts **167** in up to 89% yield (Scheme 49).[77] Notably, the cationic Michael adduct undergoes facile elimination to release α,β-unsaturated ester **168** in the presence of DBU.



Scheme 49 Pd/polyoxometalate-catalyzed C(sp^3)-H olefination.

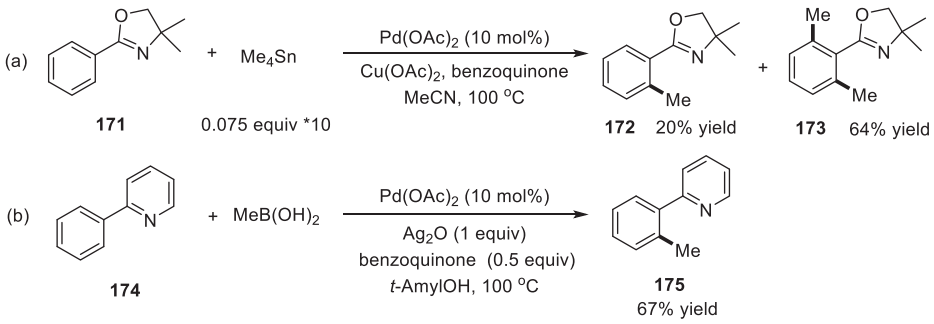
Apart from Pd(II)-initiated C(sp^3)-H olefination reactions, Baudoin and coworkers developed Pd(0)-catalyzed intramolecular C(sp^3)-H alkenylation from easily accessible bromoalkenes **169**, providing a variety of strained α-alkylidene-β-lactams **170** in up to 92% yield (Scheme 50).[78]



Scheme 50 Pd(0)-catalyzed intramolecular C(sp^3)-H alkenylation.

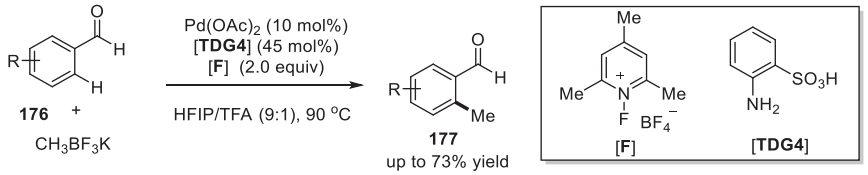
12.05.2.3 C—H bond alkylation

In 2006, Yu and coworkers developed a Pd-catalyzed alkylation of aryl C—H bonds with a variety of primary-alkyl tin reagents for the first time (Scheme 51A).[79] The alkylation reactions with benzoquinone as a crucial promoter proceeded smoothly to give mono- and dimethylation products (**172, 173**) in 20% and 64% yield, respectively. To a certain extent, however, the toxicity of organotin reagents limited its applications. They subsequently developed a Pd(II)-catalyzed alkylation with methylboronic acid (Scheme 51B).[80] Ag_2O is an efficient promoter for the transmetalation as well as co-oxidant with benzoquinone.



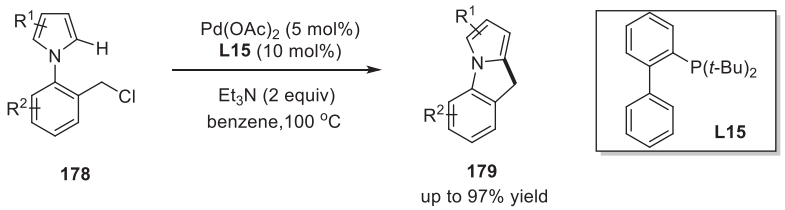
Scheme 51 Pd-catalyzed alkylation of aryl C—H bond.

Amino carboxylic acids are the most used transient directing group (TDGs) in C-H arylation reactions described above. The imine linkage was generated reversibly via aldehyde condensation to facilitate C – H activation. Chen and Sorensen utilized orthanilic acid (**TDG4**) as a transient directing group to achieve *ortho* C – H methylation of benzaldehyde **176** with potassium methyl trifluoroborate and by using 1-fluoro-2,4,6-trimethylpyridinium salt [**F**] as the oxidant (Scheme 52).[81]



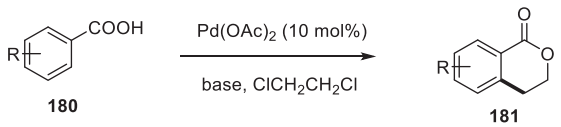
Scheme 52 *ortho* C – H methylation of benzaldehyde.

Direct intramolecular C-H alkylations of heteroarenes provide a straightforward access to condensed heterocyclicheteropolycyclic compounds. Chang and coworkers developed a Pd-catalyzed C-H cyclization of *N*-(2-halobenzyl)-substituted pyrroles (**178**) by using 2-(di-*tert*-butylphosphino) biphenyl (**L15**) as the optimal ligand, providing condensed pyrroloindoles (**179**) in up to 97% yield (Scheme 53).[82] The catalytic step involves oxidative addition of benzyl halide to Pd(0), intramolecular C-H activation, and reductive elimination.



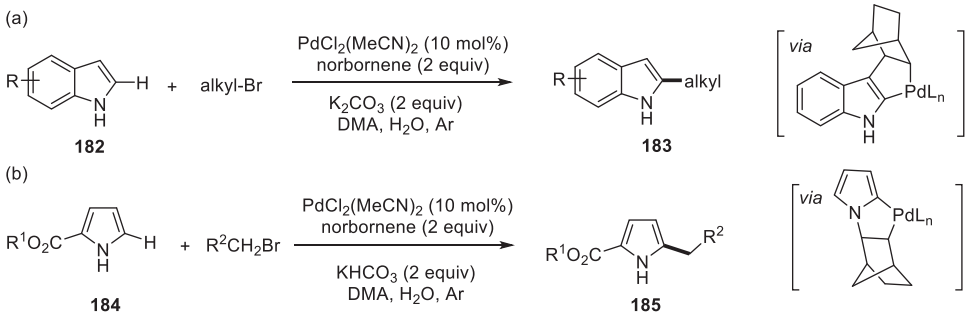
Scheme 53 Pd-catalyzed C-H cyclization of *N*-(2-halobenzyl)-substituted pyrroles.

Yu and coworkers reported a Pd(II)-catalyzed intermolecular alkylation of benzoic acids (**180**) with alkyl halides such as 1,2-dichloroethane and dibromomethane (Scheme 54). Control experiments show that direct *ortho* C-H alkylation occurs first, followed by an S_N2 reaction to give the corresponding lactone **181**. Kinetic isotope effect studies do not support the Friedel–Crafts-type reaction process.[83]



Scheme 54 Pd(II)-catalyzed intermolecular alkylation of benzoic acids.

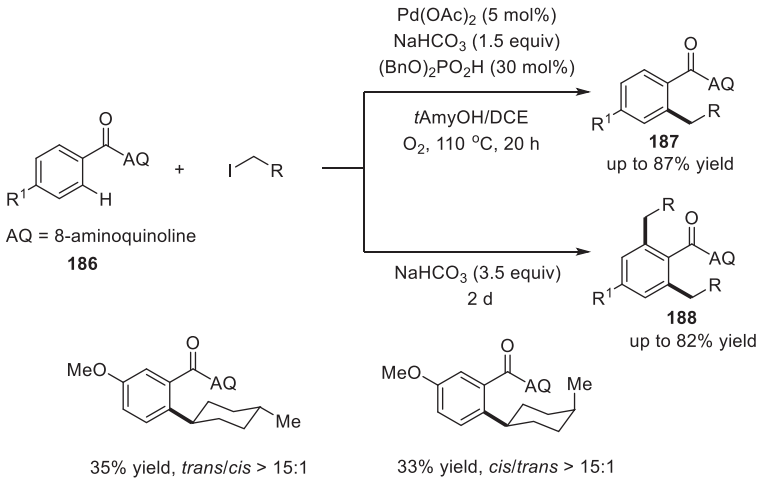
By employing a directing group on the nitrogen atom of indole, regioselective C-H functionalization at the C2 position could be achieved. Innovatively, Bach and coworkers developed a Pd-catalyzed direct C2-alkylation of free N-H indoles **182** mediated by norbornene (Scheme 55A).[84] The mechanism was proposed as follows: direct C3 palladation of indole with a Pd(II) complex leading to the formation of indole- and norbornyl-fused palladaheterocycle at the C2 position as a key intermediate, then followed by oxidative addition with an alkyl halide, reductive elimination and norbornene expulsion. This reaction is compatible with a wide range of primary alkyl bromides. Furthermore, this Pd(II)/norbornene co-catalyzed method could be applied to C-H alkylation of



Scheme 55 Pd-catalyzed C2-alkylation of free N-H indoles and pyrroles.

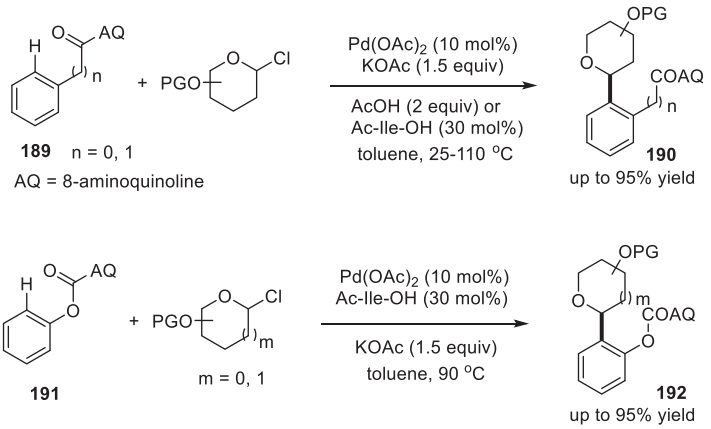
electron-deficient pyrrole derivatives **184** (Scheme 55B).[85] An electron-withdrawing substituent on pyrrole is essential since pyrrole is more electron rich and less acidic than indole derivatives.

8-Aminoquinoline (AQ) is a popular bidentate directing group for Pd-catalyzed C-H functionalizations.[86] Chen and coworkers developed a Pd-catalyzed *ortho*-C-H alkylation of *N*-quinolyl benzamides **186** with both primary and secondary alkyl halides by employing an AQ directing group (Scheme 56).[87] Interestingly, the amount of $NaHCO_3$ influenced significantly the mono- or diselectivity, most likely because HCO_3^- anion is a slightly less basic ligand in the CMD process. Notably, the reaction of an isolated palladacycle with both *cis*- and *trans*-3-methylcyclohexyl iodides gave their corresponding alkylated products with excellent stereoretention (>15/1). These results suggest that the oxidative addition of secondary alkyl iodides to palladacycle proceeds via a concerted pathway.



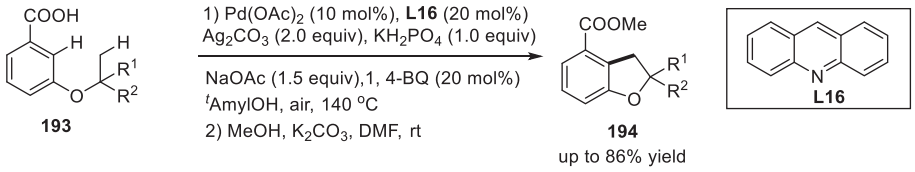
Scheme 56 Pd-catalyzed *ortho*-C-H alkylation of *N*-quinolyl benzamides with alkyl halides.

C-Aryl glycosides play an important role in drug discovery due to the high stability of C-glycosidic bonds. Chen and coworkers reported a stereoselective synthesis of C-aryl glycosides via Pd-catalyzed *ortho* C – H glycosylation of AQ-coupled benzamide and phenol derivatives **(189, 191)** with readily available glycosyl chloride donors (Scheme 57).[88] The soft aryl palladacycle nucleophile generated via C – H activation reacted with glycosyl oxocarbenium ion partners with high efficiency and excellent stereo control. These reactions also exhibited excellent functional group compatibility. It could be applied to a wide range of arene and heteroarene substrates, glycosyl chloride donors even including maltotriose and tetrasaccharide.



Scheme 57 Pd-catalyzed *ortho* C – H glycosylation.

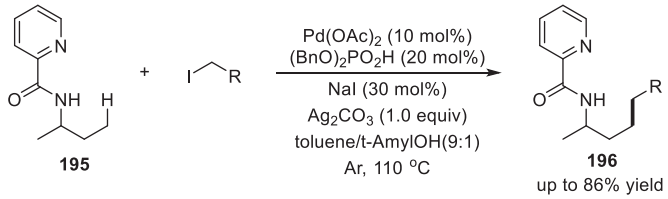
From the viewpoint of step- and atom-economy, it is the most ideal approach for C-H alkylation of arenes by oxidative coupling of $C(sp^2)$-H and $C(sp^3)$—H bonds. In 2017, Shi and coworkers developed an intramolecular oxidative coupling between phenyl- and aliphatic C—H bonds to construct a variety of dihydrobenzofurans **194** (Scheme 58).[89] Both the weakly coordinated carboxylate and acridine ligand **L16** were found to be essential for the success of this cross-coupling reaction.



Scheme 58 Pd-catalyzed oxidative C(sp^2)-H and C(sp^3)-H coupling.

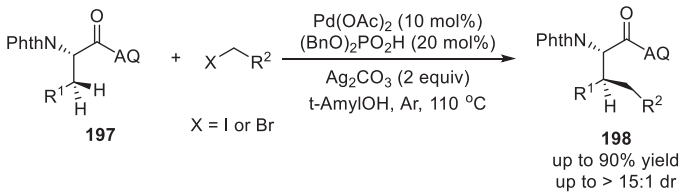
Compared with the significant achievements concerning Pd-catalyzed C(sp^2)-H alkylation, only limited progresses on unactivated C(sp^3)-H alkylations have been made. Yu and Daugulis independently developed Pd-catalyzed alkylations of C(sp^3)—H bonds with alkyl boronic acids, and with alkyl iodides, respectively. These catalytic systems were also suitable for C(sp^2)-H alkylations.[38,40,80]

Following these early works, Chen and coworkers achieved a Pd-catalyzed γ-C(sp^3) – H alkylation of aliphatic amines **195** with primary alkyl iodides by using picolinamide as a directing group (Scheme 59).[90] They proposed that this C – H alkylation reaction likely proceeds through C – H activation and subsequent oxidative addition with the alkyl iodide via an S_N2 mechanism, although a radical mechanism or Pd(III) pathway cannot be ruled out.



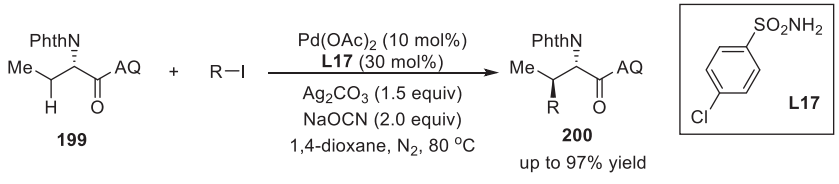
Scheme 59 Pd-catalyzed γ-C(sp^3) – H alkylation of aliphatic amines.

Soon after that, they developed a Pd-catalyzed alkylation of unactivated methylene C(sp^3)—H bonds of aminoquinolyl aliphatic carboxamides with α-haloacetate and methyl iodide. This C(sp^3)-H alkylation could also be applied to *N*-Phth-protected amino acids **197**, allowing the synthesis of various natural and unnatural amino acids in a highly diastereoselective manner (Scheme 60).[91] Additionally, isotopes could be conveniently introduced with isotopically enriched reagents.



Scheme 60 Pd-catalyzed C(sp^3)-H alkylation of *N*-Phth-protected amino acids.

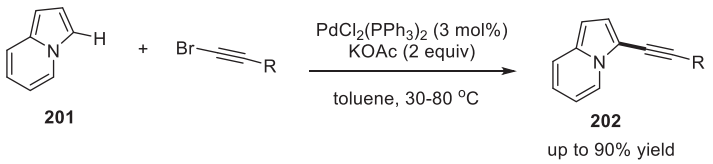
Almost at the same time, a similar work for Pd-catalyzed primary and secondary C(sp^3)—H bond alkylation with alkyl halides for the synthesis of optically active unnatural α-amino acids was also achieved by Shi and coworkers.[92] Furthermore, Shi et al. found that the addition of 4-Cl-$C_6H_4SO_2NH_2$ (**L17**) instead of $(BnO)_2PO_2H$ was critical in the alkylation of unactivated β-methylene C(sp^3)—H bonds of α-amino acids **199** (Scheme 61).[93] The stereoselective synthesis of various β, β-disubstituted α-amino acids were accomplished through sequential C(sp^3)-H alkylations. They speculated that 4-Cl-$C_6H_4SO_2NH_2$ facilitated both oxidative addition of alkyl halide to the Pd(II) center and reductive elimination for the formation of C(alkyl)-C(alkyl).



Scheme 61 Pd-catalyzed C(sp^3)—H bond alkylation promoted by 4-Cl-$C_6H_4SO_2NH_2$.

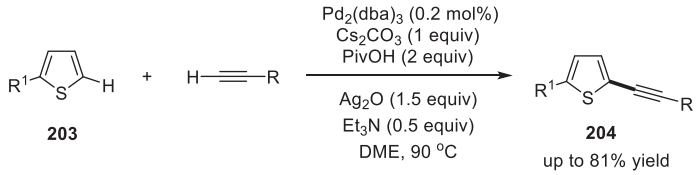
12.05.2.4 C—H bond alkynylation

Aryl and heteroaryl alkynes are highly valuable compounds widely used in contemporary organic synthesis and materials science. These compounds are commonly prepared by Sonogashira cross-coupling reactions of hetero(aryl) halides with terminal alkynes. On the other hand, great progresses on the C-H alkynylation of arenes with alkynyl halides have been made. In 2007, Gevorgyan and coworkers reported the first example of Pd-catalyzed C-H alkynylation of electron-rich *N*-fused heterocycles **201** (Scheme 62).[94] In the presence of $PdCl_2(PPh_3)_2$, the C-H alkynylation of indolizine and pyrroloquinoline etc. underwent smoothly with bromoalkynes in high regioselectivity.



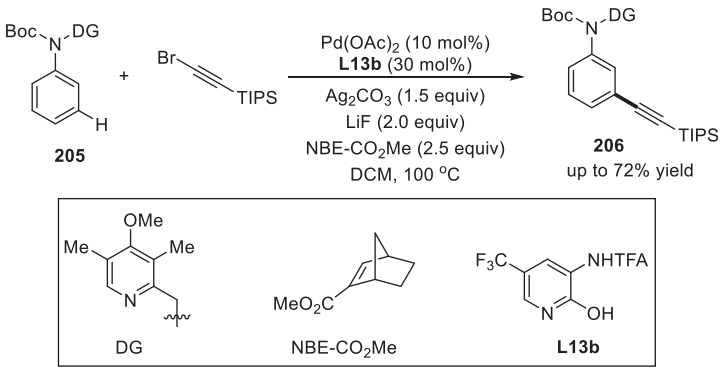
Scheme 62 Pd-catalyzed C-H alkynylation of indolizines.

The oxidative cross-coupling between (hetero)arenes and terminal alkynes is a straightforward and efficient method for constructing C(sp^2)—C(sp) bond. The challenge lies in how to avoid the formation of undesired homo-coupling (Glaser coupling) of terminal alkyne under oxidative conditions. Owing to the importance of alkynylated thiophenes in material science, natural product and medicinal chemistry, Su and coworkers developed a Pd-catalyzed cross-coupling reaction between terminal alkynes and heteroarenes such as thiophenes (**203**), furans, pyrroles and indoles in the presence of 0.2 mol% [$Pd_2(dba)_3$] (Scheme 63).[95] Interestingly, the low palladium catalyst loading is most likely responsible for overcoming alkyne homocoupling.



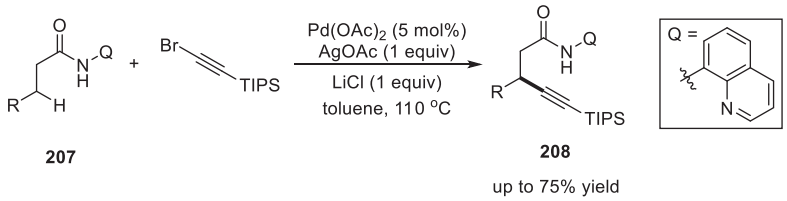
Scheme 63 Pd-catalyzed C-H alkynylation of thiophenes with alkynes.

Encouraged by the success of *meta*-C-H arylation and alkylation reactions using norbornene as a transient mediator,[35,36,84,85] Pd(II)-catalyzed *meta*-C – H alkynylation with bulky silyl-protected alkynyl bromides through a Pd(II)/Pd(IV) process was achieved by Yu and coworkers for the first time (Scheme 64). In this reaction, a modified norbornene, NBE-CO_2Me (methyl bicyclo[2.2.1] hept-2-ene-2-carboxylate),[96] was identified to be the most efficient mediator. The TFA protected 3-amino-2-hydroxy pyridine ligand (**L13b**) gave the highest selectivity of *meta*- to *ortho*- products. Thus, a variety of desired *meta*-alkynylated products **206** were obtained in up to 72% yield. Unfortunately, simple alkyl and aryl alkynyl bromides only led to a trace amount of the desired products.[97]



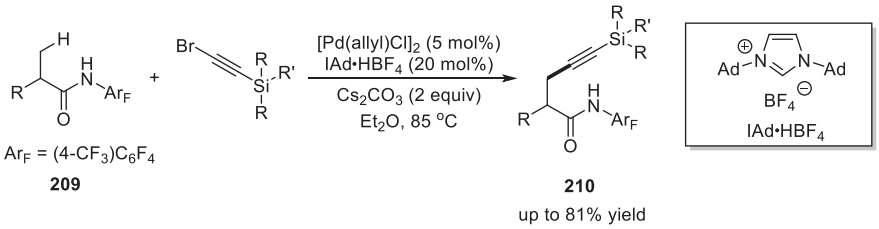
Scheme 64 Pd(II)-catalyzed *meta*-C – H alkynylation.

While the C(sp^2)—H bond alkynylation of (hetero)arenes has been accomplished by palladium catalysis, the development of C(sp^3)—H bond alkynylation is as challenging as the C(sp^3)—H bond arylation and olefination reactions. Tobisu, Chatani and coworkers reported the first example of Pd(II)-catalyzed C(sp^3)-H alkynylation of aliphatic carboxylic acids (**207**) with 8-aminoquinoline as a directing group (Scheme 65).[98] This alkynylation reaction proceeded with excellent functional group compatibility, allowing for the straightforward introduction of an ethynyl group into aliphatic acid derivatives.



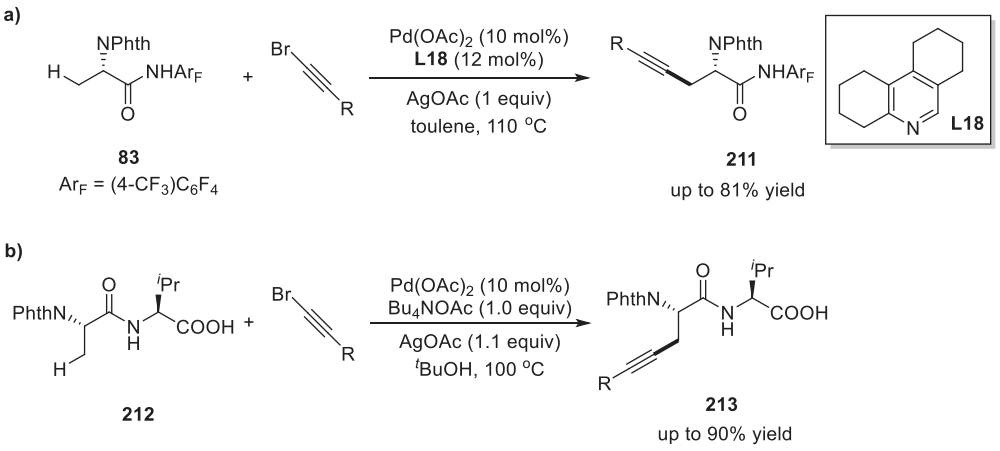
Scheme 65 Pd(II)-catalyzed C(sp^3)-H alkynylation of aliphatic carboxylic acids.

Pd(0)-initiated intermolecular C(sp^3)—H bond activations are more attractive due to the compatibility with a wide range of ligands and free of external-oxidants. Based on their work concerning Pd(0)/PR_3-catalyzed β-arylation of amides in 2009, Yu and coworkers reported a β-C(sp^3) – H alkynylation of aliphatic amides with sterically hindered alkynyl halides by using Pd(0)/NHC catalysts (Scheme 66).[99] Pd(0)-catalyzed C – H activation reaction pathway was supported by performing the reaction of *pre*-prepared alkynyl Pd(II) complex with aliphatic amides.



Scheme 66 Pd(II)-catalyzed β-C(sp^3) – H alkynylation of aliphatic amides.

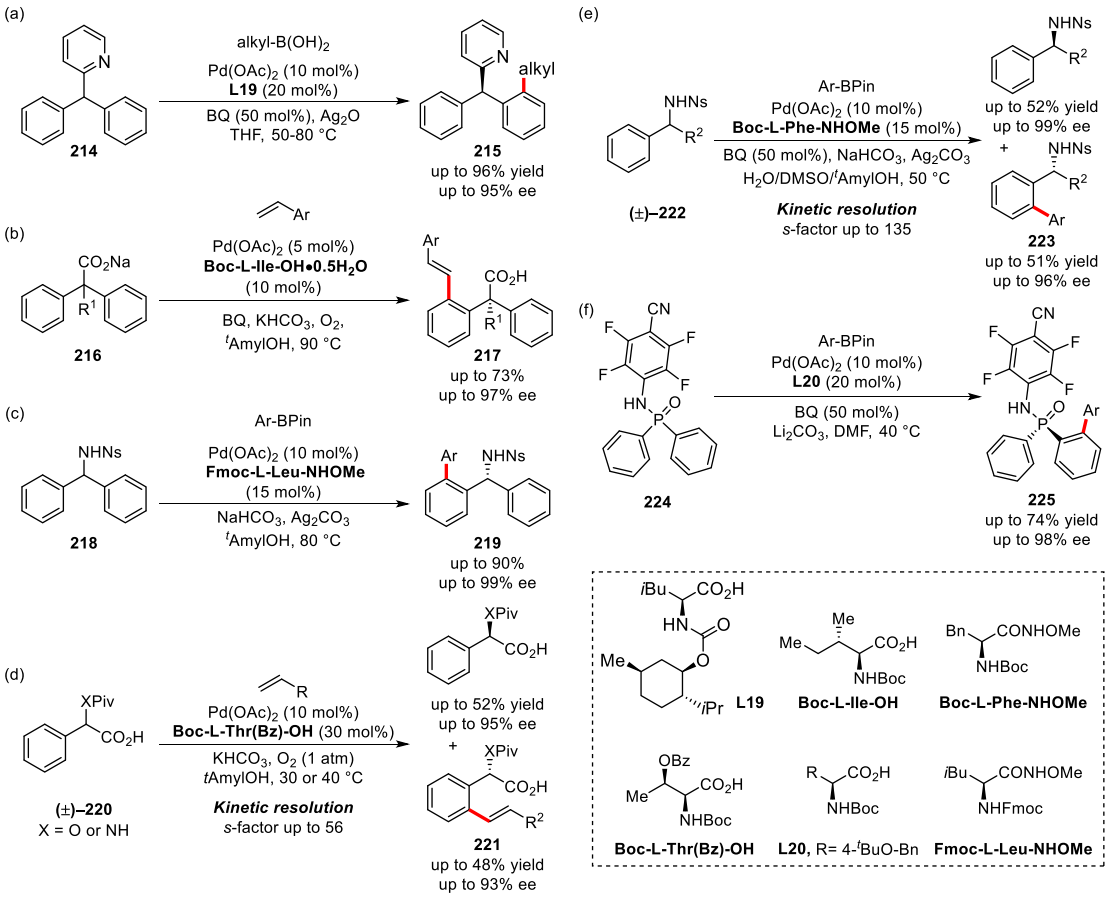
To broaden the substrate scope of C(sp^3)-H alkynylation, Yu and coworkers developed the ligand enabled C(sp^3)-H alkynylation by Pd(II)/Pd(IV) catalysis. This reaction is compatible with a wide range of carboxylic acid derivatives **83**, including α-amino acids as well as α-quaternary and cyclic amides (Scheme 67A).[100] The C(sp^3)-H alkynylation could be further extended to oligopeptides **212** with tetrabutylammonium acetate as a key additive. They proposed that the acetate anion in NBu_4OAc facilitated the C-H activation process, and that the quaternary ammonium cation enhanced the stability of the palladium species during C-H activation (Scheme 67B).[101]



Scheme 67 Pd(II)-catalyzed C(sp^3)-H alkynylation of α-amino acids and oligopeptides.

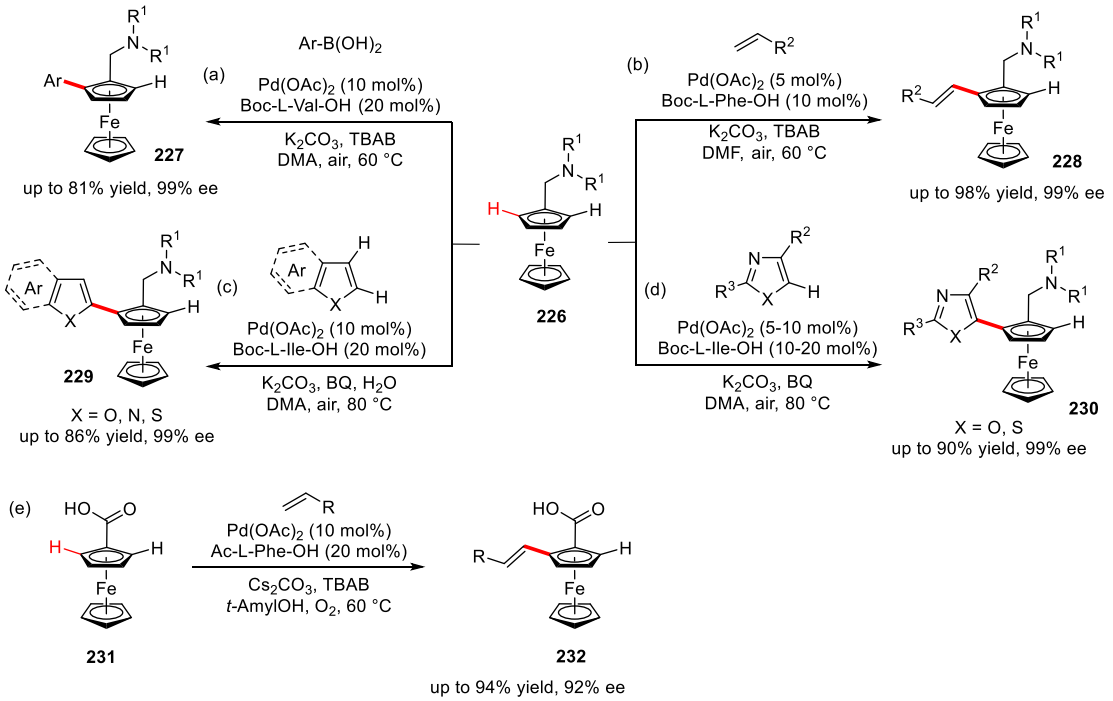
12.05.2.5 Enantioselective C-H activation

A breakthrough for Pd-catalyzed enantioselective C-H functionalization, applying the mono-*N*-protected chiral amino acids (MPAAs) as viable ligands, was first made by the Yu group. Prochiral pyridines **214** reacted with alkylboronic acids in the presence of $Pd(OAc)_2$ and (−)-Men-L-Leu-OH (**L19**), affording triarylmethane compounds **215** in up to 96% yield with 95% ee (Scheme 68A).[102a] This work greatly promoted the development of Pd-catalyzed asymmetric C—H bond functionalizations. Later, the Yu group extended the method to the carboxylate or *N*-nosyl group directed asymmetric C—H bond olefination and arylation (Scheme 68B and C).[102b,c] Kinetic resolution, which relies on the different reaction rates of enantiomers, is widely used in organic synthesis. In 2015, Yu and coworkers described a kinetic resolution of racemic mandelic and phenylglycine pivalate derivatives **220** via dehydrogenative Mizoroki–Heck reaction (Scheme 68D).[102d] In addition, C-H arylation of N-nosyl benzylamines **222** with arylboronic acid pinacol esters was achieved, provideind enantioenriched bezylamine derivatives **223** with up to 135 s value (Scheme 68E).[102e] The utilization of Pd(II)/Pd(0) catalysis also led to the synthesis of *P*-stereogenic phosphoamides. Han and workers found that MPAA ligand **L20** provided high levels of enantiocontrol in the desymmetric C-H arylation of phosphoamides compound **224**. The reaction could be successfully conducted on a gram-scale, and the utility of this methodology was further demonstrated by derivatization of products **225** to potentially useful ligands without significant erosion in enantiopurity (Scheme 68F).[102f]



Scheme 68 Pd-catalyzed enantioselective C(sp^2)—H bond functionalization to construct central chirality.

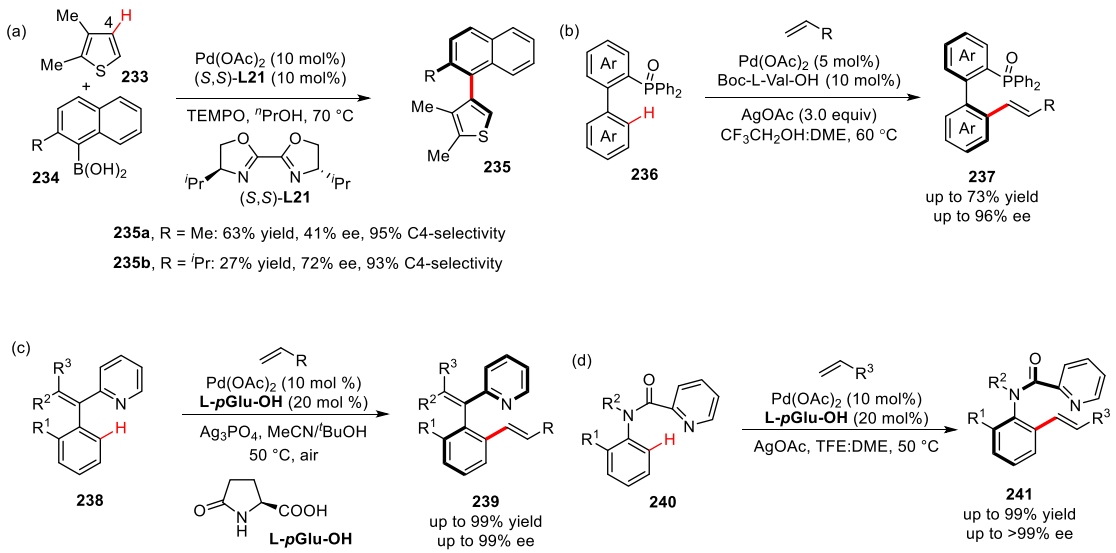
Based on the Sokolov's and Richards' works regarding the synthesis of planar chiral ferrocene palladacycle compounds with stoichiometric amounts of MPAA, several groups developed Pd/MPAA-catalyzed enantioselective Cp—H bond functionalization using the Pd(II)/Pd(0) catalytic system. In 2013, Gu, You and their coworkers achieved Pd-catalyzed asymmetric C-H arylation of dialkylaminomethylferrocene derivatives **226** with arylboronic acids by using Boc-L-Val-OH as the chiral ligand. This reaction could well tolerate various substituted arylboronic acids, affording their corresponding mono-arylated ferrocene derivatives **227** in up to 81% yield with 99% ee (Scheme 69A).[103a] Meanwhile, Wu, Cui and their coworkers also achieved an asymmetric oxidative Heck reaction using Pd/MPAA catalyst under similar conditions. Various olefins, such as vinylcyclohexanes, acrylates and styrene



Scheme 69 Pd-catalyzed enantioselective C(sp^2)—H bond functionalization to construct planar chirality.

derivatives were found to be suitable for this reaction with up to 98% yield and 99% ee (Scheme 69B).[103b] To further improve the atom economy, the You group accomplished an enantioselective twofold C-H oxidative cross-coupling reaction of ferrocene **226** with heteroarenes in up to 86% yield with 99% ee (Scheme 69C).[103c] Unfortunately, electron-deficient and electron-neutral arenes, such as imidazole, oxazole and pentafluorobenzene did not occur under the optimized conditions. In addition, the You group found that oxazoles and thiazoles were also suitable substrates in the Pd(II)-catalyzed enantioselective C-H/C-H heteroarylation of ferrocenes **226** (Scheme 69D).[103d] This method showed excellent regioselectivity toward C5—H bond of various substituted oxazoles and thiazoles. Apart from dialkylaminomethyl as a feasible directing group, other directing groups were less investigated in Pd(II)-catalyzed asymmetric C—H bond functionalization of ferrocenes. Until recently, the carboxylic acid was identified as an effective directing group in the Pd-catalyzed *ortho*-alkenylation reaction reported by Wu, Cui, and coworkers. Planar chiral 1,2-disubstituted ferrocenecarboxylic acids **232** were generated in up to 94% yield with 92% ee (Scheme 69E).[103e]

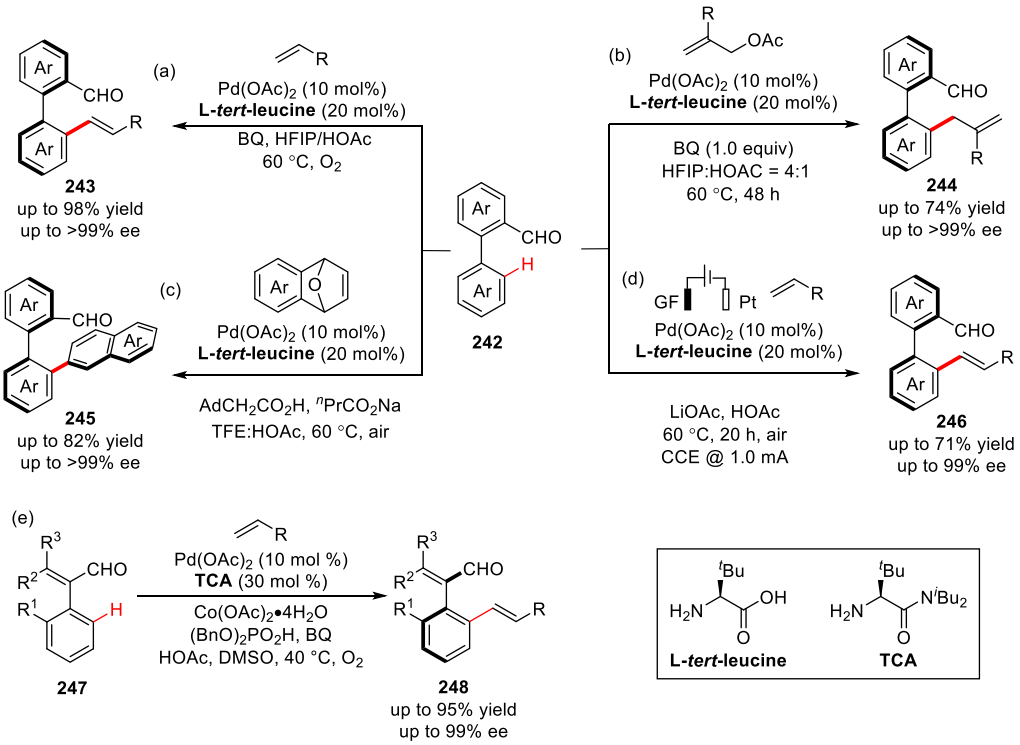
Under Pd(II)/Pd(0) catalysis, the efficient construction of axially chiral compounds has also been successfully realized. In 2012, Yamaguchi, Itami and coworkers reported the Pd-catalyzed asymmetric coupling reaction of thiophene **233** and arylboronic acids **234** to construct sterically hindered heteroaromatic biaryl compounds. With chiral bisoxazoline **L21** as the ligand and TEMPO as the oxidant, the corresponding axially chiral thiophenes **235a** were obtained in 63% yield with 41% ee. With the steric hindrance increased, the ee value was further improved to 72%, albeit with decreased yield (27%)(Scheme 70A).[104a] In 2017, the Yang group



Scheme 70 Pd-catalyzed enantioselective C(sp^2)—H bond functionalization to construct axial chirality.

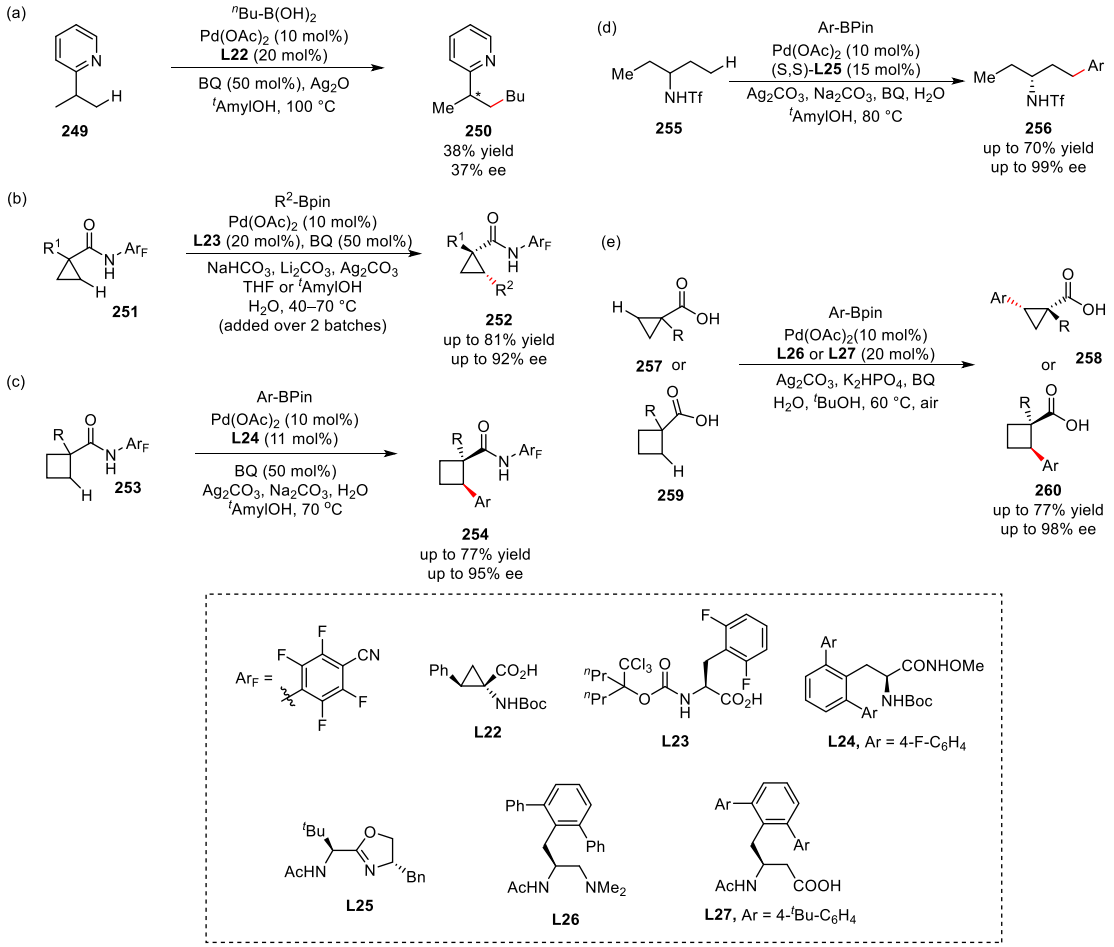
used phosphine oxide as the directing group to develop a Pd-catalyzed asymmetric alkenylation reaction, constructing various axially chiral biaryl phosphine oxides **237** efficiently in up to 73% yield with 96% ee (Scheme 70B).[104b] Shi and coworkers accomplished a highly atroposelective synthesis of axially chiral styrenes **239** bearing an open-chained alkene via asymmetric C-H olefination reaction in up to 99% and 99% ee assisted by L-pyroglutamic acid (Scheme 70C).[104c] This reaction could be also applicable to the enantioselective synthesis of atropisomeric anilides **241** in up to 99% yield with 99% ee (Scheme 70D).[104d]

The transient directing group strategy has been widely utilized in the C–H arylation reactions as described (Section 12.05.2.1). In 2017, the Shi group successfully applied this strategy for the asymmetric synthesis of axially chiral compounds. With *tert*-leucine as a chiral transient directing group, the enantioselective C—H bond alkenylation reaction proceeded smoothly with oxygen as the oxidant, generating the axially chiral alkenyl substituted biaryl compounds **243** with up to 99% ee (Scheme 71A). [105a] The kinetic resolution process of biaryl compounds was also studied, with *s* value up to 600. Hereafter, they extended this strategy to the asymmetric allylation of biaryl compounds. The allyl-substituted biaryl compounds **244** were obtained in up to 74% yield and 99% ee by using *tert*-leucine as the chiral transient directing group and benzoquinone (BQ) as the oxidant (Scheme 71B).[105b] Additionally, the Shi group also successfully realized the asymmetric C-H naphthylation reaction of biaryl compounds with 7-oxabenzonorbornadiene (Scheme 71C).[105c] Further transformation of the naphthylation product **245** provided an efficient chiral aldehyde catalyst in the asymmetric reaction of (*E*)-chalcone with glycine derived amides. A novel enantioselective palladaelectro-catalyzed C–H olefination reaction was achieved by Ackermann et al. through the synergistic cooperation with the transient directing group in 2020. Enantioenriched biaryls **246** were obtained in up to 71% yield with 99% ee (Scheme 71D).[105d] This method also provides an access to novel chiral BINOL, dicarboxylic acid and spirene which are potentially valuable in asymmetric catalysis. Soon after, with bulky amino amide **TCA** as a transient directing group, an effective and practical method to construct a new type of axially chiral styrene by Pd-catalyzed enantioselective C-H olefination reaction was reported by the Shi group. Various axially chiral styrenes **248** were generated in up to 95% yield and 99% ee (Scheme 71E).[105e] The axially chiral styrene carboxylic acids obtained by further transformation exhibited superior enantiomeric control in the Co(III)-catalyzed enantioselective C(sp^3)-H amidation reaction.



Scheme 71 Synthesis of axially chiral compounds by the transient directing group strategy.

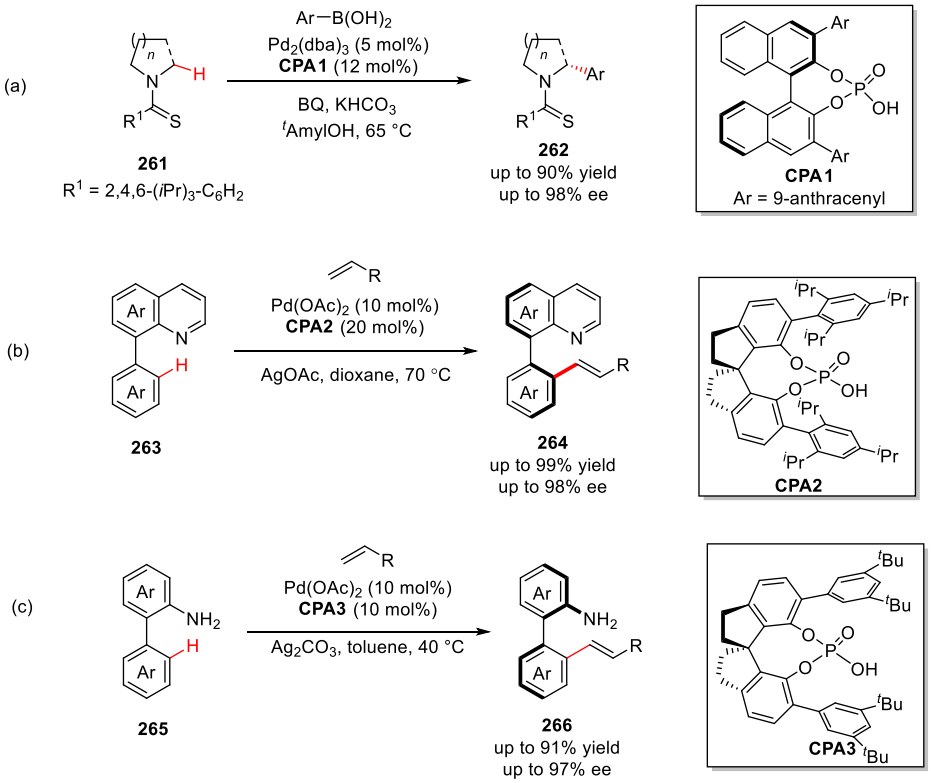
The pioneering example of Pd-catalyzed enantioselective C(sp^3)-H functionalization was reported by Yu in 2008. The directed C(sp^3) – H butylation of 2-isopropylpyridine **249** with *t*-BuB(OH)$_2$ was achieved by employing cyclopropyl amino acid **L22** as the ligand under Pd(II)/Pd(0) catalysis, albeit in 38% yield with 37% ee (Scheme 72A).[106a] In 2011, the amide-directed intermolecular



Scheme 72 Pd-catalyzed enantioselective C(sp^3)—H bond functionalization to construct central chirality.

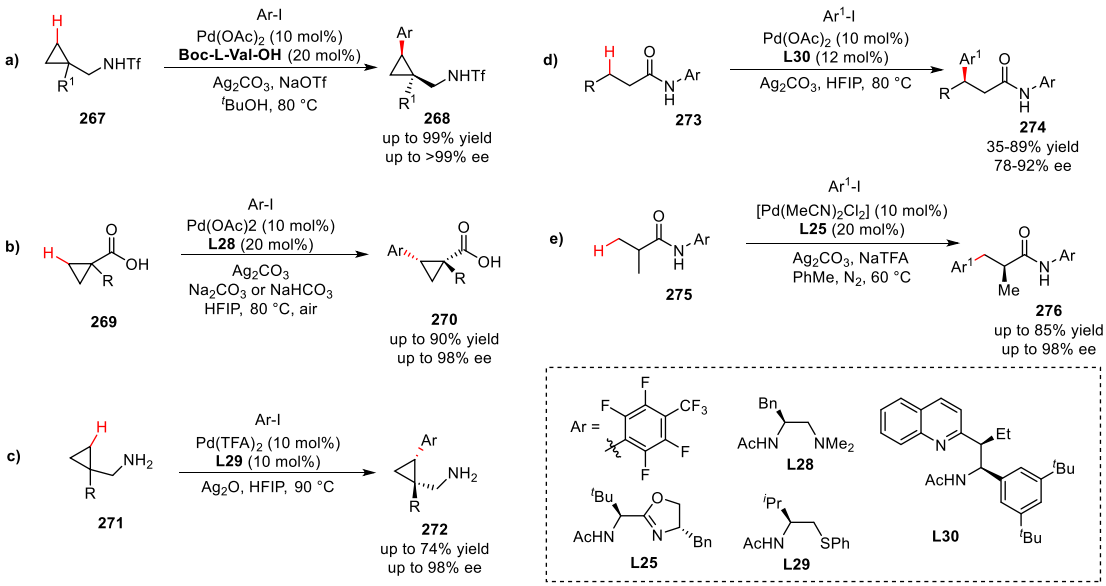
asymmetric C(sp^3)-H arylation of cyclopropane **251** with organoboron reagents was developed in up to 81% yield with 92% ee (Scheme 72B).[106b] This methodology was later extended to asymmetric C(sp^3) – H arylation of cyclobutyl amides **253** (Scheme 72C).[106c] In 2018, they achieved Pd(II)-catalyzed asymmetric γ-C(sp^3) – H arylation of alkyl amines **255** via desymmetrization by using chiral acetyl-protected aminomethyl oxazoline **L25** (APAO) as the optimal ligand. Various vinyl- or arylboron reagents can be used as coupling partners (Scheme 72D).[106d] Carboxylic acids are commonly used feedstocks. Pd-catalyzed asymmetric C(sp^3) – H arylation of cyclopropane carboxylic acids **257** and **259** with an inherent directing group was realized with chiral monoprotected aminoethyl amine ligand **L26 or L27** (Scheme 72E).[106e] This reaction provides a new method for preparing chiral carboxylic acid derivatives **258** and **260** with high efficiency.

The combination of chiral phosphoric acid (CPA) with palladium catalysis has also been demonstrated to enable enantioselective C – H functionalizations. In 2016, the Yu group reported that Pd(II)-catalyzed enantioselective C(sp^3) – H α-arylation of thioamide **261** with aryl boronic acid, affording enantioenriched products **262**. Among the tested ligands, chiral phosphoric acid **CPA1** gave the best results in up to 90% yield and 98% ee (Scheme 73A).[107a] The Shi group achieved an asymmetric C-H alkenylation reaction of 8-arylquinoline **263** using chiral SPINOL-derived phosphoric acid **CPA2** combined with $Pd(OAc)_2$, constructing a class of axially chiral quinoline derivatives with high efficiency. With silver acetate as an oxidant, axially chiral alkenyl-substituted 8-arylquinoline derivatives **264** were obtained with up to 98% ee (Scheme 73B).[107b] The free amine could also act as a directing group to enable the Pd(II)-catalyzed asymmetric C(sp^3)-H alkenylation reaction. Various axially chiral biaryl-2-amines **265** were obtained in up to 91% yield and up to 97% ee in the presence of chiral phosphate anion of **CPA3** (Scheme 73C).[107c] In a gram-level synthesis, the loading of **CPA3** could be reduced to 1 mol% without any erosion in terms of enantioselectivity.



Scheme 73 Enantioselective C – H functionalizations enabled by the combination of palladium and chiral phosphoric acid.

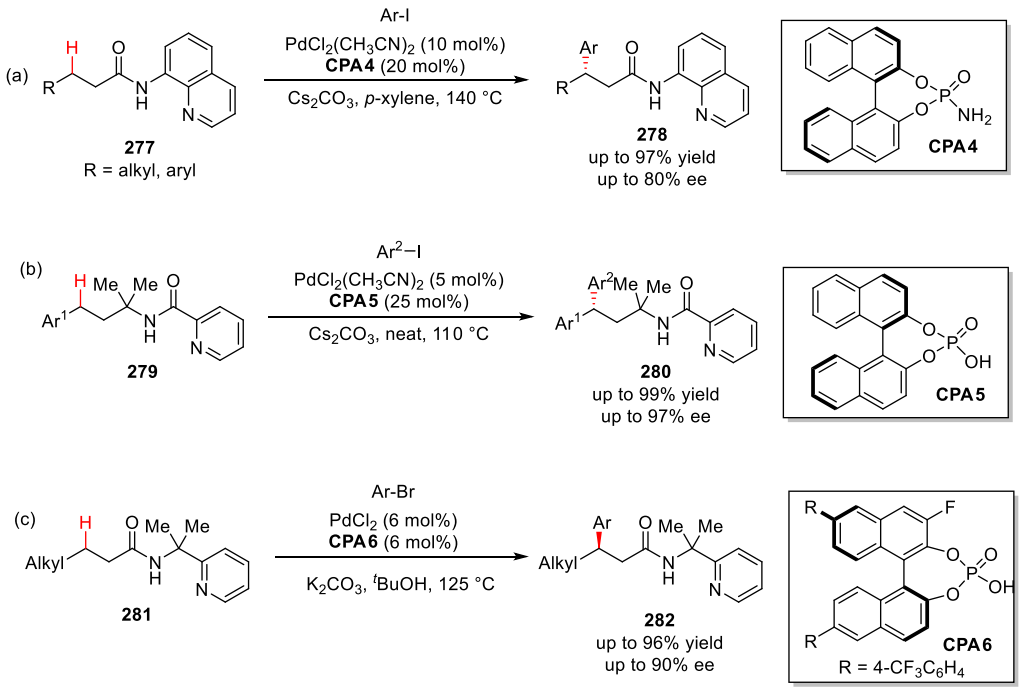
Besides these Pd(II)-initiated asymmetric C – H functionalizations through Pd(II)/Pd(0) catalytic cycle under oxidative conditions, notable progresses on asymmetric C(sp^3) – H functionalizations have also been made through Pd(II)/Pd(IV) catalytic cycle. An elegant example of Pd(II)-catalyzed asymmetric C(sp^3)—H bond arylation was accomplished by the Yu group in 2015. In this work, trifluoromethyl-protected cyclopropylmethylamine **267** was coupled with aryl iodides to provide arylation products **268** with up to >99% ee (Scheme 74A).[108a] Both oxidative addition and reductive elimination were promoted by the addition of silver



Scheme 74 Asymmetric C(sp^3) – H functionalizations through Pd(II)/Pd(IV) catalytic cycle.

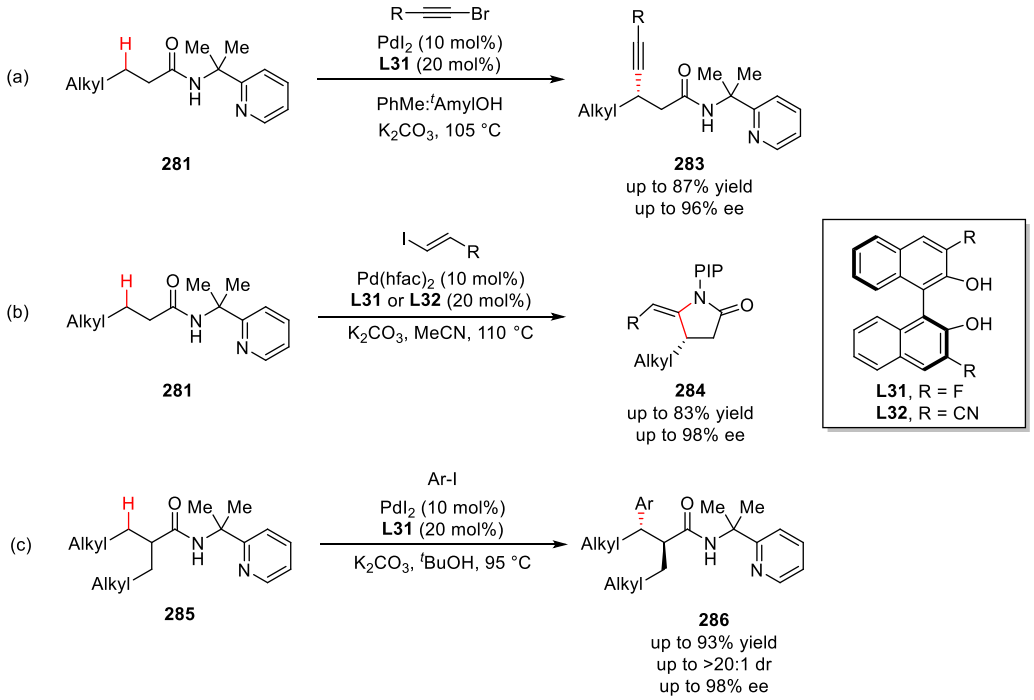
carbonate. In addition, coupling a wide range of α-substituted cyclopropanecarboxylic acids **269** with aryl iodides was accomplished by chiral monoprotected aminoethyl amine ligand **L28** in up to 90% yield with 98% ee (Scheme 74B).[108b] Recently, they also realized Pd-catalyzed enantioselective C(sp^3) – H arylation of free aliphatic amines **271** with a chiral bidentate thioether ligand **L29** (Scheme 74C).[108c] In 2016, Yu, Houk and coworkers reported a procedure for asymmetric C(sp^3)—H bond arylation of acyclic amide derivatives **273**. With the bidentate acetyl-protected aminoquinoline **L30** as the optimal ligand, diverse arylated amide products **274** were obtained in 35–89% yields with 78–92% ee (Scheme 74D).[108d] Bidentate *N*-acetyl-protected aminomethyl chiral oxazoline **L25** (APAO) could enable the enantioselective arylation of isobutyramide **275** in up to 85% yield with 98% ee (Scheme 74E).[108e]

In 2015, the Duan group demonstrated for the first time that chiral phosphoramide **CPA4** could be utilized in the generation of stereochemical C(sp^3)-H activation events through Pd(II)/Pd(IV) catalytic cycle albeit with relatively low enantioselective control (up to 80% ee) (Scheme 75A).[109a] One year later, Chen, He and coworkers achieved picolinamide-directed benzylic C(sp^3) – H arylation of amides **279** with aryl iodides under slightly modified conditions. With BINOL-derived phosphate **CPA5**, a variety of structurally multiple arylation products **280** were obtained in up to 99% yield and 97% ee (Scheme 75B).[109b] In 2018, Shi and coworkers reported a Pd(II)-catalyzed asymmetric C-H arylation of unbiased methylene β-C(sp^3)—H bonds, combining a strongly coordinating bidentate 2-pyridinylisopropyl (PIP) directing group with chiral phosphoric acid (**CPA6**) (Scheme 75C).[109c]



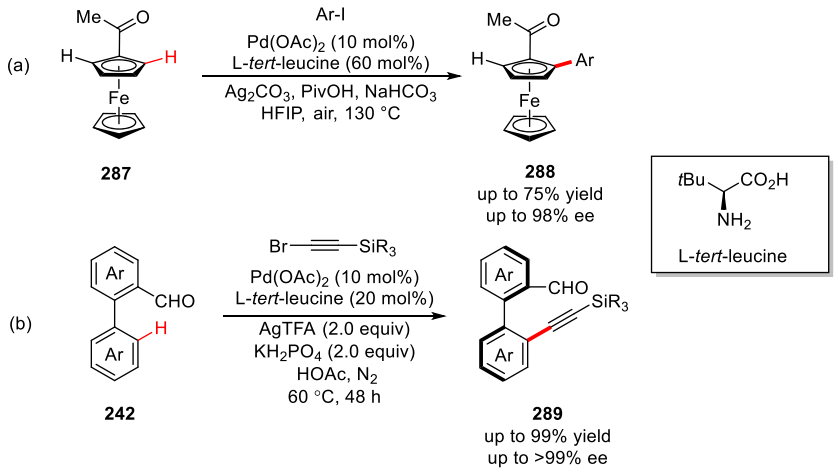
Scheme 75 Asymmetric C(sp^3)-H arylation enabled by Pd/chiral phosphoric acid (phosphoramide).

BINOLs were introduced by the Shi group as suitable ligands in Pd(II)-catalyzed enantioselective alkynylation of methylene β-C(sp^3)—H bonds in 2017. 3,3′-Fluorinated-BINOL **L31** was identified to have a prominent effect on both reactivity and enantioselectivity (up to 96% ee) (Scheme 76A).[110a] Subsequently, Shi and coworkers described an elegant cascade reaction involving Pd(II)-catalyzed asymmetric aliphatic methylene C(sp^3)-H olefination and aza-Wacker cyclization through *syn*-aminopalladation. The γ-lactams **284** with a broad range of functionalities were obtained with up to 98% ee (Scheme 76B).[110b] Recently, the synthesis of acyclic aliphatic amides **286** bearing continuous chiral centers was accomplished via Pd(II)-catalyzed enantioselective methylene C(sp^3)-H arylation. The method can be applicable to a wide range of aryl iodides, providing a practical platform for constructing α,β-chiral aliphatic amides **286** in up to 93% yield with >20:1 dr and 98% ee (Scheme 76C).[110c]



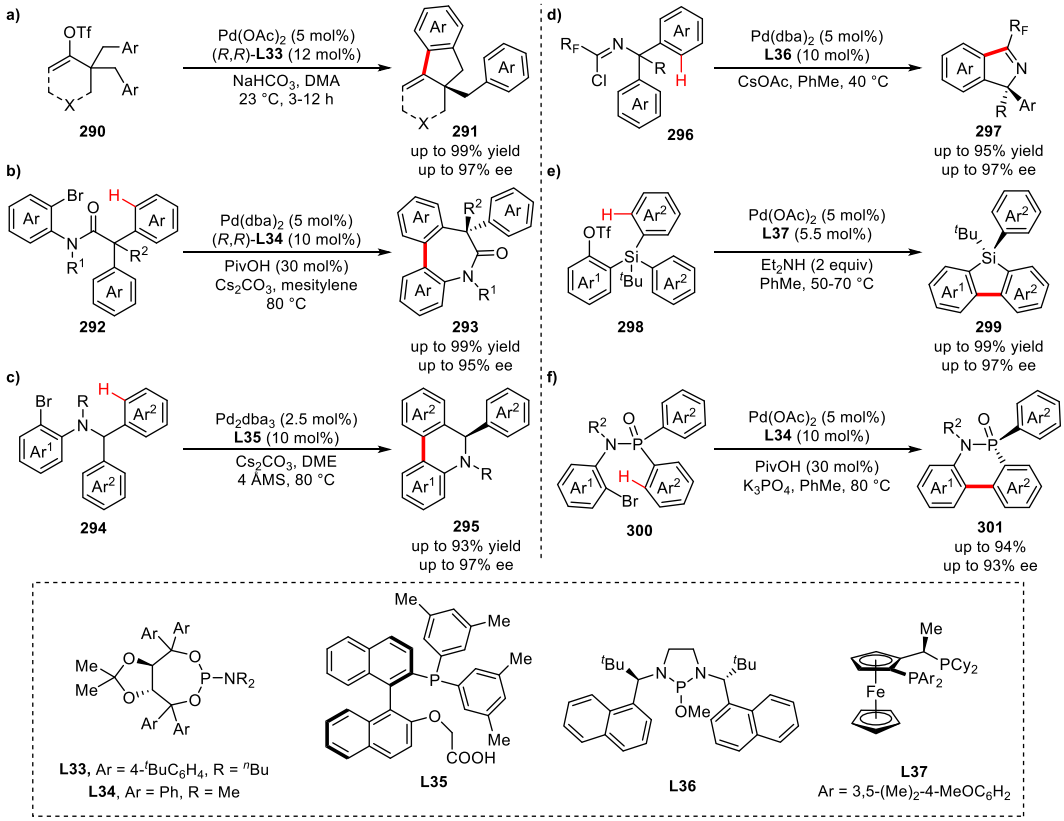
Scheme 76 Enantioselective C(sp^3) – H alkynylation, alkenylation, and arylation enabled by Pd/ BINOLs.

In 2018, Jin, Xu and coworkers employed L-*tert*-leucine as a transient directing group to achieve Pd-catalyzed enantioselective C(sp^2)-H arylation of ferrocenyl ketones **287** (Scheme 77A).[111a] In general, various electron-withdrawing aryl iodides, such as nitro, ester and amide, were well tolerated, while neutral and electron-rich aryl iodides showed lower reactivity. In the same year, the Shi group also applied this transient directing group strategy to enantioselective C(sp^3)—H bond alkynylation reaction of biaryl compounds **242**. Various axially chiral alkynyl substituted biaryl compounds **289** were obtained with up to 99% ee (Scheme 77B).[111b]



Scheme 77 Pd-catalyzed enantioselective C(sp^2)-H arylation by transient directing group strategy.

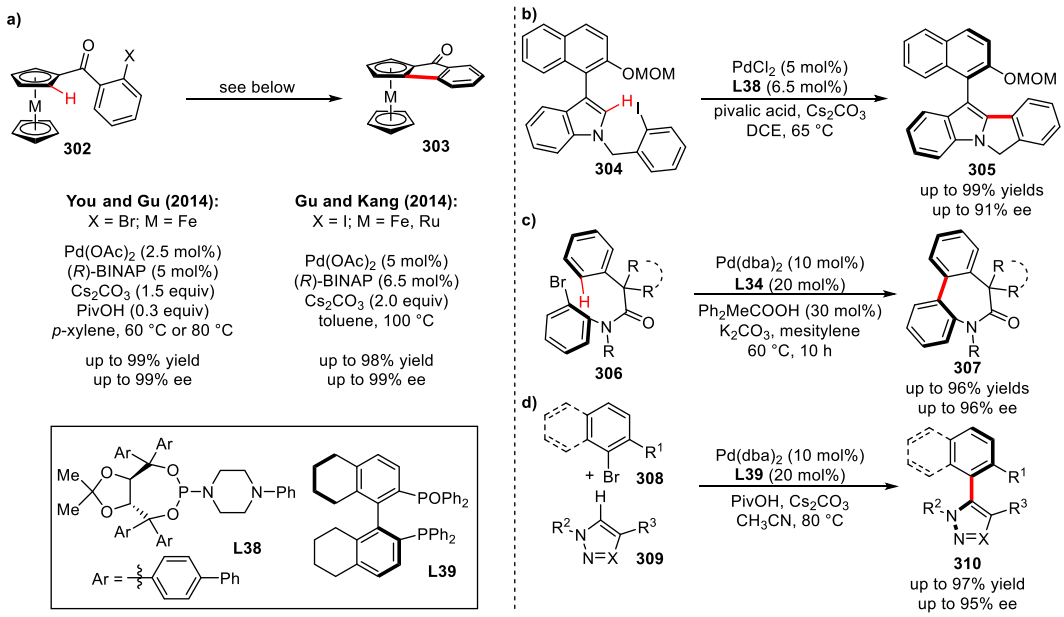
The pioneering example of asymmetric C–H arylation reaction via Pd(0)/Pd(II) catalysis was developed by the Cramer group in 2009. The intramolecular arylation of vinyl triflates **290** gave chiral indanes **291** bearing an all-carbon quaternary stereocenter in up to 99% yield and 97% ee (Scheme 78A).[112a] In 2013, Saget and Cramer extended this method to the asymmetric C–H arylation of amides **292**, providing a variety of dibenzozeheptanones **293** in up to 99% yield with 95% ee. It is worth mentioning that this reaction proceeds via a rare eight-member palladacycle (Scheme 78B).[112b] In 2018, Baudoin and coworkers reported the design and synthesis of novel chiral difunctional ligands by incorporating the phosphine and carboxylic acid moieties into a binaphthyl backbone. The optimal ligand **L35** enabled asymmetric C(sp^2)-H arylation reaction, resulting in 5,6-dihydro-phenanthridine **295** in up to 93% yield with 97% ee (Scheme 78C).[112c] Subsequently, the Cramer group disclosed an enantioselective synthesis of 1*H*-isoindoles **297** by asymmetric C-H arylation of trifluoroacetimidoyl chlorides **296** in the presence of phosphordiamidite ligand **L36** (Scheme 78D).[112d] In 2012, Shintani, Hayashi and coworkers developed a Pd-catalyzed enantioselective synthesis of Si-stereogenic dibenzosiloles **299** through desymmetrization of triarylsilanes **298** with Josiphos-type ligand **L37** (Scheme 78E).[112e]



Scheme 78 Central chirality construction by Pd(0)-catalyzed C-H arylation reactions.

The development of highly efficient synthesis of P-chiral ligands has been an important topic due to their wide applications in asymmetric catalysis. An asymmetric C-H arylation of prochiral phosphinic amides **300** was described by the Duan group in 2015, providing azaphosphinine oxides **301** bearing a P-stereogenic center in up to 94% yield with 93% ee (Scheme 78F).[112f]

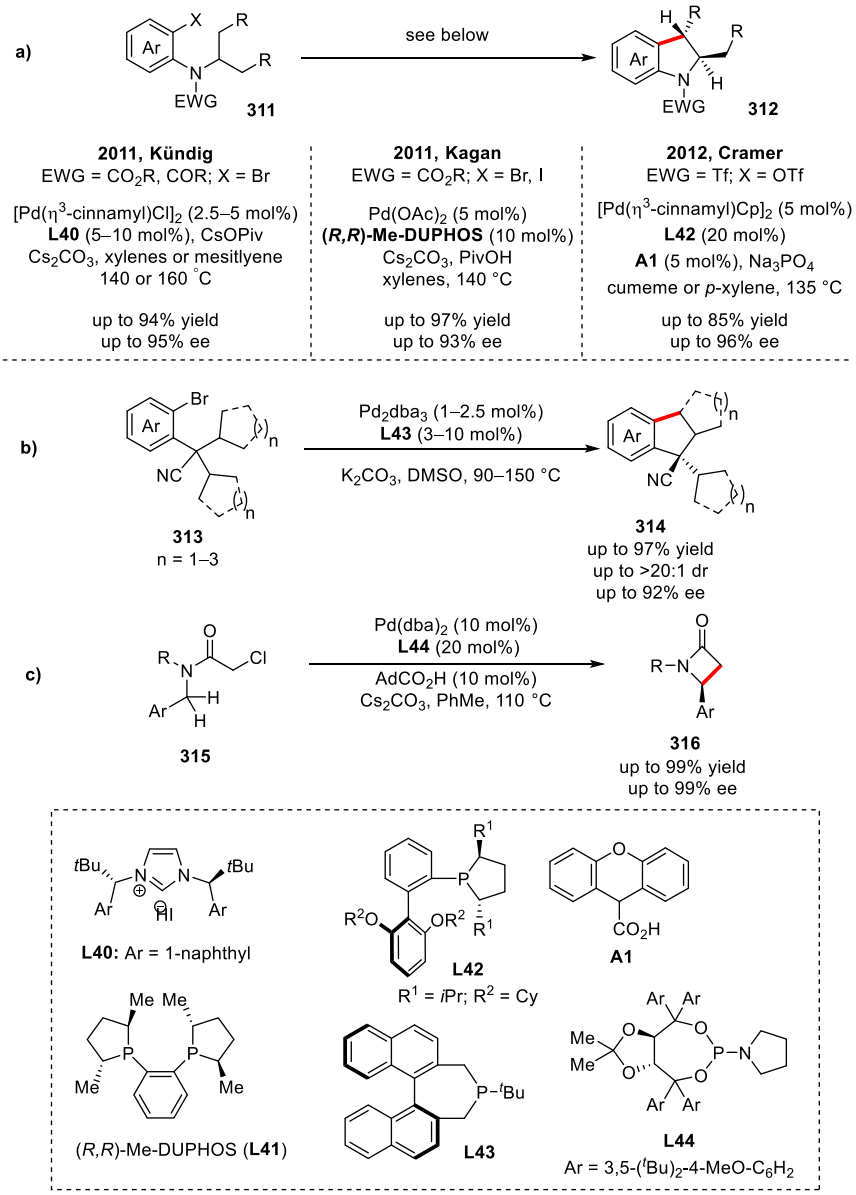
A great number of asymmetric C-H activation for constructing axial and planar chiral compounds have also been disclosed. In 2014, You and Gu, and Gu and Kang independently reported the synthesis of planar chiral ferrocenes by enantioselective intramolecular C-H arylation. You and Gu developed a Pd-catalyzed asymmetric cyclization of 2-bromobenzoylferrocenes **302** with BINAP as the ligand, affording arylated products **303** in up to 99% yield and 99% ee.[113a] At the same time, Gu, Kang and co-workers disclosed the same C-H arylation reaction of aryl iodides under similar conditions (Scheme 79A).[113b] Of particular note,



Scheme 79 Axial and planar chirality construction by Pd(0)-catalyzed C-H arylation reactions.

ruthenocene derivatives were also suitable substrates. In 2017, the Gu group developed an intramolecular C-H arylation for the construction of indole-based atropisomers **305**. With TADDOL-phosphoramidite **L38**, the products were obtained in up to 99% yield with 91% ee in this dynamic kinetic resolution (Scheme 79B).[113c] The synthesis of axially chiral dibenzazepinones **307** similarly by intramolecular C-H arylation was reported by the Cramer group in 2015. Excellent enantiocontrol was achieved, by employing a simple TADDOL-derived phosphoramidite ligand **L34**. DFT calculations indicated that C–H activation proceeded via an enantiodetermining CMD step to generate a configurationally stable 8-membered palladacycle (Scheme 79C).[113d] Very recently, they realized an intermolecular enantioselective C-H arylation of heteroarenes **309** with aryl bromides **308**, providing an efficient access to atropisomeric heterobiaryls **310** in up to 97% yield with 95% ee (Scheme 79D).[113e]

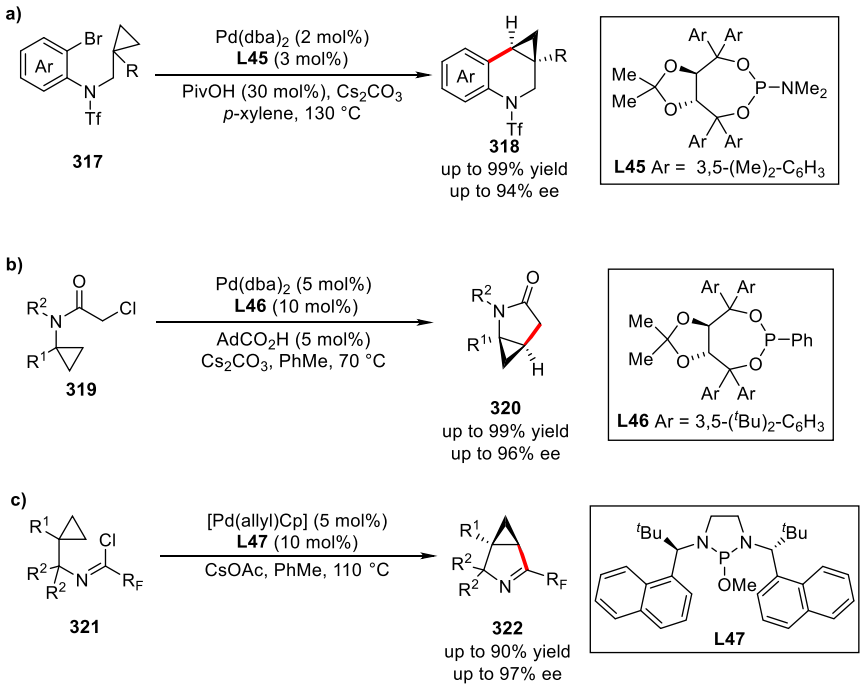
Several groups have been engaged in the Pd(0)-catalyzed asymmetric C(sp^3)—H bond functionalization reactions for the synthesis of enantioenriched indoline derivatives. In 2011, Kündig and coworkers pioneeringly achieved the asymmetric C—H bond arylation of *N*-cycloalkyl substituted carbamates **311** by a chiral Pd complex derived from a bulky NHC ligand (from precursor **L40)** (Scheme 80A).[114a] The same year, Kagan and coworkers found that chiral bisphosphine (*R, R*)-Me-DuPhos (**L41**) could be utilized in Pd-catalyzed C—H bond arylation reaction.[114b] In 2012, the Cramer group synthesized a new class of monodentate phosphine ligand **L42**, which could efficiently promote C-H arylation of **311** in up to 85% yield with 96% ee.[114c] Baudoin et al. applied an intramolecular C-H arylation to the asymmetric synthesis of fused cyclopentane compounds. The combination of $Pd(OAc)_2$ and binepine ligand **L43** could give an array of desired products **314** in up to 97% yield with up to > 20:1 dr and 92% ee (Scheme 80B).[114d] β-Lactams **316** could be prepared from



Scheme 80 Pd(0)-catalyzed asymmetric C(sp^3)—H bond functionalizations.

chloroacetamides **315** by an intramolecular C-H alkylation (Scheme 80C).[113e] The palladium catalyst derived from bulky phosphoramidite ligand **L44** together with adamantyl carboxylic acid as a co-catalyst provided excellent enantioselectivity.

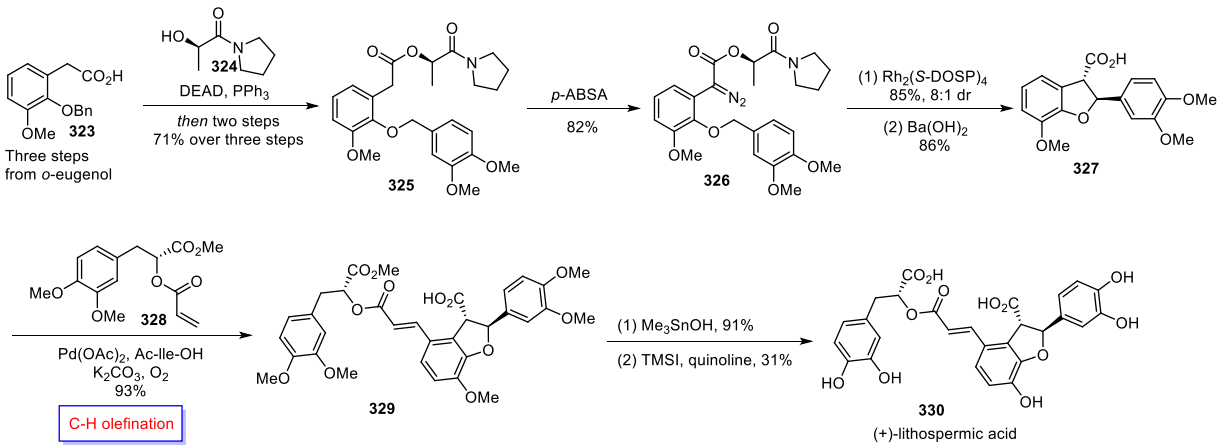
Cyclopropane motifs are found in many natural products and bioactive compounds. The Cramer group accomplished an efficient access to functionalized enantioenriched tetrahydroquinolines **318** through the direct C—H bond functionalization of cyclopropanes **317** (Scheme 81A).[115a] Remarkably, a gram-scale reaction could be completed with only 1 mol% Pd catalyst. With TADDOL-derived phosphoramidite **L46** as chiral ligand in combination with adamantane-1-carboxylic acid as a cocatalyst, an array of γ-lactams **320** could also be accessed via the intramolecular alkylation of cyclopropyl C(sp^3)—H bonds (Scheme 81B).[115b] In 2017, the Cramer group reported that a new diazaphospholane ligand **L47** enabled highly enantioselective cyclopropane C—H bond activation with trifluoroacetimidoyl chlorides **321** as electrophilic partners (Scheme 81C).[115c] The resulting cyclic ketimines **322** reacted smoothly with diverse nucleophiles in one-pot process, yielding multi-substituted pyrrolidines.



Scheme 81 Pd(0)-catalyzed asymmetric C(sp3)–H functionalizations of cyclopropanes.

12.05.2.6 Applications in organic synthesis

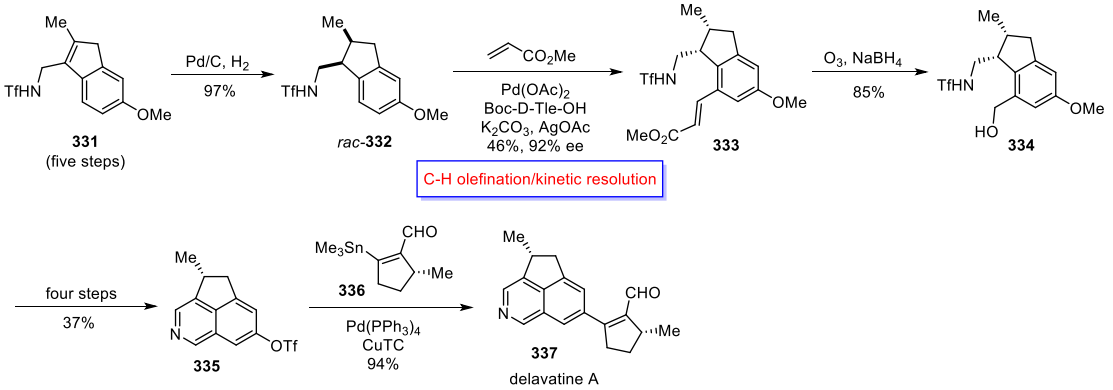
Versatile C-H functionalization reactions have witnessed wide applications in the total synthesis of naturally occurring compounds with interesting biological activity. Several notable examples are introduced here. The total synthesis of (+)-lithospermic acid was accomplished in 12 steps and 11% overall yield from *o*-eugenol, reported by the Yu group (Scheme 82). First, acid **323** from readily



Scheme 82 The total synthesis of (+)-lithospermic acid.

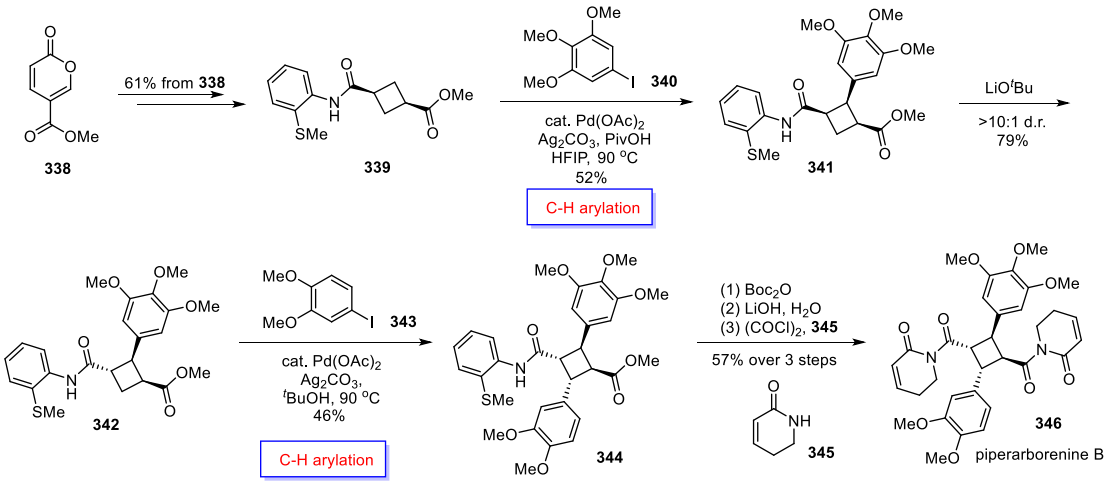
available o-eugenol in three steps was esterified with chiral hydroxyamide **324** and underwent two-step sequence to give **325**. Second, treatment of **325** with diazo transfer reagent followed by a diastereoselective carbene insertion and ester hydrolysis provided the *trans*-dihydrobenzofuran core **327**. Gratifyingly, Pd-catalyzed C(sp^2)–H olefination with olefin **328** directed by the free carboxyl group furnished the protected natural product **329** in 93% yield. Finally, demethylation of **329** gave (+)-lithospermic acid (**330**).[116]

Shen, Li, Zhang and co-workers accomplished an asymmetric total synthesis of delavatine A on a gram-scale, via a longest linear sequence of 13 steps (Scheme 83). First, a *syn*-selective hydrogenation of **331**, prepared from a commercially available indanone over five steps, delivered racemic **332**. Second, kinetic resolution of **332** through Pd-catalyzed triflamide-directed C-H olefination provided enantioenriched olefinated product **333** in 46% yield on multigram scale. After ozonolysis/reduction, a four-step sequence gave the tricyclic coupling partner **335**. The Stille coupling with pulegone-derived fragment **336** finally afforded delavatine A (**337**).[117]



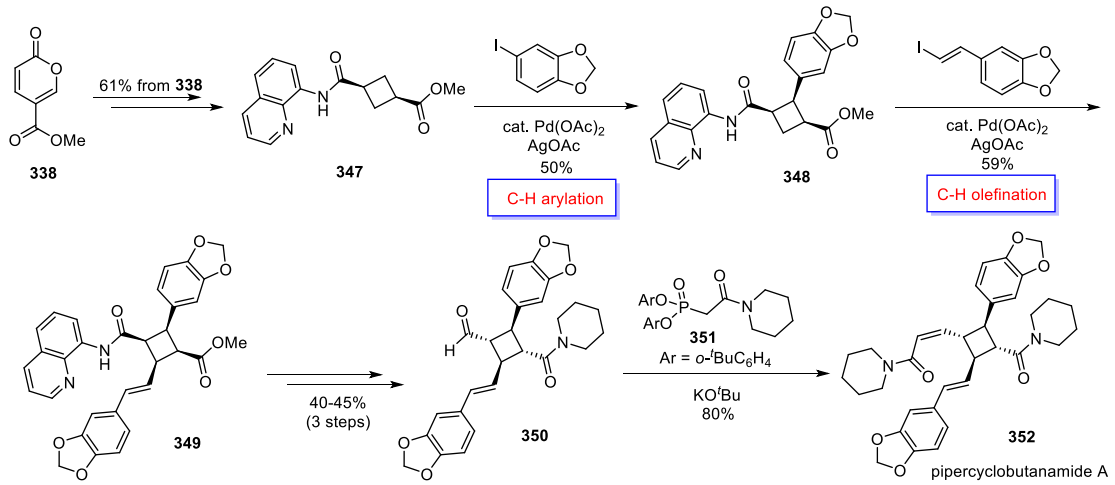
Scheme 83 The total synthesis of delavatine A.

In 2011, Baran and co-workers achieved a rapid divergent total synthesis of piperarborenine B (7 steps, 7% overall yield, Scheme 84). The concise routes demonstrate the power of guided C-H functionalization logic to enable a fundamentally novel approach to cyclobutane natural product synthesis. Notable elements of this synthesis include: (1) a one-step, stereo-controlled preparation of **339** from methyl coumalate (**338**); (2) sequential C(sp^3)-H arylation reactions of **339**; (3) divergent epimerization of **341** to provide both proposed piperarborenine stereoisomers; (4) second arylation of **342**, followed by ester hydrolysis and acylation with **345** finished piperarborenine B (**346**).[118]



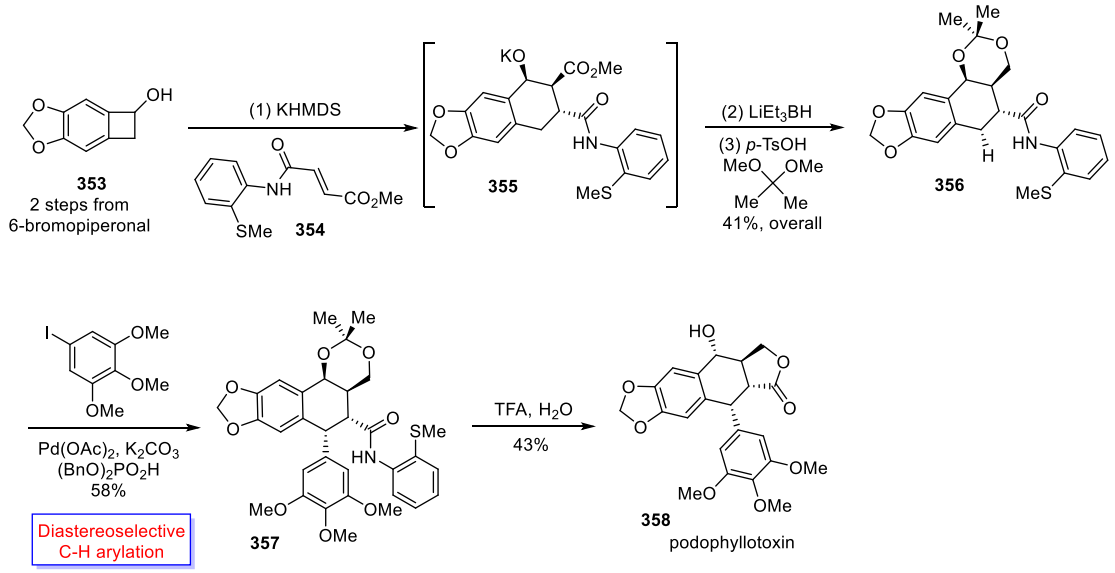
Scheme 84 Total synthesis of piperarborenine B.

Taking advantage of this method, a concise synthesis of pipercyclobutanamide A (**352**) was obtained from methyl coumalate (**338**) in 7 steps with 5% overall yield (Scheme 85). Salient features of the synthesis include: (1) sequential Pd-catalyzed C-H olefination and C-H arylation on an unactivated cyclobutane ring; (2) stereo-controlled access to highly strained all *cis* substituted cyclobutanes; (3) direct conversion of aminoquinoline amides to aldehydes.[119]



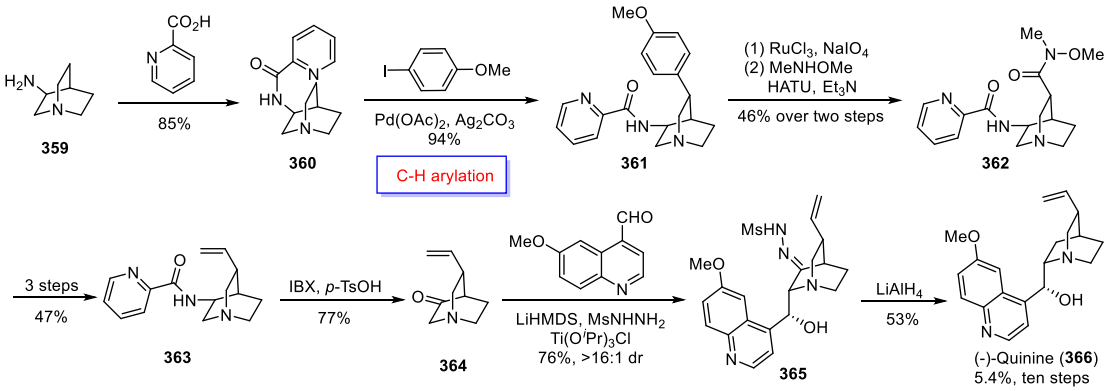
Scheme 85 Total synthesis of the proposed structure of pipercyclobutanamide A.

Maimone and coworkers realized a concise total synthesis of podophyllotoxin in six steps, enabled by a late-stage directed Pd-catalyzed C(sp^3)–H arylation reaction (Scheme 86). Deprotonation of free cyclobutanol **353** (2 steps from 6-bromopiperonal) and a subsequent highly diastereoselective cycloaddition with 2-methylthioaniline-containing amide **354** generated intermediate **355**, which underwent in situ reduction and protection to afford acetal **356**. Importantly, a C–H arylation installed the requisite aryl motif in **357** as a single diastereomer, which could then be directly cyclized under acidic conditions to give podophyllotoxin (**358**).[120]



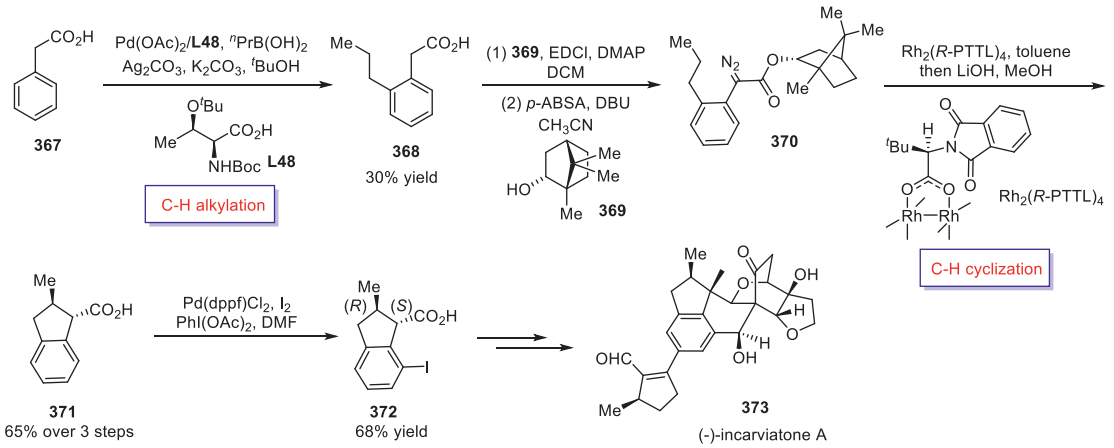
Scheme 86 Total synthesis of podophyllotoxin.

The implementation of C(sp^3)–H arylation strategy could also be applied into the construction of (–)-quinine (Scheme 87). In 2018, Maulide and coworkers reported an elegant synthesis of quinine in 10 steps based on two stereoselective key steps consisting of 1 C-H activation and one aldol reaction. Starting with **359**, installation of a picolinamide handle to give **360** enabled a diastereoselective C(sp^3)–H arylation of the quinuclidine scaffold. The arylated product **361** can be oxidatively manipulated to reveal the free acid and amidated to the corresponding Weinreb amide **362**, followed by a three-step sequence for the de novo generation of the vinyl group in **363**. The subsequent oxidation, diastereoselective aldol addition and Wolff-Kishner reduction furnished (–)-quinine (**366**).[121]



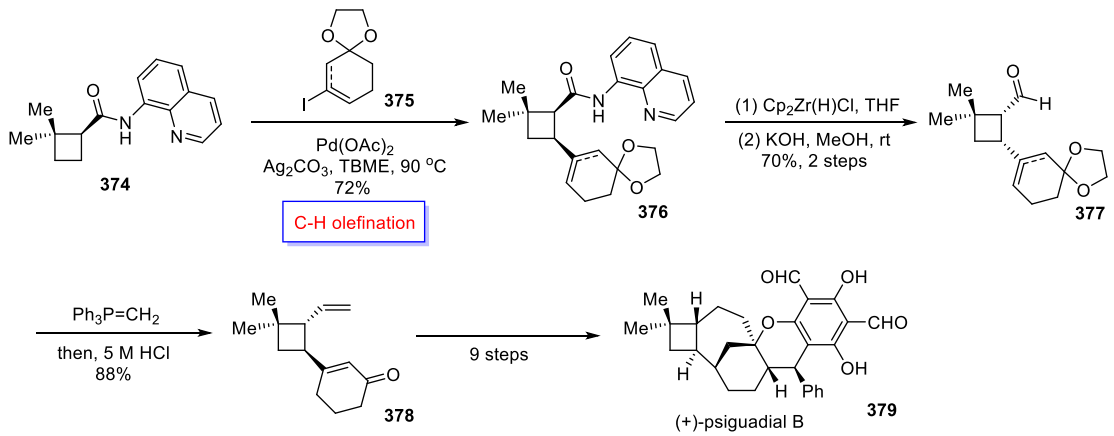
Scheme 87 Total synthesis of (–)-quinine.

Incarviatone A is a hybrid natural product, which revealed as a potent inhibitor of monoamine oxidase. The enantioselective synthesis of (−)-incarviatone A was reported in 2015 by Li, Lei and coworkers (Scheme 88). The *n*-propyl group was introduced to the phenyl ring by the carboxylic acid directed C-H alkylation. Subsequently, the cyclopentane ring in **371** was constructed by intramolecular Rh(II)-catalyzed C-H insertion from diazo precursor **370**. The carboxylic acid directed, Pd^{II}-catalyzed C-H iodination afforded **372** in a scalable manner. Overall, (−)-incarviatone A was obtained in 14 steps starting from commercially available phenylacetic acid.[122]



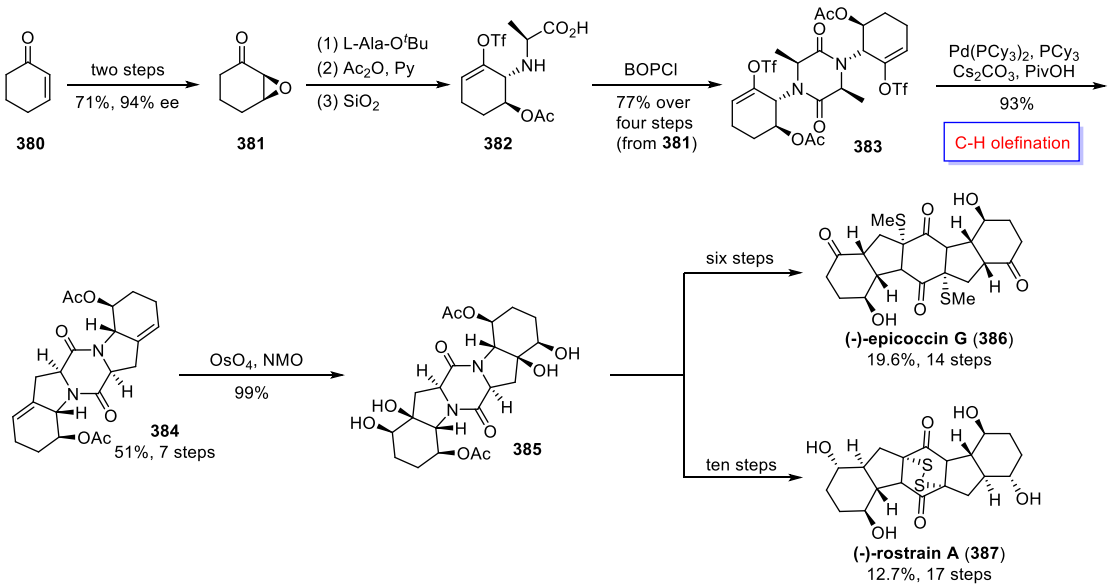
Scheme 88 Total synthesis of (–)-incarviatone A.

The total synthesis of the cytotoxic natural product (+)-psiguadial B (**379**) was completed in 15 steps from diazoketone **374**, employing Pd-catalyzed C(sp^3)–H alkenylation as the key C—C bond forming reaction towards constructing the overall skeleton for the target molecule (Scheme 89). Reduction of the amide, treatment with KOH in methanol, methylenation and hydrolysis provided (+)-**378**, which could give the natural product (+)-psiguadial B in nine steps.[123]



Scheme 89 Total synthesis of (+)-psiguadial B.

Thesmar and Baudoin successfully achieved the asymmetric total synthesis of the natural dithiodiketopiperazines (–)-epicoccin-G and (–)-rostratin A in 14 and 17 steps, respectively, with high overall yields from inexpensive starting materials (Scheme 90). The common precursor **385** to access both target molecules was readily synthesized using an enantioselective organocatalytic epoxidation and a bidirectional C(sp^3)–H alkenylation strategy to close the pentacycle as the key steps.[124]



Scheme 90 The total synthesis of (–)-epicoccin G and (–)-rostratin A.

12.05.3 Rh-catalyzed C—H bond functionalization

Rh-catalyzed C-H functionalization has witnessed significant progress over the past decades. There are mainly two accepted reaction cycles, exemplified by C-H alkylation with alkene (Fig. 4A, Rh(I)/Rh(III) cycle), C-H arylation with aryl halide (Fig. 4B, Rh(I)/

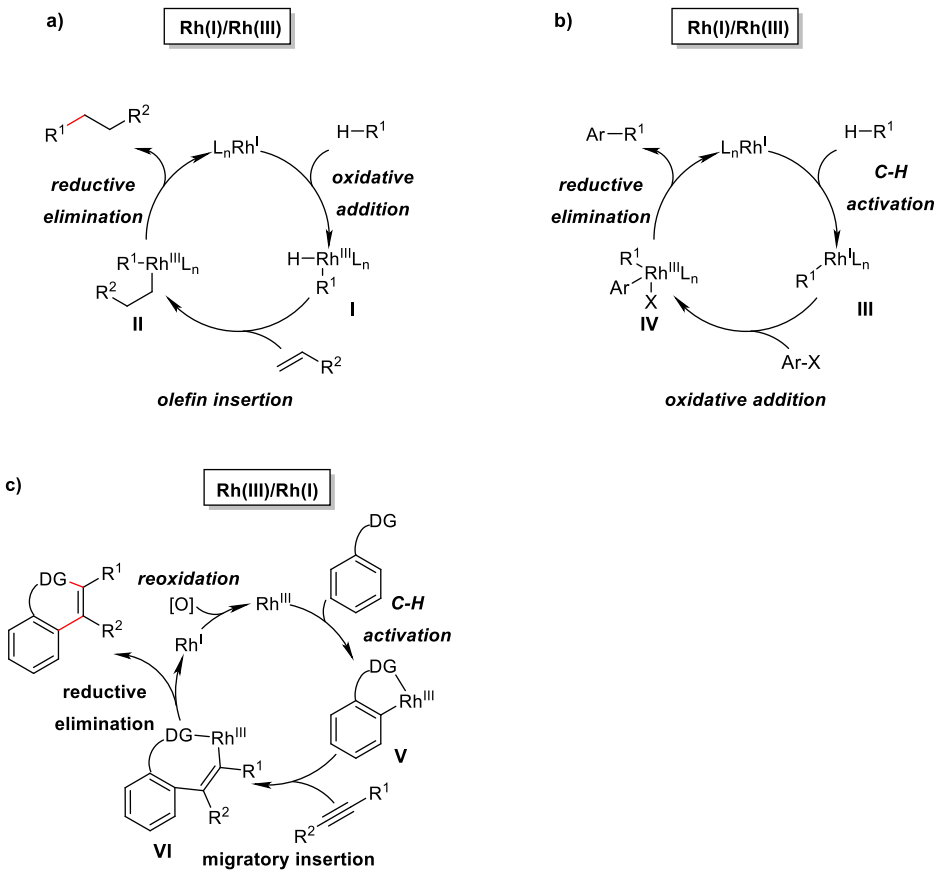
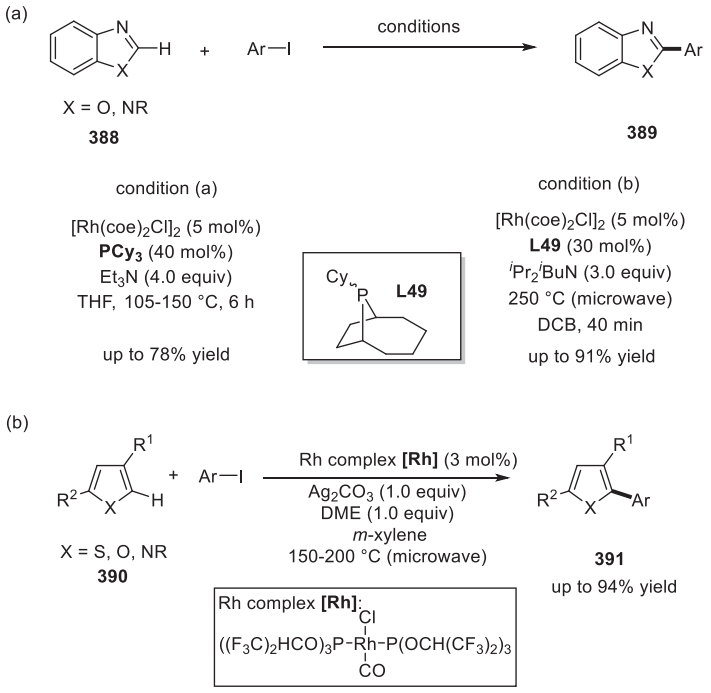


Fig. 4 Catalytic cycles for Rh-catalyzed C-H functionalization, (a) Rh(I)/Rh(III) catalytic cycle (olefin insertion), (b) Rh(I)/Rh(III) catalytic cycle (oxidative addition of aryl halide), (c) Rh(III)/Rh(I) catalytic cycle.

Rh(III) cycle) and C-H annulation with alkyne (Fig. 4C, Rh(III)/Rh(I) cycle). For the C-H alkylation with alkene, the Rh(I)-catalyzed reaction initiates via oxidative addition of a Rh(I) species into the C—H bond, giving Rh–H complex (**I**). Subsequent migratory insertion into the alkene, followed by reductive elimination, provides the alkylation product and regenerates the active Rh(I) catalyst (Fig. 4A). For the C-H arylation with aryl halide, Rh(I)-catalyzed reaction initiates via concerted metallation deprotonation (CMD) to give Rh – R complex (**III**). Subsequent oxidative addition of aryl halide, followed by reductive elimination, provides the arylation product and regenerates the active Rh(I) catalyst (Fig. 4B). For the Rh(III)-catalyzed C-H annulation with alkyne, the directing group assisted C—H bond activation step occurs via concerted metalation-deprotonation (CMD) mechanism, giving Rh(III) intermediate (**III**), which inserts alkyne to form a rhodacycle (**IV**). Then reductive elimination gives the desired annulation product and generates a rhodium(I) species which can undergo oxidation to regenerate the catalytically active rhodium(III) species (Fig. 4C).

12.05.3.1 C—H bond arylation

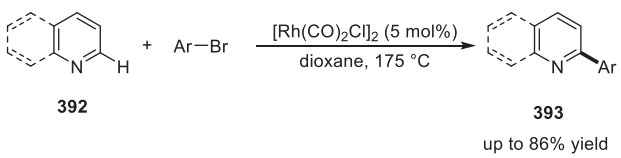
In 2004, Bergman, Ellman and coworkers pioneeringly reported Rh(I)-catalyzed C-H arylation of a variety of heterocycles, providing the arylated products in moderate to good yields (Scheme 91A, left). Then, the bulky trialkylphosphine **L49** (mixture of two isomers) significantly improved the yield and widened the scope of the Rh-catalyzed C-H arylation of *N*-heterocycles (**388**). The unique structure of [4.2.1]-Cy-Phob ligand (**L49**) maintains the spatial and electronic properties of PCy_3, while reducing the tendency of PCy_3 to undergo dehydrogenation. The use of more hindered amine base (*i*-Pr_2*i*-BuN) and the microwave heating significantly improved the reaction efficiency. Under the optimized conditions, this reaction was also suitable for a wide range of aryl bromides besides aryl iodides (Scheme 91A, right).[125]



Scheme 91 Rh(I)-catalyzed C-H arylation of heteroarenes.

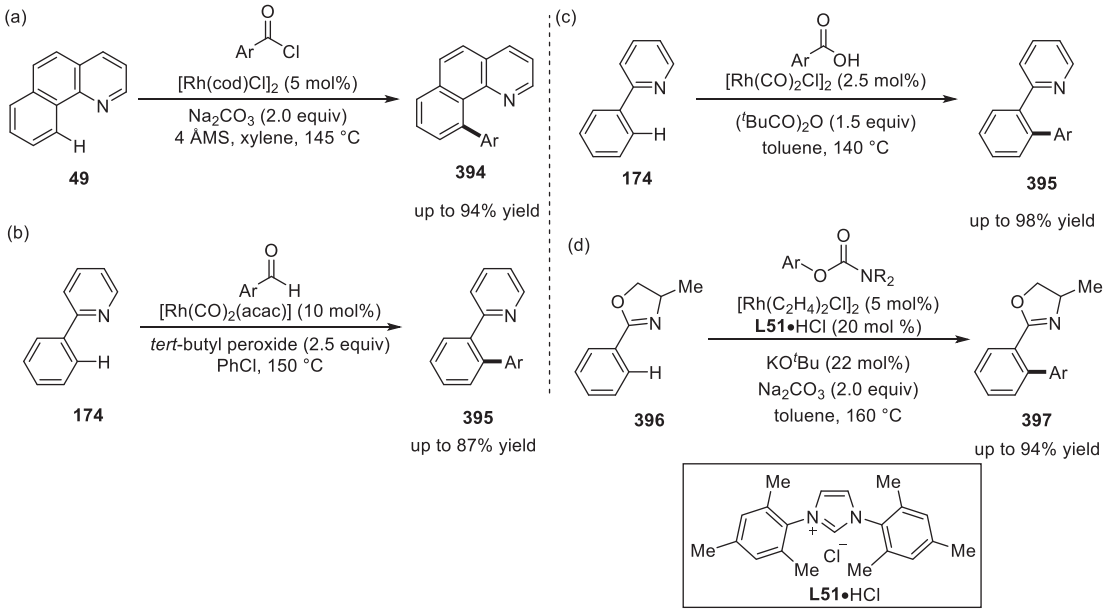
In 2006, the catalytic C-H arylation of heteroarenes **390** (thiophenes, furans and pyrroles) with broad substrate scope in the presence of electron-deficient Rh catalyst **[Rh]** was developed by Itami and coworkers. The rhodium catalyst bearing a strongly π-accepting ligand, prepared from $[Rh(CO)_2Cl]_2$ and $P[OCH\text{-}(CF_3)_2]_3$, is stable in air, realizing catalytic C-H arylation of heteroarenes that shows high activity paired with broad scope (Scheme 91B).[126]

The selective *ortho*-arylation of pyridine was also enabled by electron-deficient Rh catalysts. The C-H arylation of pyridine and quinoline derivatives (**392**) at the C2 position with aryl bromides took place in the presence of $[Rh(CO)_2Cl]_2$ without any additives, giving the arylation products (**393**) in up to 86% yield (Scheme 92).[127]



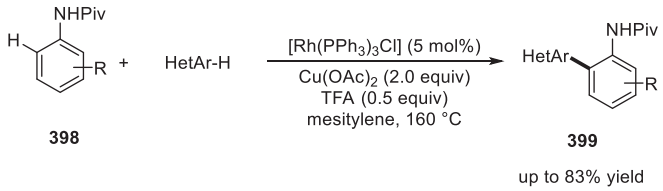
Scheme 92 Rh(I)-catalyzed C-H arylation of pyridines with aryl bromides.

In 2008, Zhao and Yu realized an efficient regioselective C-H arylation of benzoquinoline (**49**) by Rh(I) catalysis with acid chloride as the coupling partner under ligand-free conditions via decarbonylative C-H activation (Scheme 93A).[128a] Then, Li and coworkers discovered a novel method for the synthesis of biaryl compounds (**395**), involving oxidative decarbonylative coupling of 2-phenylpyridine (**174**) with aryl aldehydes (Scheme 93B).[128b] In 2013, the Shi group reported the cross-coupling of aryl carboxylic acids with 2-phenylpyridine (**174**) through the decarbonylation of carboxylic acids. This method exhibits a broad substrate scope with benzoic acids (Scheme 93C).[128c] Chatani, Tobisu and coworkers reported a Rh-catalyzed cross-coupling of aryl carbamates with arenes bearing a 4-methyl-4,5-dihydrooxazol-2-yl directing group (**396**) by using an in situ generated bis(NHC) (**L51**) complex of Rh(I) as the catalyst. (Scheme 93D).[128d]



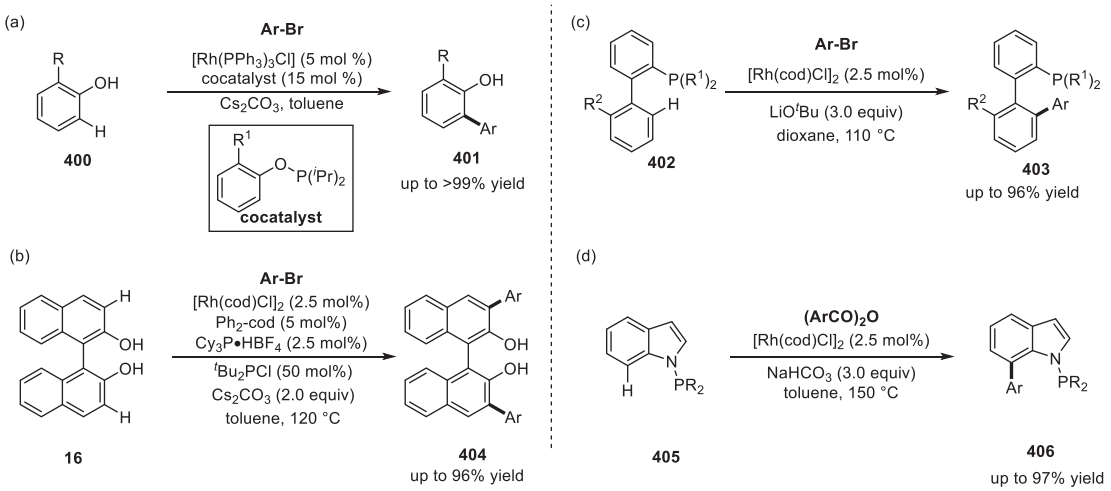
Scheme 93 Rh(I)-catalyzed C-H arylations with benzoyl chlorides, aryl aldehydes, aryl carboxylic acids and aryl carbamates.

In 2004, You and coworkers found that a novel catalytic system, composed of the Wilkinson catalyst [$Rh(PPh_3)_3Cl$] and TFA, enabled highly regioselective C-H cross-coupling reactions of aromatic amines (**398**) with various of heteroarenes (benzothiophene, benzofuran, etc.) through twofold direct C-H functionalizations (Scheme 94).[129] This method provides a convenient access to highly extended π-conjugated heteroarenes (**399**) from readily available substrates.



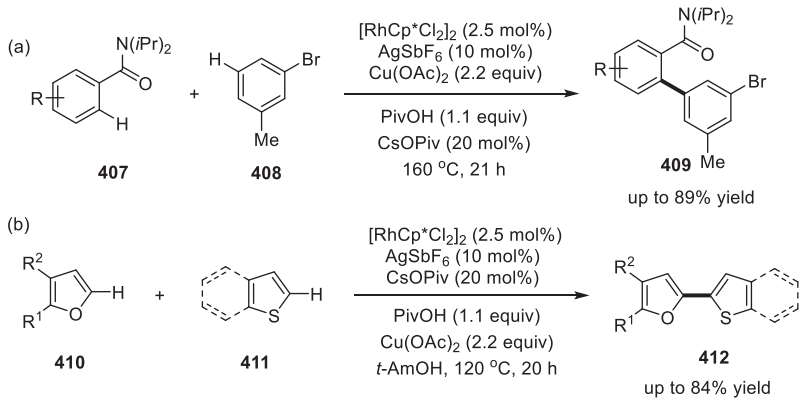
Scheme 94 Rh(I)-catalyzed C-H arylation of aromatic amines with heteroarenes.

Despite the presence of coordination, phosphine can still be used as a transient or pre-installed directing group to achieve C—H bond activation. In 2003, major breakthrough was made by Bedford and colleagues, who developed a Rh-catalyzed *ortho*-arylation of substituted phenol (**400**) using phosphinates as a cocatalyst (Scheme 95A).[130a] Then, Ye and coworkers applied this protocol to develop a highly efficient Rh-catalyzed one-step synthetic route to 3,3′-diaryl BINOLs (**404**) from BINOLs (**16**) and readily available aryl halides. The diene ligand (Ph_2-cod:1,5-diphenylcycloocta-1,5-diene) used in the newly developed system proved to greatly promote the C-H arylation reaction (Scheme 95B).[130b] In 2017, the Shi group constructed a structurally diverse substituted monophosphine ligand library (**403**) by Rh(I)-catalyzed C-H arylation reaction of commercially available ligands (**402**). This direct coupling reaction with various aryl bromides or aryl chlorides by using the dialkyl or diaryl phosphino directing group proceeded smoothly free of an external ligand (Scheme 95C).[130c] They subsequently reported an efficient C7-selective direct decarbonylative arylation of indoles (**405**) by Rh(I) catalysis with the aid of a P^{III}-directing group. Inexpensive and commercially available carboxylic acids or anhydrides were employed as the coupling partner in this reaction (Scheme 95D).[130d]



Scheme 95 Rh(I)-catalyzed *ortho*-arylations directed by built-in P^{III} groups.

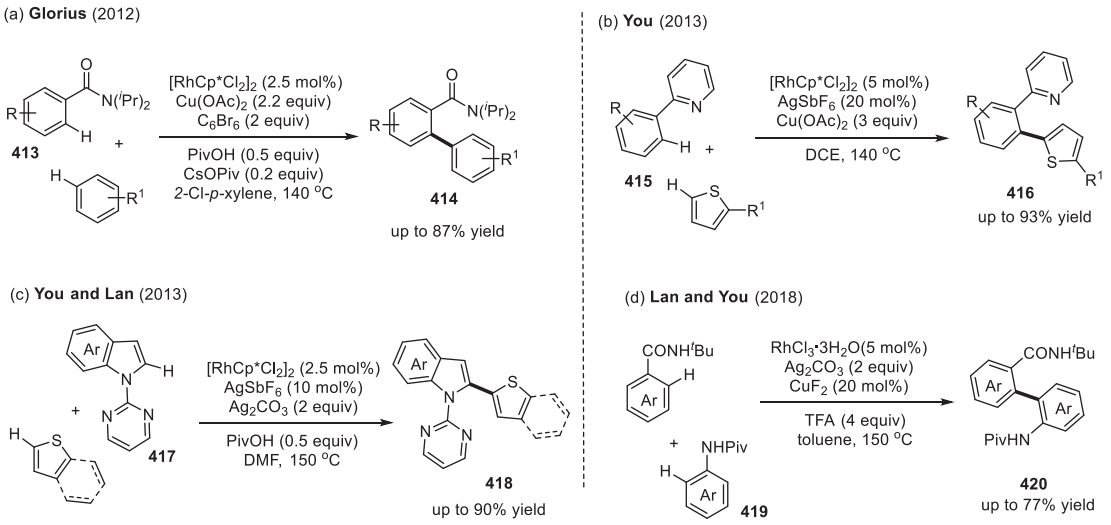
Besides Pd- and Rh(I)-catalysts, Rh(III) catalysts have also been shown to be particularly efficient for C-H arylation. In 2012, Glorius and coworkers reported a Rh(III)-catalyzed Ar-Ar cross-coupling by means of double C-H functionalization between benzamides (**407**) and halobenzenes (Scheme 96A).[131] Indeed, these halobenzenes (**408**) act as not only the coupling partners, but also cooxidants and/or catalyst modifiers. The kinetic isotope effect (KIE) experiments clearly suggest that the C—H bond activation occurs on both coupling partners. The scope of this transformation is broad with regard to both coupling partners, leading to the regioselective formation of valuable *meta* substituted biphenyl products (**409**) in up to 89% yield.



Scheme 96 Rh(III)-catalyzed dehydrogenative aryl-aryl bond formation.

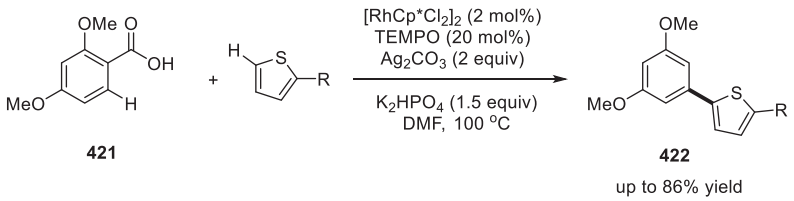
Meanwhile, they demonstrated Rh(III)-catalyzed cross-dehydrogenative coupling (CDC) of furans (**410**) with benzothiophenes or thiophenes (**411**), leading to the corresponding 2,2′-bi(heteroaryl) compounds (**412**) in up to 84% yield and excellent regioselectivity (Scheme 96B).[132] Additionally, the reaction conditions could also be applied to the cross-coupling of *N*-benzylindoles and benzyl protected 2-acetylpyrroles.

In 2012, Glorius and coworkers also realized a Rh(III)-catalyzed dehydrogenative cross-coupling reaction of a large range of simple arenes and heterocycles with benzamides (**413**) (Scheme 97A).[133a] Hexabromobenzene (C_6Br_6) as a key additive enabled a highly chemo- and regioselective dehydrogenative cross-coupling reactions. In 2013, You and coworkers reported a Rh(III)-catalyzed oxidative cross-coupling of phenylpyridines (**415**) with thiophenes by twofold C-H functionalization, providing a direct access to π-conjugated systems (**416**) (Scheme 97B).[133b] Afterwards, Rh(III)-catalyzed dehydrogenative coupling of indoles/pyrroles (**417**) with heteroarenes was described by You, Lan and coworkers (Scheme 97C).[133c] This strategy can effectively suppress the homo-coupling pathway, and dramatically extend the substrate scope, showcasing the beneficial aspect of the Rh(III) catalysis. In 2018, Lan, You and coworkers reported a Cp^*-free $RhCl_3$/TFA catalytic system to enable an oxidative C-H/C-H cross-coupling reaction of *N*-acylanilines (**419**) and benzamides through a dual-chelation-assisted strategy (Scheme 97D).[133d] The $RhCl_3$/TFA catalytic system exhibits high catalytic activity and excellent functional group tolerance.



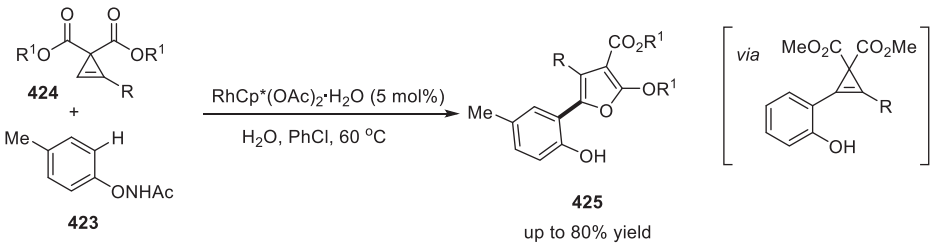
Scheme 97 Rh(III)-catalyzed oxidative C-H/C-H cross-coupling reactions.

In 2015, Su and coworkers reported a tandem Rh(III)-catalyzed C-H arylation/Ag-catalyzed decarboxylative C-H/C-H cross-coupling of carboxylic acids (**421**) with thiophenes (Scheme 98).[134] This method is compatible with a broad range of functional groups and substitution patterns on the arene ring.



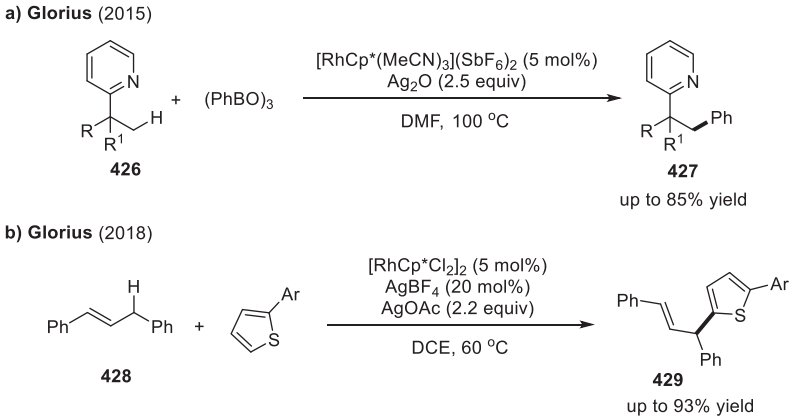
Scheme 98 Rh(III)-catalyzed decarboxylative C-H arylation of thiophenes.

In 2018, Glorius and coworkers developed a Rh(III)-catalyzed coupling of *N*-phenoxyacetamide (**423**) with cyclopropenyl esters (**424**) for the synthesis of arylated furans (**425**) (Scheme 99).[135] Mechanistic studies suggested that the arylated furans are formed via arylation of the cyclopropenyl esters followed by cycloisomerization.



Scheme 99 Rh(III)-catalyzed arylation and cycloisomerization of cyclopropenes.

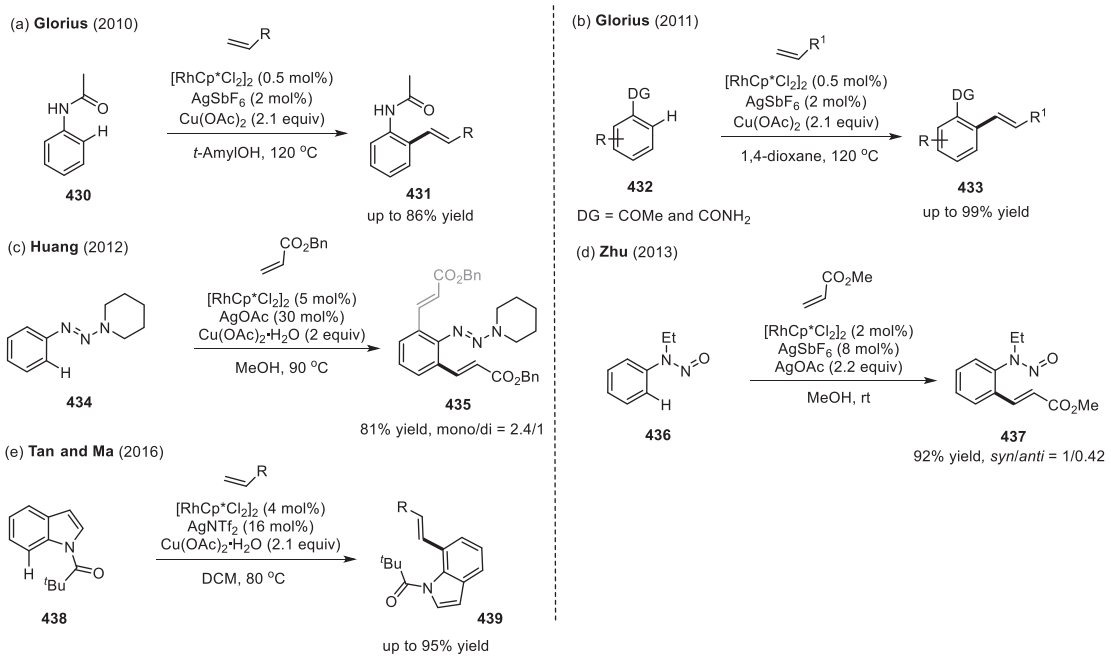
Although many exciting achievements have been made in Rh(III)-catalyzed C(sp^2)-H functionalization, on the contrary, much less research attention has been devoted to the activation of C(sp^3)—H bonds. In 2015, the Cp*Rh(III)-catalyzed arylation of unactivated C(sp^3)—H bonds was realized by the Glorius group (Scheme 100A).[136a] Various 2-alkylpyridine derivatives (**426**) reacted smoothly with diverse triarylboroxines. This method efficiently built new C(sp^3)—aryl bonds and afforded functionalized pyridine derivatives (**427**) in up to 85% yield. Subsequently, they also reported an elegant non-directed and cross-dehydrogenative coupling of allylic C(sp^3)—H bonds with C(sp^2)—H bonds of (hetero)arenes (Scheme 100B).[136b]



Scheme 100 Rh(III)-catalyzed C(sp^3)-H arylations.

12.05.3.2 C—H bond alkenylation

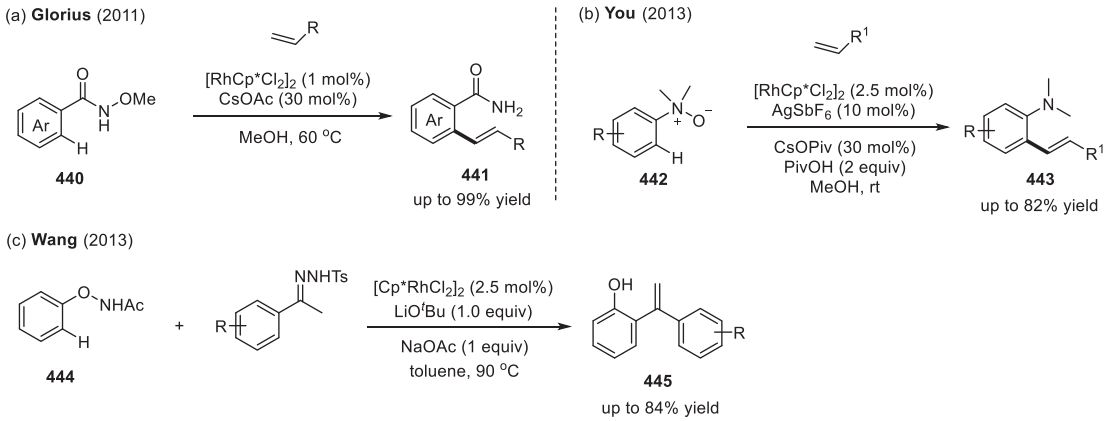
The oxidative Heck reaction, utilizing a C—H instead of a C—X bond, avoids the need for prior functionalization steps and is thus more atom-economic and versatile. In 2010, Glorius and coworkers reported a Rh(III)-catalyzed oxidative C-H olefination of acetanilides (**430**) with styrenes or ethylene (Scheme 101A).[137a] In addition, electron-poor substrates such as acetophenones and benzamides are also suitable substrates in this C-H activation process. In 2011, they extended this method to *ortho* C-H olefination reaction of acetophenones and benzamides with alkenes under identical optimized conditions (Scheme 101B).[137b] Furthermore, both electron-poor and electron-rich styrenes were well tolerated. In 2012, Huang and coworkers reported the first triazene-directed Rh(III)-catalyzed oxidative olefination reactions under mild conditions (Scheme 101C).[137c] The triazene directing group could either be removed at room temperature in quantitative yield, or undergo further transformations, such as cross-coupling reactions. In 2013, Zhu and coworkers developed a Rh(III)-catalyzed C-H olefination of arenes (**436**) by using an *N*-nitroso directing group (Scheme 101D).[137d] Competition experiments suggest that electrophilic aromatic substitution (EAS), rather than concerted metalation-deprotonation (CMD), is responsible for the C-H functionalization step. The kinetic isotope effect (KIE) experiments support a reaction pathway involving electrophilic C-H activation as the turnover-limiting step. A five-membered rhodacycle is the key intermediate in the catalytic cycle. In 2016, Tan, Ma and coworkers reported a highly efficient method for the Rh(III)-catalyzed



Scheme 101 Rh(III)-catalyzed oxidative C-H alkenylations.

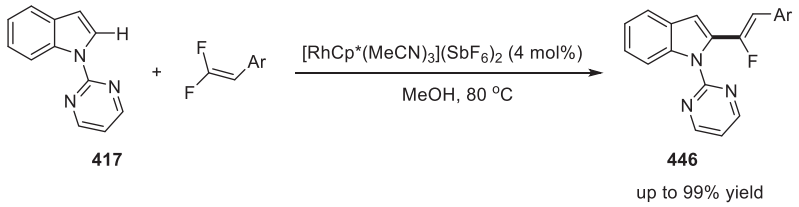
C7-selective olefination of *N*-pivaloylindole derivatives (**438**) (Scheme 101E).[137e] In this process, the size of the directing group plays an important role. With larger acyl groups, higher selectivity for the C7-position and conversion were observed.

Generally, the use of an external oxidant is problematic due to the cost factors and stoichiometric waste produced by the external oxidant. An efficient Rh(III)-catalyzed oxidative olefination of *N*-methoxybenzamides was reported by the Glorius group. In this reaction, the N—O bond cleavage acts as an internal oxidant without any external oxidants (Scheme 102A).[138a] In the presence of 1 mol% $[Cp^*RhCl_2]_2$, the reaction of *N*-methoxybenzamide (**440**) provided around 99% of the desired olefination product (**441**), together with a small amount of the diolefination product, whereas benzamide largely remained unreacted. These results clearly showed that the *N*-methoxy amide group acts as not only an internal oxidant but also a better DG than the *N*-unsubstituted primary amide. In 2013, You and coworkers also developed Rh(III)-catalyzed C-H olefination of tertiary aniline *N*-oxides (**442**), which acted as an internal oxidant (Scheme 102B).[138b] In 2014, Wang and coworkers developed an efficient synthesis of *ortho*-alkenyl phenols (**445**) via Rh(III)-catalyzed C—H bond functionalization of *N*-phenoxyacetamides (**444**) with *N*-tosylhydrazones/diazoesters similarly taking advantage of internal N—O bond cleavage for oxidation (Scheme 102C), similarly taking advantage of internal N—O bond cleavage for oxidation.[138c]



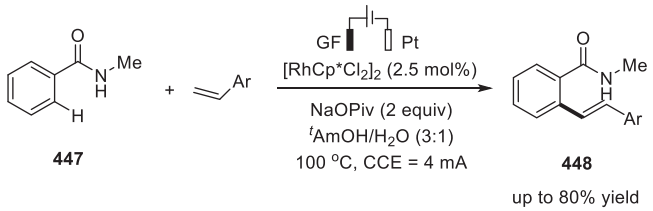
Scheme 102 Rh(III)-catalyzed C-H alkenylations with substrates bearing an internal oxidant.

In 2015, Feng, Loh and coworkers presented a Rh(III)-catalyzed tandem C-H/C-F activation for the synthesis of (hetero)arylated monofluoroalkenes (**446**) (Scheme 103).[139] The use of readily available *gem*-difluoroalkenes as electrophiles provided a highly efficient and operationally simple method for the introduction of α-fluoroalkenyl motifs onto (hetero)arenes (**417**) under oxidant-free conditions. Furthermore, the alcoholic solvent and the in-situ generated hydrogen fluoride were found to be beneficial in this transformation, indicating the possibility of the involvement of a hydrogen bond activation mode with regards to the C—F bond cleavage step.



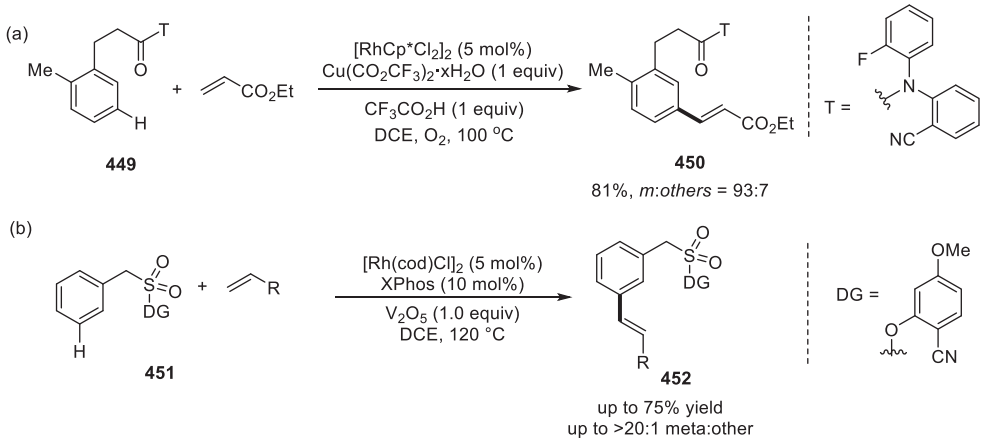
Scheme 103 Rh(III)-catalyzed α-fluoroalkenylation of indoles.

In recent years, electrosynthesis has gained significant attention owing to the use of waste-free and inexpensive electric current as a redox equivalent, thereby avoiding the use of costly chemical redox agents. In 2020, Ackermann and coworkers realized a Rh(III)-catalyzed electrooxidative C-H olefination of benzamides (**447**) (Scheme 104).[140] Notably, both electron-poor and electron-rich styrenes bearing sensitive functional groups such as bromo, hydroxyl, and nitro groups were well tolerated.



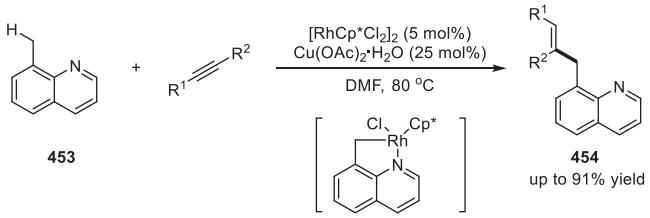
Scheme 104 Rh(III)-catalyzed electrooxidative C-H olefination of benzamides.

In 2017, Sun, Yu and coworkers developed a Rh(III)-catalyzed *meta*-C-H olefination of hydrocinnamic acid derivatives (**449**) using a modified U-shaped mononitrile template (Scheme 105A).[141] The KIE ($k_H/k_D = 1.8$) suggested that the *meta*-C—H bond cleavage may be the rate-determining step. In 2017, Maiti and coworkers applied 2-hydroxy-4-methoxy benzonitrile template to achieve a Rh(III)-catalyzed *meta*-selective olefination of benzylsulfonyl esters (**451**) and phenylacetic acid esters using XPhos as the ligand (Scheme 105B).[142] Complete mono-selectivity was achieved for a broad range of substrates with various olefins and functional groups attached to arene.



Scheme 105 Rh(III)-catalyzed *meta*-C-H olefination.

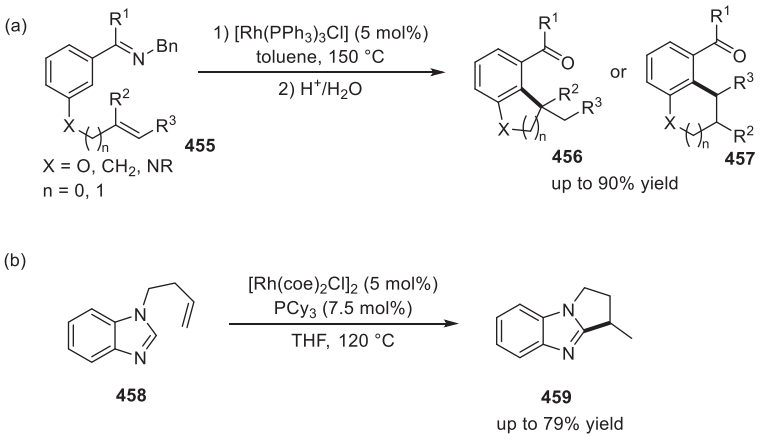
In 2014, Wang and coworkers developed a Rh(III)-catalyzed alkenylation reaction of 8-methylquionline (**453**) with alkynes to afford 8-allylquinolines (**454**) in up to 91% yield (Scheme 106).[143] Notably, the reaction is highly regio- and stereoselective. A catalytically competent five-membered rhodacycle was structurally characterized, thus revealing the key intermediate in the catalytic cycle.



Scheme 106 Rh(III)-catalyzed C(sp^3)-H alkenylation of 8-methylquionline.

12.05.3.3 C—H bond alkylation

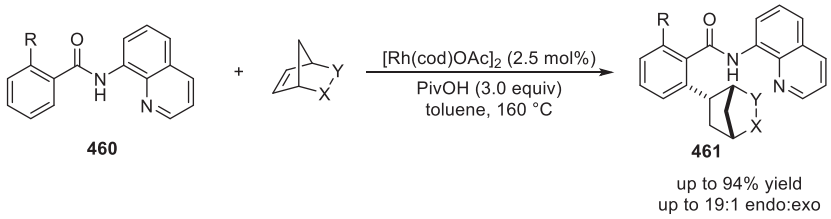
In 2001, Bergman and Ellman developed a novel method for the synthesis of functionalized tetralane, indane, dihydroindole, and dihydrobenzofuran derivatives by using imine directed C—H bond functionalization in up to 90% yield and with high selectivity (Scheme 107A).[144] This method is well tolerated with different tether lengths, the incorporation of heteroatoms into the tether, and multiple substituents on olefins. In addition, the cyclization products can undergo diverse transformations.



Scheme 107 Rh(I)-catalyzed intramolecular C-H coupling of alkene.

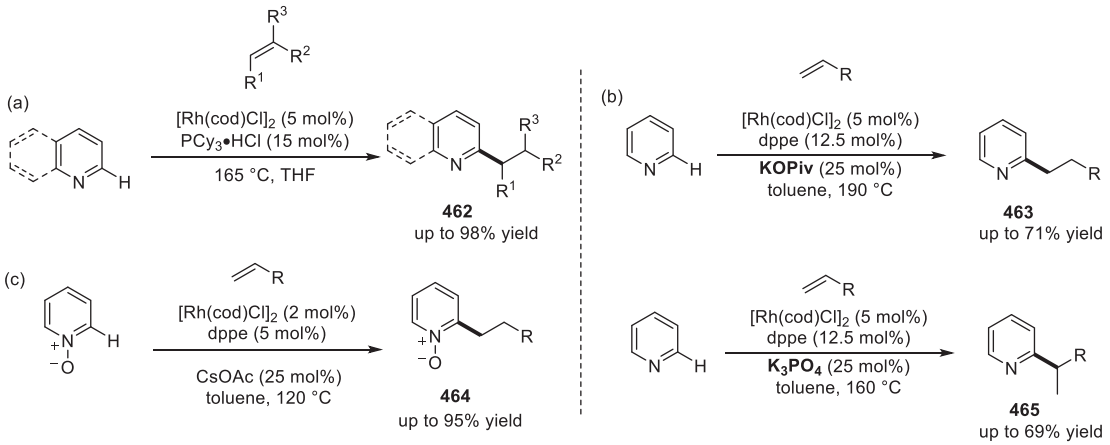
They also developed a general method for C-H alkylation without the directing group. The new carbocyclization could be applied to the construction of both five and six membered rings via intramolecular coupling of an alkene to benzimidazole (**458**). Various substrates including mono-, di-, and trisubstituted alkenes allowed the formation of tricyclic products (**459**) in up to 79% yield (Scheme 107B).[145]

In 2007, the Chatani group reported an unusual example of *endo*-selective hydroarylation with norbornene. 8-Aminoquinoline as a directing group is critical to the success of this reaction (Scheme 108).[146] The addition of a sterically bulky carboxylic acid enhanced the internal selectivity. A high degree of *endo*-selectivity was obtained for a variety of substrates (**460**) with excellent functional group tolerance.



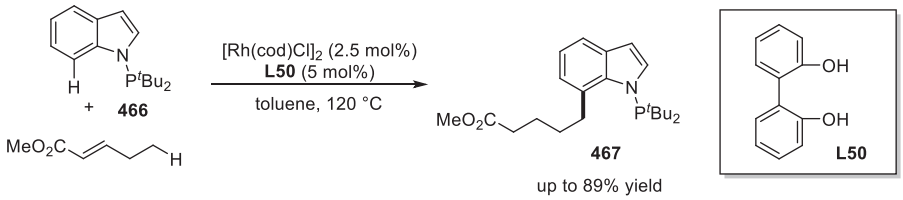
Scheme 108 Rh(I)-catalyzed hydroarylation with norbornene.

Many achievements have been made by Bergman, Ellman and coworkers in the field of Rh(I)-catalyzed C-H alkylation with alkenes. They developed intermolecular C-H alkylation of pyridine and quinoline derivatives with acrylates and acrylamides in 2007. Steric interactions caused by the *ortho*-substituent presumably increased the equilibrium from an N-bound to a C-bound Rh complex by undertaking efforts to isolate intermediate complexes and performing DFT calculations on model structures (Scheme 109A).[147a] In Rh(I)-catalyzed *ortho*-selective alkylation of azines, a complete linear or branched selectivity was controlled exclusively by a catalytic amount of base (Scheme 109B).[147b] A highly efficient rhodium catalyst system for the direct hydroheteroarylation reaction was reported by Cho, Chang and coworkers in 2012 (Scheme 109C).[148] A base co-catalyst was crucial for the hetereoarene C—H bond activation step. This method exhibited a broad substrate scope with various substituted electron-deficient pyridine *N*-oxides. The identical catalytic system could also be applicable to the hydroheteroarylation of alkynes with excellent regio- and stereoselectivity.



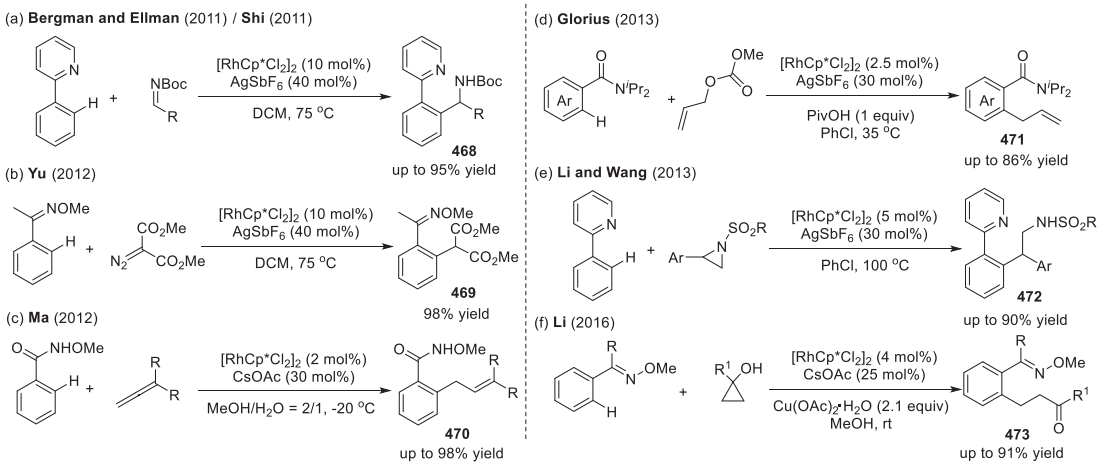
Scheme 109 Rh(I)-catalyzed intermolecular C-H alkylation of pyridine, pyridine *N*-oxide and quinoline derivatives.

In 2018, the Shi group developed an effective system for Rh(I)-catalyzed remote terminal hydroarylation of indoles (**466**) and anilines by introducing a N-P^{t}Bu$_2$ directing group. This transformation was realized through long-range olefin isomerization (Scheme 110).[149] With the aid of a sterically hindered NP^{t}Bu$_2$ as the optimal directing group, the reaction overrides electronic biases at the indole C3-position and the conjugate reactivity of actived olefins to generate the indole C7-alkylation products (**467**) with excellent regioselectivity.



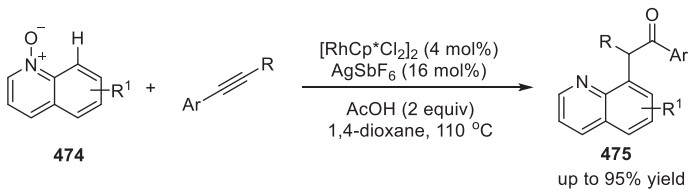
Scheme 110 Rh(I)-catalyzed remote terminal hydroarylation of indoles.

In 2011, the groups of Bergman and Ellman, and the Shi group independently reported Rh(III)-catalyzed C-H addition of 2-arylpyridines to *N*-Boc- and *N*-sulfonyl-imines, giving branched amine products (**468**) in up to 95% yield (Scheme 111A).[150a] The method was compatible with many common functional groups, such as ketone, aldehyde, ester, halide, trifluoromethyl, amide, and nitro. In 2012, Yu and coworkers reported a Rh(III)-catalyzed intermolecular coupling of diazomalonates with arene C—H bonds (Scheme 111B).[150b] In most cases, arenes with oxime, carboxylic acid, and amine as the directing group could couple with diazomalonates with excellent regioselectivity and functional group tolerance. In 2012, Ma and coworkers developed a Rh(III)-catalyzed allylation of *N*-methoxybenzamides with poly-substituted allenes (Scheme 111C).[150c] In 2013, Glorius and coworkers demonstrated a Rh(III)-catalyzed intermolecular C-H allylation reaction by using readily available allyl carbonates as the allyl sources (Scheme 111D).[150d] The reaction proceeded under mild conditions with excellent γ-selectivity and displaying a broad substrate scope. In 2013, Li, Wang and coworkers achieved a Rh(III)-catalyzed C-C coupling of aziridines with electron-poor arenes, affording a variety of *β*-branched amines (**472**) (Scheme 111E).[150e] In 2016, Li and coworkers achieved the first combination of C—H bond activation with ring opening of cyclopropanols under Rh(III)-catalysis, affording *β*-aryl ketones (**473**) (Scheme 111F).[150f]



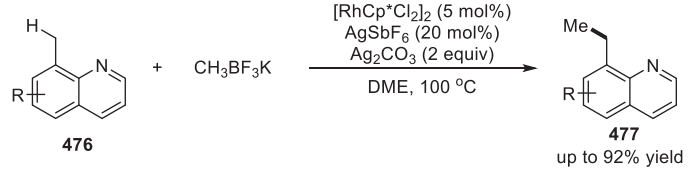
Scheme 111 Rh(III)-catalyzed C-H alkylations.

In 2014, Li and coworkers developed a Rh(III)-catalyzed coupling of quinoline *N*-oxide (**474**) with internal alkynes, leading to the synthesis of substituted acetophenones (**475**) in up to 95% yield (Scheme 112).[151] In this process, the *N*-oxide acts as both a directing group for C-H activation and an oxidant.



Scheme 112 Rh(III)-catalyzed coupling of quinolone *N*-oxides with alkynes.

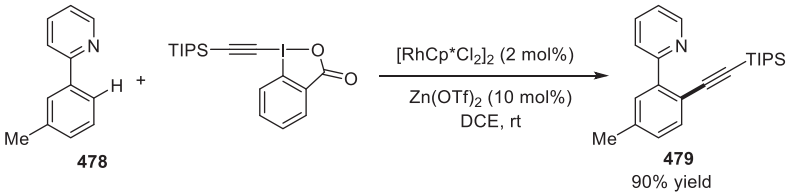
In 2020, Rh(III)-catalyzed highly regioselective C(sp^3)-H methylation of 8-methylquinolines (**476**) with bench stable organoboron reagent was described by the Sharma group (Scheme 113).[152] This process was achieved through direct alkylation instead of hydroarylation of olefin. Substituted 8-ethylquinolines (**477**) were obtained in up to 92% yield through the direct functionalization of primary C(sp^3)—H bond.



Scheme 113 Rh(III)-catalyzed C(sp^3)-H alkylation of 8-methylquinolines.

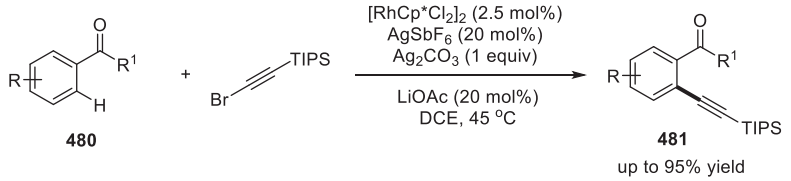
12.05.3.4 C—H bond alkynylation

Although aryl alkynes are usually prepared from aryl halides with alkynes by the Sonogashira reaction, it is desirable and attractive to take advantage of the abundance of C—H bonds in arenes by Rh(III)-catalyzed C-H direct functionalization. In 2014, the Li group and the Loh group independently developed an efficient Rh(III)-catalyzed C-H alkynylation of (hetero)arenes (**478**) using hypervalent iodine-alkyne reagents (Scheme 114).[153a,b] Heterocycles, *N*-methoxy imines, azomethine imines, secondary carboxamides, azo compounds, *N*-nitrosoamines, and nitrones were all feasible directing groups to enable *ortho* C-H alkynylation. It is worth noting that Rh(III)-catalyzed C-H alkynylation of indoles can proceed in mixer mills under solvent-free conditions reported by the Bolm group.[153c]



Scheme 114 Rh(III)-catalyzed C-H alkynylation with hypervalent iodine-alkyne reagent.

In 2018, Echavarren and coworkers reported a Rh(III)-catalyzed C(sp^2)-H alkynylation with bromoalkynes (Scheme 115).[154] Amine, thioether, sulfoxide, sulfone, carbamate, and phenol esters are suitable directing groups in this transformation. Furthermore, the experimental and theoretical mechanistic studies suggested that the Rh(III)-catalyzed C-H alkynylation occurs by a turnover-determining C-H activation, wherein a five-membered ring metallacycle is formed by an electrophilic aromatic substitution process.

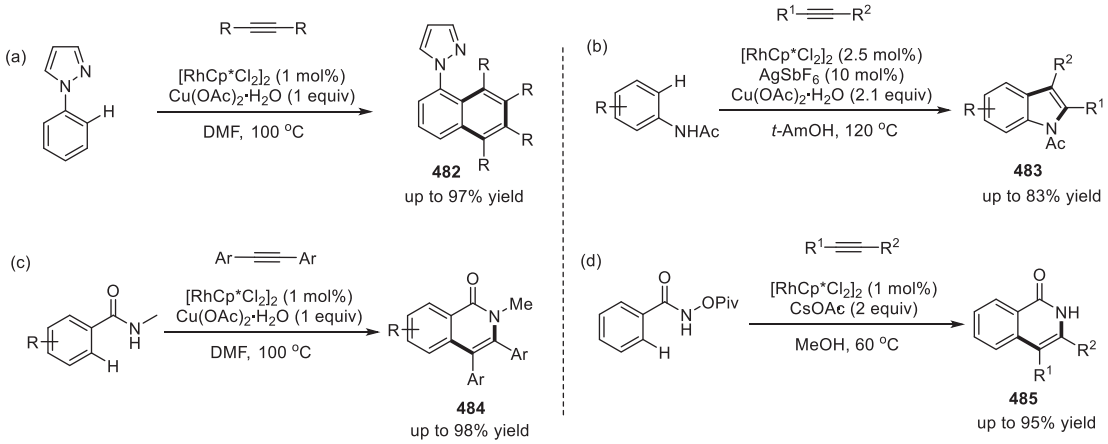


Scheme 115 Rh(III)-catalyzed C-H alkynylation with bromoalkynes.

12.05.3.5 C—H bond annulation

Polycyclic heteroarenes have attracted considerable attention because of their interesting electrochemical and photochemical properties. Structurally diverse polycyclic arenes could be accessed by annulation of C—H bond with alkynes, alkenes, allenes and diazo compounds.

In 2008, Satoh, Miura and coworkers demonstrated that polyarylated naphthyl- and anthrylazole derivatives (**482**) were efficiently constructed by the direct coupling of phenylazoles with internal alkynes in the presence of a rhodium catalyst and a copper oxidant (Scheme 116A).[155a] In 2008, Fagnou and coworkers reported a novel method for the construction of highly

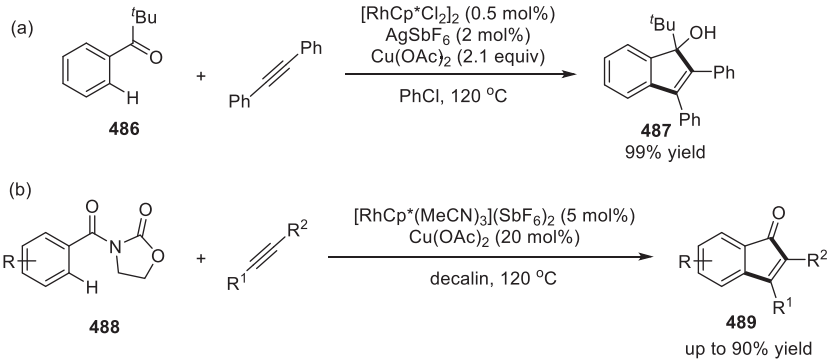


Scheme 116 Rh(III)-catalyzed C(sp^2)-H annulations with alkynes.

functionalized indoles (**483**) based on a Rh(III)-catalyzed C – H annulation of acetanilides with alkynes (Scheme 116B).[155b] In 2010, Rovis et al. developed a Rh(III)-catalyzed oxidative C-H annulation for the synthesis of isoquinolones (**484**) via a transient five-membered rhodacycle generated from *ortho* C-H/N-H activation. Additionally, unsymmetrical alkynes were also suitable substrates, leading to isoquinolones with high regioselectivity (Scheme 116C).[155c] The mechanistic studies suggested that C-H activation is involved in the turnover-limiting step. Competition experiments indicated that the regioselectivity is largely governed by steric factors of alkyne.

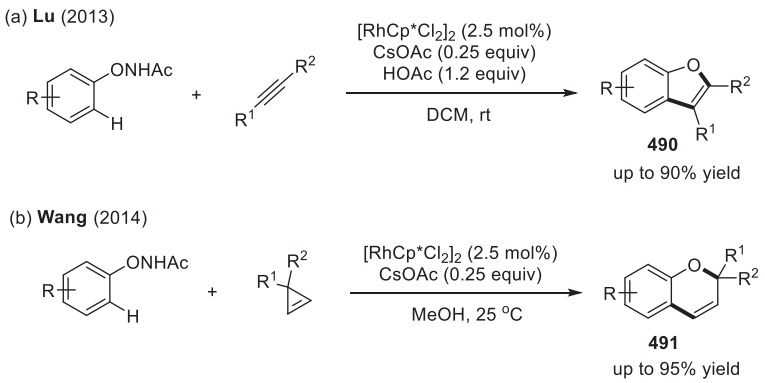
In 2011, Fagnou and coworkers reported a Rh(III)-catalyzed redox-neutral isoquinolone (**485**) synthesis (Scheme 116D).[155d] The N—O bond in the substrate was cleaved during the reaction and found to obviate the need for an external oxidant. The annulations with alkenes led to the formation of 3,4-dihydroisoquinolones. Mechanistic investigations revealed that concerted metalation-deprotonation (CMD) is proposed to be the turnover limiting step. In addition, DFT calculations are also consistent with a stepwise C—N bond reductive elimination/N—O bond oxidative addition mechanism.

In 2011, the Glorius group and the Cheng group independently developed Rh(III)-catalyzed C-H annulations of phenone derivatives (**486**) with internal alkynes, giving diverse indenol derivatives (**487**) (Scheme 117A).[156a,b] Amides have proved to possess sufficient electron density to coordinate with the metal center to facilitate the *ortho* metalation. In 2012, Shi and coworkers developed a Rh(III)-catalyzed C-H annulation between benzimides (**488**) and alkynes for the synthesis of indenones (**489**) (Scheme 117B).[156c] The proper directing ability and electrophilicity of *N*-benzoyloxazolidinones provided a handle for the annulation with concomitant C-H and C-N cleavage.



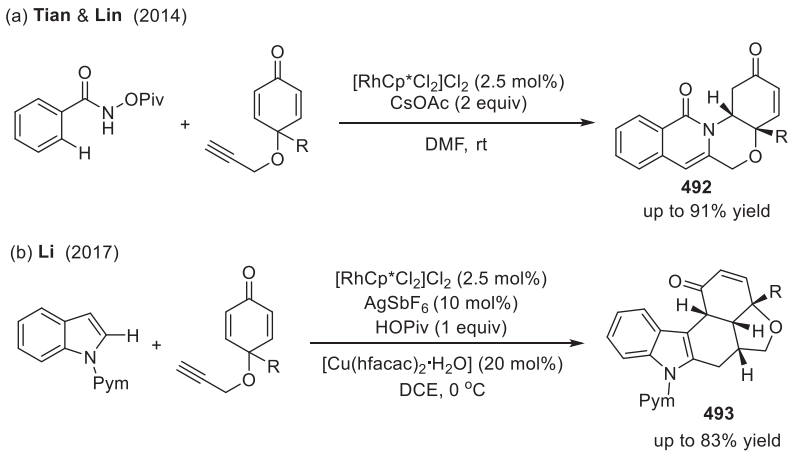
Scheme 117 Rh(III)-catalyzed C-H annulation of aryl ketones/benzimides with alkynes.

In 2013, Lu, Liu and coworkers disclosed a mild Rh(III)-catalyzed redox-neutral C-H functionalization of *N*-phenoxyacetamides with alkynes for the synthesis of benzofuran derivatives (**490**) through C—C/C—O bond formation (Scheme 118A).[157a] With cyclopropene as a three-carbon unit, Wang and coworkers also realized a Rh(III)-catalyzed annulation of *N*-phenoxyacetamide, leading to 2*H*-chromenes (**491**) in 2015 (Scheme 118B).[157b]



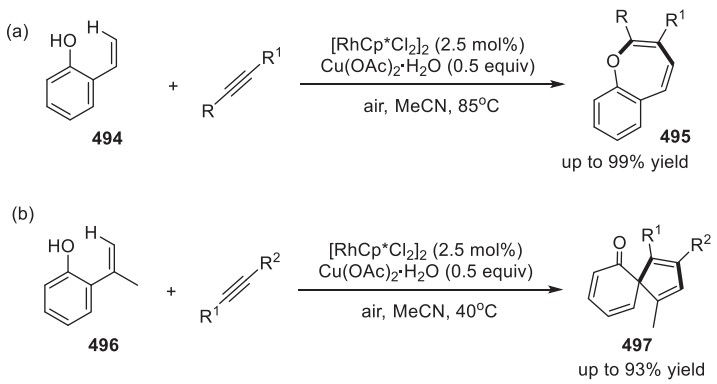
Scheme 118 Rh(III)-catalyzed redox-neutral C-H annulation of *N*-phenoxyacetamides.

In 2014, Lin and coworkers reported a Cp*Rh(III)-catalyzed cyclization of *N*-hydroxybenzamides and alkyne-tethered cyclohexadienone for the formation of tetracyclic isoquinolones (**492**) (Scheme 119A).[158a] In 2017, Li and coworkers reported Rh(III)-catalyzed C-H activation of indoles and coupling with 1,6-enynes for the formation of fused cycles. The alkyne insertion follows 2,1-regioselectivity with an intramolecular Diels–Alder reaction to afford [6,5]-fused cycles (**493**) in up to 83% yield (Scheme 119B).[158b]



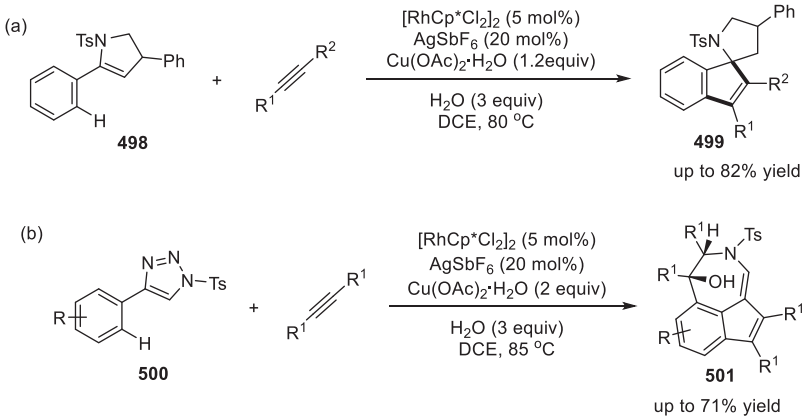
Scheme 119 Rh(III)-catalyzed couplings of indoles with 1,6-enynes.

In 2014, Gulías and coworkers developed a Rh(III)-catalyzed [5 + 2] cycloaddition of vinylphenols (**494**) with alkynes (Scheme 120A).[159a] The reaction generated highly valuable benzoxepine skeletons (**495**) by cleavage of the terminal C—H bond of the alkenyl moiety. Surprisingly, the reaction of 2-(prop-1-en-2-yl)phenol (**496**) and alkynes underwent a dearomatizing [3 + 2] annulation, giving highly appealing spirocyclic products (**497**) in up to 93% yield (Scheme 120B).[159b] This reaction involves the cleavage of the terminal C—H bond of the alkenyl moiety and the dearomatization of the phenol ring.



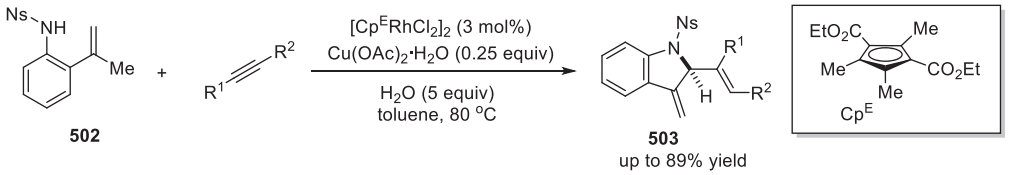
Scheme 120 Rh(III)-catalyzed C-H annulation of 2-alkenylphenols and alkynes.

In 2014, Li and coworkers described a novel Rh(III)-catalyzed [3 + 2] annulation of 5-aryl-2,3-dihydro-1*H*-pyrroles (**498**) with internal alkynes for building a spirocyclic ring system (**499**) with excellent functional group tolerance and good regioselectivity (Scheme 121A).[160a] In 2015, they presented a Rh(III)-catalyzed [3 + 2]/[5 + 2] sequential annulation of 4-aryl 1-tosyl-1,2,3-triazoles (**500**) with internal alkynes through dual C-H functionalization for the synthesis of indeno-[1,7-cd]azepin-1-ols (**591**) in up to 71% yield (Scheme 121B).[160b]



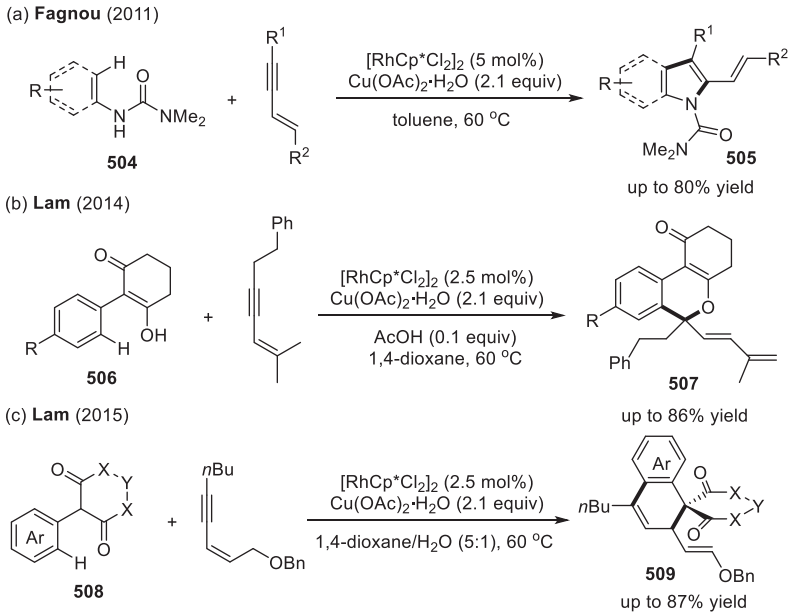
Scheme 121 Rh(III)-catalyzed [3 + 2] annulation with alkynes.

In 2018, Mascareñas, Gulías and coworkers discovered that a Rh(III) complex bearing an electron-deficient η⁵-cyclopentadienyl ligand could enable an unusual annulation between alkynes and 2-alkenyl anilides (**502**), giving synthetically appealing 2-substituted indolines (**503**) in up to 89% yield (Scheme 122).[161] Mechanistic experiments revealed that this transformation involves an unusual rhodium migration with a concomitant 1,5-*H* shift.



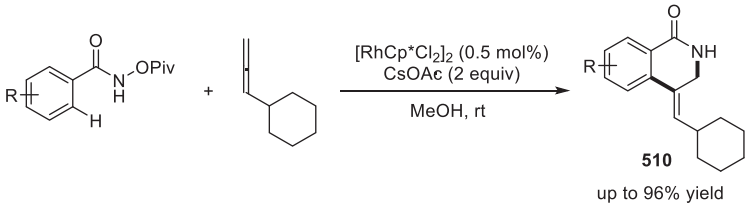
Scheme 122 Rh(III)-catalyzed annulation between alkynes and 2-alkenyl anilides.

In 2011, Fagnou and coworkers developed a Rh(III)-catalyzed [3 + 2] annulation of acetanilides (**504**) with 1,3-enynes, leading to the construction of unsymmetrical 2,3-disubstituted indoles (**505**) and pyrroles in up to 80% yield (Scheme 123A).[162a] In 2014, Lam and coworkers discovered a new mode of Rh(III)-catalyzed oxidative annulation of 2-aryl cyclic 1,3-dicarbonyl compounds (**506**) with 1,3-enyne containing an allylic hydrogen *cis* to alkyne as a one-carbon partner (Scheme 123B).[162b] This unexpected transformation was proposed to occur through double C-H activation, involving a hitherto rare example of the 1,4-migration of Rh(III) species. Subsequently they reported Rh(III)-catalyzed all-carbon [3 + 3] oxidative annulation of 5-arylbarbituric acids (**508**) with 1,3-enynes (Scheme 123C).[162c] This annulation further demonstrated the power of alkenyl-to-allyl 1,4-Rh(III) migration in generating electrophilic allylrhodium species for the construction of polycyclic systems.



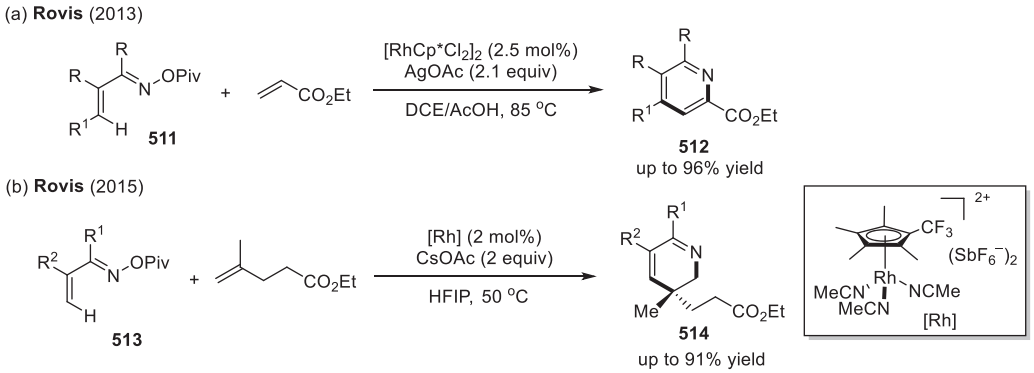
Scheme 123 Rh(III)-catalyzed annulation with 1,3-enynes.

In 2012, Glorius and coworkers developed an efficient Rh(III)-catalyzed intermolecular annulation of benzamide derivatives with allenes for the synthesis of 3,4-dihydroisoquinolin-1(2*H*)-ones (**510**) (Scheme 124).[163] This reaction features high regio- and stereoselectivity, broad substrate scope for both coupling partners, and excellent functional group tolerance.



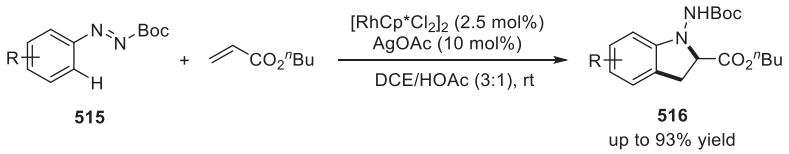
Scheme 124 Rh(III)-catalyzed intermolecular annulation of benzamides with allenes.

In 2013, Rovis and coworkers developed Rh(III)-catalyzed regioselective synthesis of pyridines (**512**) from alkenes and α,β-unsaturated oxime esters (Scheme 125A).[164a] Mechanistic studies suggested that heterocycle formation proceeds via reversible C-H activation, alkene insertion, and a C—N bond formation/N—O bond cleavage process. Encouraged by this work, they then developed an efficient Rh(III)-catalyzed synthesis of semi-saturated pyridine derivatives (**514**) (Scheme 125B).[164b] A significant ligand effect was observed that the electron-deficient trifluoromethyl-substituted Cp^*CF_3 ligand was the optimal one.



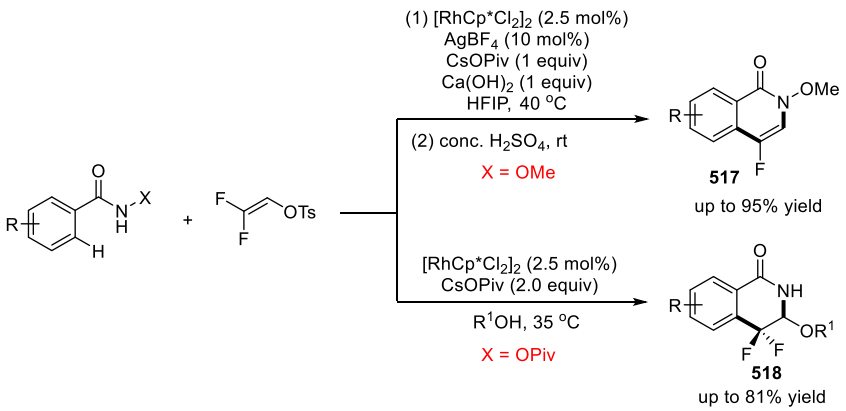
Scheme 125 Rh(III)-catalyzed C-H annulation with alkenes.

In 2015, Glorius and coworkers reported Rh(III)-catalyzed synthesis of 1-aminoindolines (**516**) from arylsubstituted diazenecarboxylates (**515**) and alkenes (Scheme 126).[165] Mechanistic studies supported that this transformation proceeds via reversible C-H activation, alkene insertion, and Grignard-type addition. This intermolecular annulation proceeded at room temperature, featuring free of external oxidants and broad substrate scope.



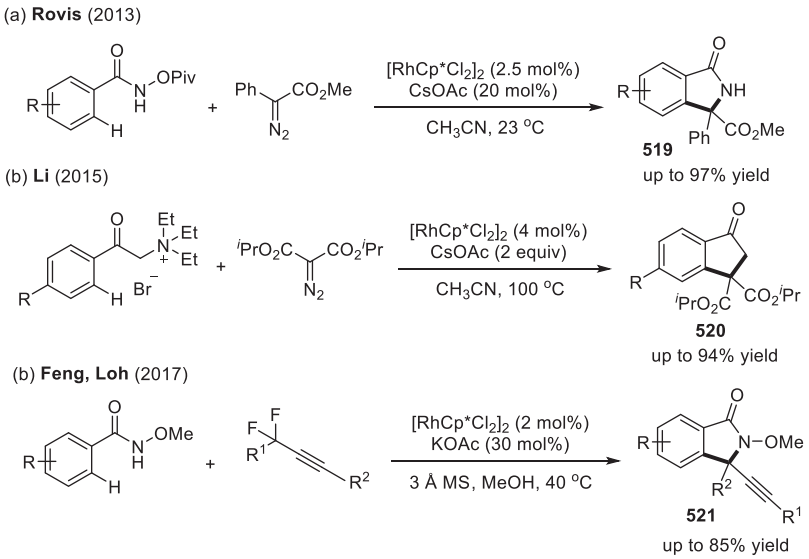
Scheme 126 Rh(III)-catalyzed intermolecular annulation of diazenecarboxylates and alkenes.

In 2017, Li, Wang and coworkers reported Rh(III)-catalyzed C-H annulation of benzamides with 2,2-difluorovinyl tosylate for the synthesis of fluorinated heterocycles (Scheme 127).[166] With *N*-OMe benzamide as a directing group, the reaction delivered a monofluorinated alkene with the retention of the tosylate functionality. Subsequent one-pot acid treatment allowed the efficient synthesis of 4-fluoroisoquinolin-1(2*H*)-ones (**517**) in up to 95% yield. When *N*-OPiv benzamides were used, [4 + 2] cyclization occurred to provide *gem*-difluorinated dihydroisoquinolin-1(2*H*)-ones (**518**) in up to 81% yield.



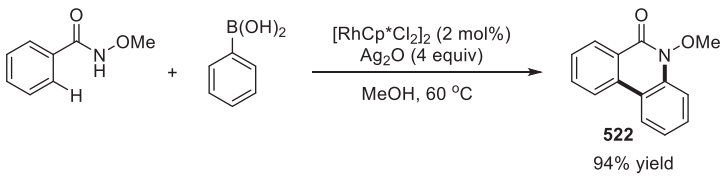
Scheme 127 Rh(III)-catalyzed C-H annulation of benzamides with 2,2-difluorovinyl tosylate.

In 2013, Rovis and coworkers demonstrated that diazo compounds could be applied in Rh(III)-catalyzed C-H functionalization reaction to afford lactam derivatives (**519**) in up to 97% yield (Scheme 128A).[167a] Mechanistic experiments suggested that C-H activation is irreversible and involved in the turnover-limiting step. Subsequently, Wang, Li and coworkers also realized Rh(III)-catalyzed redox-neutral C-H coupling of phenacyl ammonium salts with diazoesters to afford benzocyclopentanones (**520**) in up to 94% yield. In this reaction, the quaternary ammonium group acted as an oxidizing directing group to facilitate the *ortho* C-H activation (Scheme 128B).[167b] α,α-Difluoromethylene alkyne could be used as a nontraditional one-carbon reaction partner. In 2017, Feng, Loh and coworkers reported a novel method for the construction of isoindolin-1-one derivatives (**521**) via Rh(III)-catalyzed [4 + 1] annulation reaction (Scheme 128C).[167c]



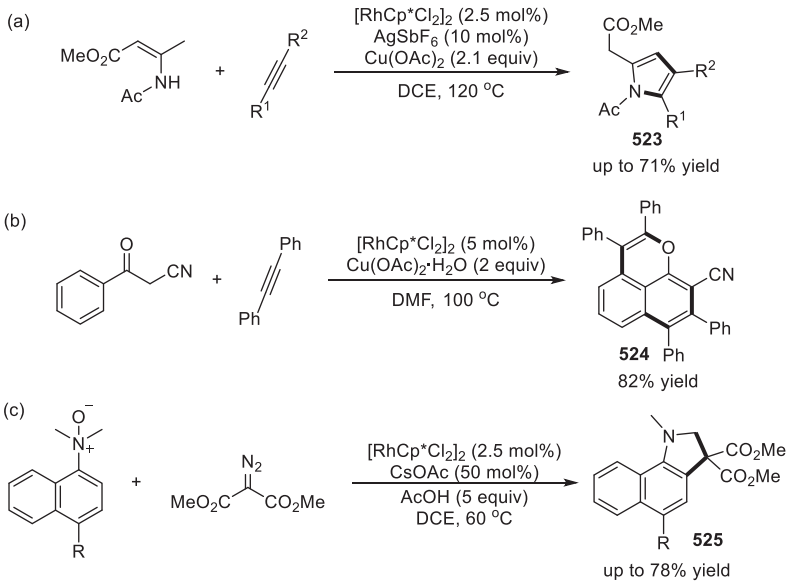
Scheme 128 Rh(III)-catalyzed coupling with α-diazoesters and α,α-difluoromethylene alkyne.

In 2012, Cheng and coworkers demonstrated a Rh(III)-catalyzed dual C-H activation of *N*-methoxybenzamides with aryl boronic acids (Scheme 129).[168] The catalytic reaction provided various substituted phenanthridinones (**522**) in excellent yields with high regioselectivity through C-C and C—N bond formation.



Scheme 129 Rh(III)-catalyzed annulation of benzamides with aryl boronic acid.

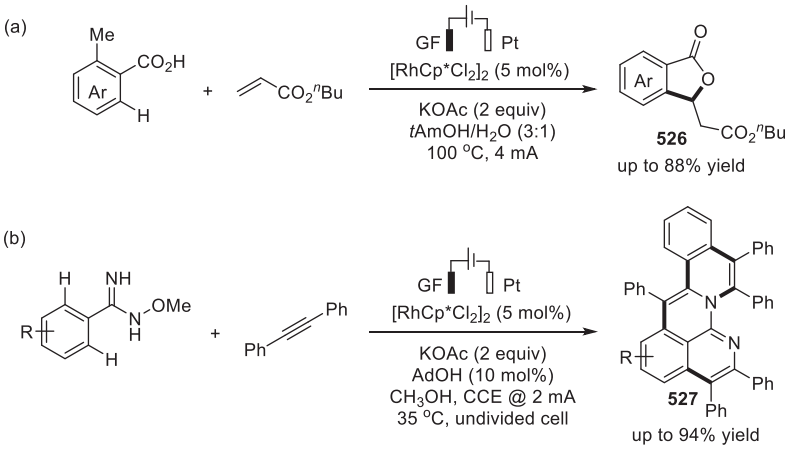
In 2010, Glorius and coworkers reported a novel Rh(III) catalyzed C(sp^3)-H functionalization of enamines and successive coupling with unactivated alkynes for the synthesis of multi-substituted pyrroles (**523**) in up to 71% yield (Scheme 130A).[169a] In 2012, Wang and coworkers described a Rh(III)-catalyzed cascade oxidative annulation reaction of benzoylacetonitrile with alkyne, affording substituted naphtho[1,8-*bc*]pyrans (**524**) in 82% yield (Scheme 130B).[169b] Moreover, this cascade annulation reaction with unsymmetrical alkynes is highly regioselective. Further experiments suggested that the first-step reaction proceeds by sequential cleavage of C(sp^2)-H/C(sp^3)—H bonds and annulation with an alkyne, leading to 1-naphthols. Subsequently, 1-naphthols reacted with alkyne by cleavage of C(sp^2)—H/O—H bonds to afford the 1:2 coupling products.



Scheme 130 Rh(III)-catalyzed C(sp^3)-H annulation with alkyne or diazo compound.

In 2015, Zhou, Yang, Zhu and coworkers developed an unprecedented Rh(III)-catalyzed regioselective redox-neutral annulation reaction of 1-naphthylamine *N*-oxides with diazo compounds by dual cleavage of C(sp^3)-H/C(sp^2)—H bonds to form biologically important 1*H*-benzo[*g*]indolines (**525**) (Scheme 130C). This coupling reaction proceeds under mild reaction conditions without the requirement of external oxidants.[169c]

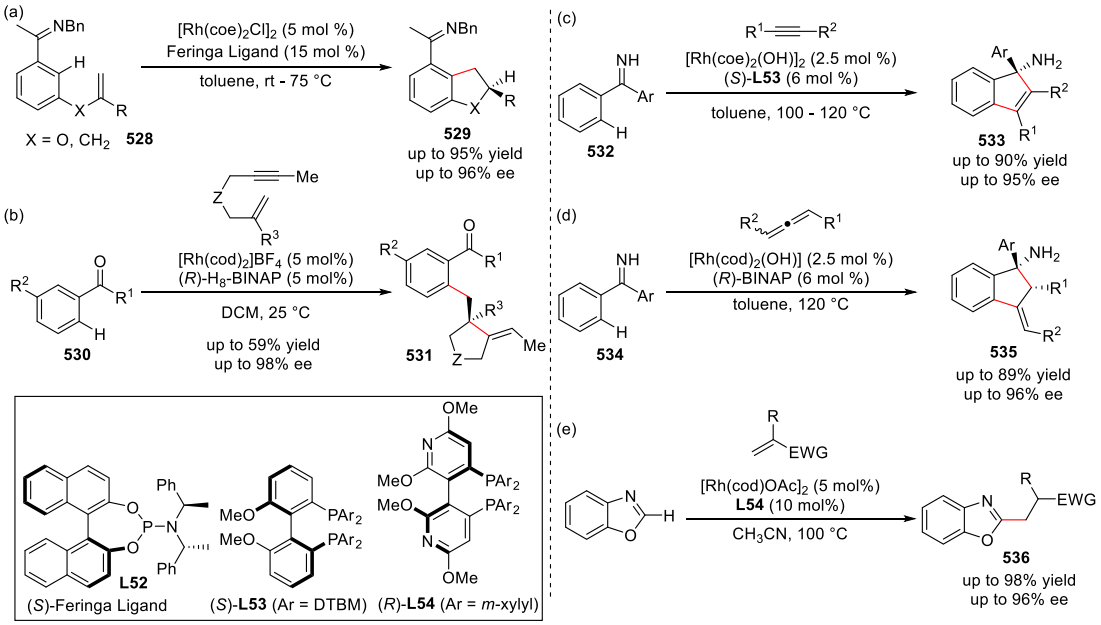
In 2018, Ackermann and coworkers described electrochemical Rh(III)-catalyzed C-H/C-H coupling reactions of benzoic acids with acrylates, generating H_2 as the sole byproduct (Scheme 131A).[170] In 2020, Ackermann and coworkers reported a modular electrochemical synthesis of *aza*-PAHs (**527**) via a Rh(III)-catalyzed cascade C-H annulation of *O*-methylamidoximes with alkynes (Scheme 131B).[171] The electrosynthesis displays broad substrate scope and excellent functional group tolerance, including iodo and azido groups.



Scheme 131 Rh(III)-catalyzed electrochemical C-H activation.

12.05.3.6 Enantioselective C-H activation

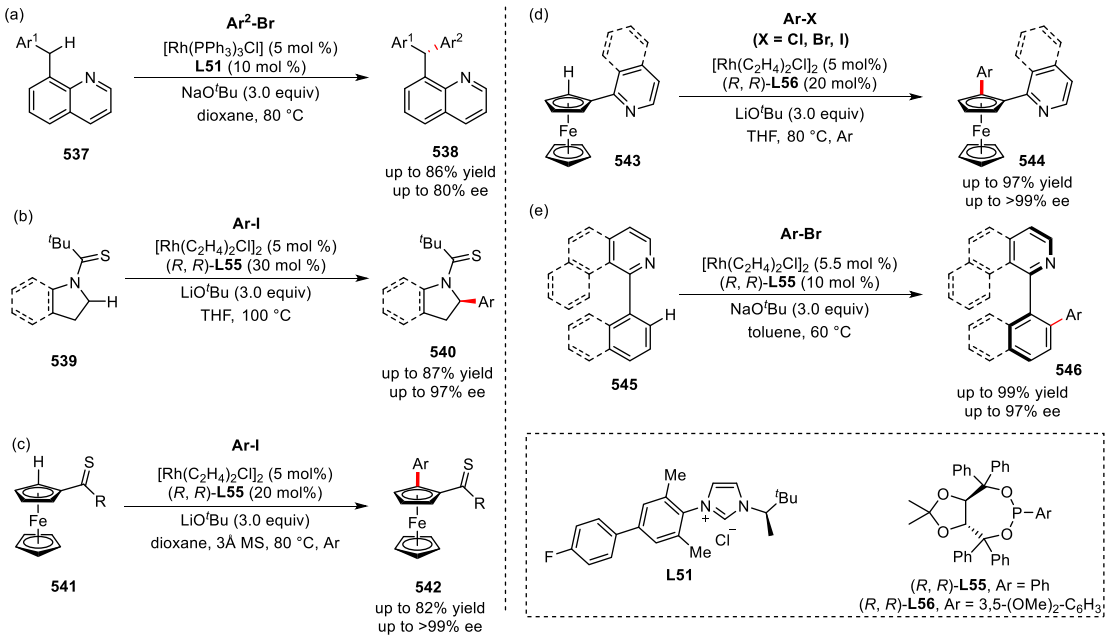
In 2004, Bergman, Ellman and coworkers described a highly enantioselective intramolecular imine-directed C-H/olefin coupling reaction by using Rh(I)/chiral phosphoramidite complex (Scheme 132A).[172a] Then the Tanaka group utilized a cationic Rh(I)/(*R*)-H_8-BINAP species to achieve C—H bond functionalization of electron-rich aryl ketones (**530**), which reacted with 1,6-enynes to give *ortho*-functionalized aryl ketones (**531**) with excellent regio- and enantioselectivity (Scheme 132B).[172b] In 2011, the Cramer group developed an asymmetric Rh(I)-catalyzed C-H annulation of unsubstituted ketimines (**532**) with internal alkynes



Scheme 132 Rh(I)-catalyzed asymmetric C(sp^2)-H functionalizations.

(Scheme 132C).[172c] Subsequently, they extended the catalytic system to the C-H annulation reaction with racemic allenes (Scheme 132D).[172d] The use of readily available racemic allenes and unprotected ketimines (**534**) significantly increased the complexity of the target molecules, thereby providing synthetically valuable, highly substituted indenylamines. In 2013, the Rovis group accomplished an enantioselective hydroheteroarylation reaction of benzoxazoles and α-substituted methacrylate compounds (Scheme 132E).[172e] This reaction delivered various elaborated benzoxazole products (**536**) in moderate to good yields and excellent enantioselectivity.

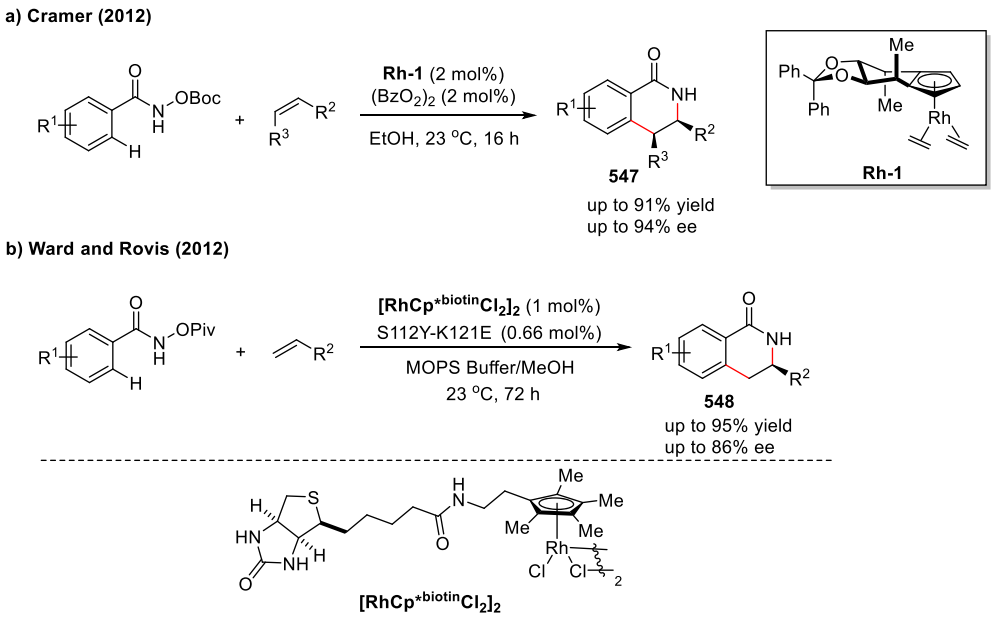
In 2016, Glorius and coworkers reported an elegant example of Rh(I)-catalyzed asymmetric intermolecular C(sp^3)-H arylation (Scheme 133A).[173a] Enantioenriched triarylmethanes (**538**) were obtained with up to 80% ee by using a chiral NHC ligand (**L51**). Subsequently, the same group reported an enantioselective arylation of various heterocycles such as tetrahydroquinolines, piperazines, piperidines, pyrrolidines, azetidines, and azepanes (Scheme 133B).[173b] The combination of a Rh(I) precatalyst and



Scheme 133 Rh(I)-catalyzed asymmetric C(sp^2)-H arylations.

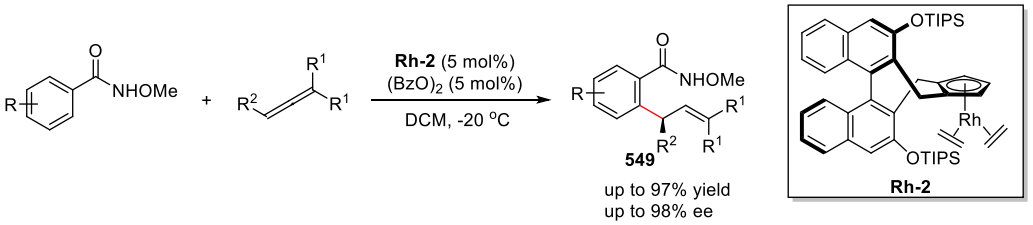
monodentate phosphonite ligand (**L55**) was shown to be a powerful catalytic system to generate various important enantioenriched arylative heterocycles. This redox-neutral method provided a new synthetic approach to α-*N*-arylated heterocycles (**540**) with high chemo- and enantioselectivity (up to 97% ee). You, Gu, and coworkers developed Rh(I)-catalyzed thioketone-directed asymmetric C–H arylation of ferrocenes (**541**) with **L55** (Scheme 133C).[173c] Aryl iodides were used as the coupling partners, leading to planar chiral ferrocenes (**542**) in good yields and excellent enantioselectivity (up to 82% yield, 99% ee). More recently, they also reported Rh(I)-catalyzed pyridine assisted enantioselective C–H arylation of ferrocenes (**543**) with aryl halides (Scheme 133D).[173d] This method proceeded with excellent levels of mono-arylation selectivity, enantioselectivity, and high catalytic efficiency. The relatively low catalyst loading (down to 1 mol% based on [Rh]) improved the practicality of the reaction. Notably, You group also developed an efficient Rh(I)-catalyzed atroposelective C – H arylation of heterobiaryls (**545**) in up to 99% yield and 97% ee (Scheme 133E).[173]

Chiral Cp ligands enabled asymmetric rhodium catalysis have emerged to be an extremely useful synthetic tool to achieve enantioselective C-H functionalizations. In 2012, the Cramer group pioneeringly reported that Rh(III) complexes bearing a class of simple C_2-symmetric Cp derivatives (**Rh-1**) proved to be highly efficient for the [4 + 2] annulation reaction of benzamides and alkenes (Scheme 134A).[174a] Simultaneously, Ward, Rovis and coworkers ingeniously synthesized a biotinylated [Cp*Rh(III)] complex and combined it with engineered tetrameric streptavidin (tSav) to create an artificial metalloenzyme, which proved to be highly efficient for the same type reaction (Scheme 134B).[174b]



Scheme 134 Rh(III)-catalyzed enantioselective [4 + 2] annulation reactions.

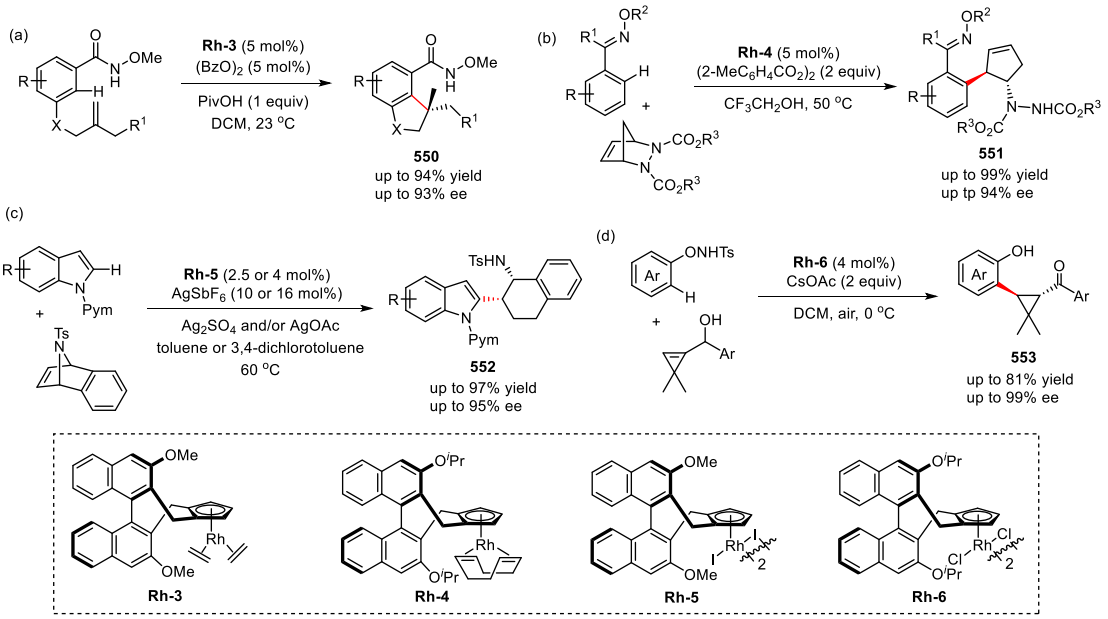
In 2013, the Cramer group reported highly tunable chiral Cp ligands based on binaphthyl backbone. The chiral environment at the metal center originates from both the rigid backwall and the 3,3′-substituents of BINOL-derived Cp ligands. The corresponding Rh complex (**Rh-2**) was used for enantioselective C–H allylation of *N*-methoxybenzamides with allenes, giving **549** up to 97% yield and 98% ee (Scheme 135).[175]



Scheme 135 Enantioselective C–H allylation of *N*-methoxybenzamides with allenes.

Subsequently, Cramer and coworkers reported an enantioselective Rh(III)-catalyzed hydroarylation, and functionalized dihydrobenzofurans (**550**) bearing a quaternary stereocenter with 93% ee were obtained (Scheme 136A).[176a] Notably, the *meta*-alkoxy group acts as a secondary directing group, which allows for the site-selective reaction at the more hindered *ortho*-position.

In 2019, they reported an enantioselective C-H activation/ring-opening sequence of aryl ketoxime ethers and 2,3-diazabicyclo [2.2.1]hept-5-enes for the construction of highly functionalized 2-arylated cyclopentenyl amines (**551**) (Scheme 136B).[176b] The transformation was enabled by the combination of a chiral Cp^{x}Rh(I)(cod) complex (**Rh-4**) with a matching aroyl peroxide



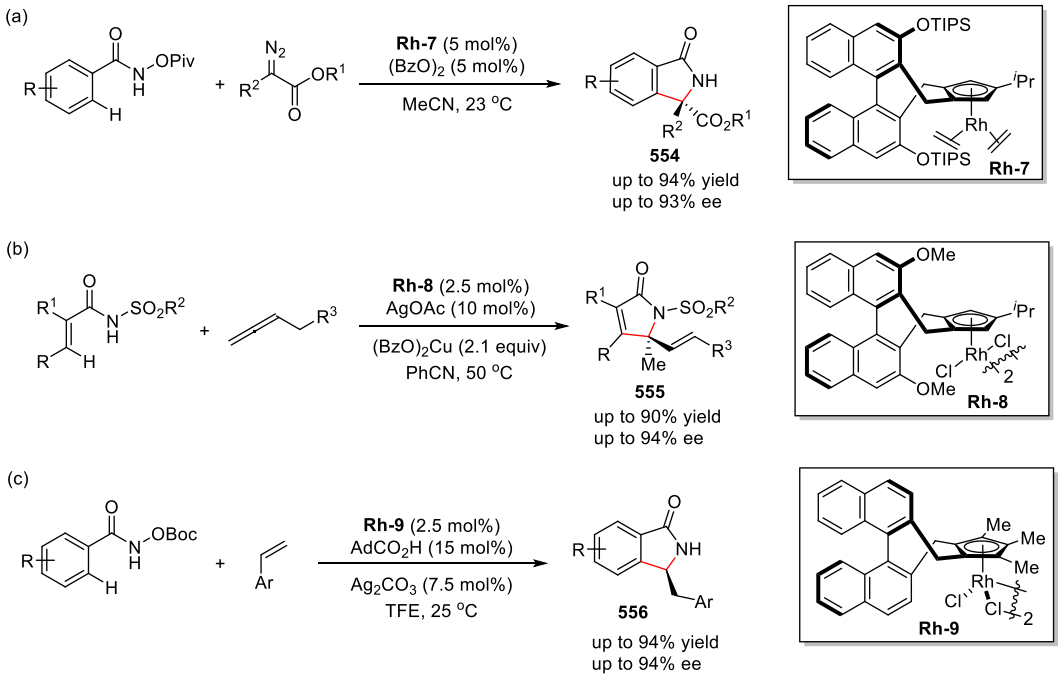
Scheme 136 Rh(III)-catalyzed asymmetric C(sp^2)-H functionalizations.

additive for the oxidative catalyst activation. Notably, both the cyclooctadiene group and the aroyl peroxide additive displayed pronounced effects on the reaction efficiency and enantioinduction.

In 2019, Zheng, Li and coworkers realized Rh(III)-catalyzed C-H activation of indoles and desymmetrizative coupling with 7-azabenzonorbornadienes (Scheme 136C).[176c] $AgSbF_6$ was found to enhance the catalytic activity by suppressing C3-H activation of the indoles.

Cyclopropane rings are a prominent structural motif in biologically active molecules. A dual directing group-assisted C-H activation strategy was used to realize a mild and redox-neutral Rh(III)-catalyzed C-H activation and cyclopropylation of *N*-phenoxylsulfonamides with cyclopropenyl secondary alcohols (Scheme 136D).[176d] Integrated experimental and computational mechanistic studies revealed that the reaction proceeds via a Rh^V nitrenoid intermediate, and Noyori-type outer sphere concerted proton-hydride transfer from the secondary alcohol to the Rh═N bond produces the observed *trans* selectivity.

Asymmetric Rh-catalyzed C-H annulations have emerged as a novel enabling method for the rapid construction of cyclic products. In 2014, Cramer and coworkers reported a mild and highly enantioselective Rh(III)-catalyzed [4 + 1] C-H annulation to access functionalized isoindolones (**554**) in up to 94% yield and 93% ee (Scheme 137A).[177a] In 2019, Cramer and coworkers realized an enantioselective alkenyl C-H activation of acrylamides by chiral Cp^xRh(III) complexes (**Rh-8**) and their subsequent

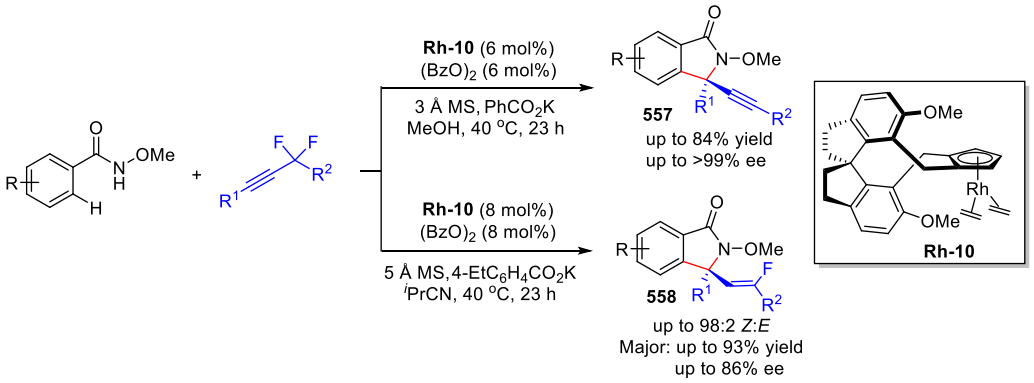


Scheme 137 Rh(III)-catalyzed asymmetric [4 + 1] C-H annulation.

C—C and C—N bond formation with allenes (Scheme 137B).[177b] This net [4 + 1]-annulation gave a straightforward access to chiral functionalized α,β-unsaturated γ-lactams (**555**) with a quaternary stereocenter in good enantioselectivity. Notably, allene serves as a one-carbon unit in the [4 + 1] annulation.

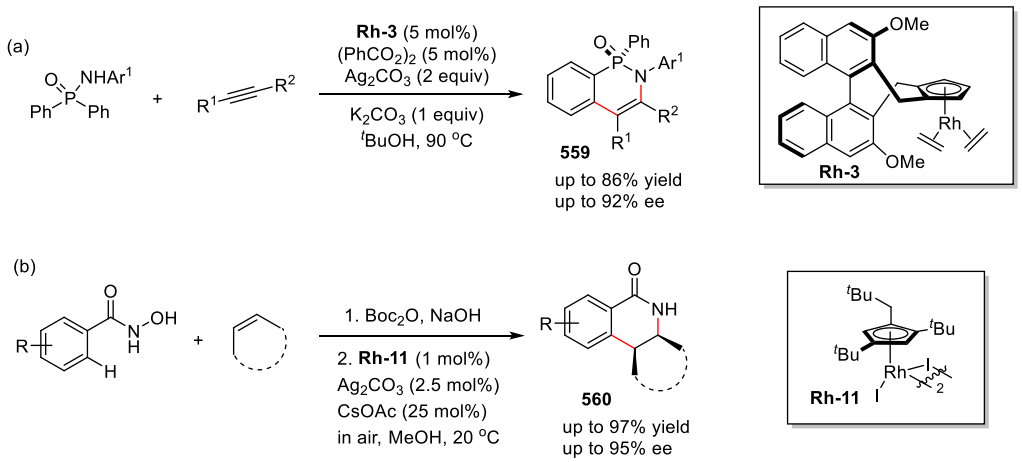
Of particular note, the multi-substituents on the Cp ring exhibited distinct reactivity, chemo- and regioselectivity in a few C–H functionalization reactions. In 2020, You and coworkers designed a series of chiral binaphthyl-based Cp^xRh bearing multi-substituent groups on the Cp ring to tune the steric and electronic effects, by utilizing $Co_2(CO)_8$-mediated [2 + 2 + 1] cyclization as a key step in ligand formation. Employing such a chiral Cp^xRh (**Rh-9**) bearing trimethyl-substituents on the Cp ring, unprecedented enantioselective [4 + 1] annulation reaction of benzamides and alkenes was achieved, yielding a variety of isoindolinones (**556**) in up to 94% yield with 94% ee (Scheme 137C).[177c]

In 2018, the Wang group reported a solvent-dependent enantioselective synthesis of alkynyl and monofluoroalkenyl isoindolinones from *N*-methoxybenzamides and α,α-difluoromethylene alkynes with the SCpRh catalyst (**Rh-10**) developed by the You group (Scheme 138).[178] The alkynyl isoindolinones (**557**) were generated in MeOH whereas the monofluoroalkenyl isoindolinones (**558**) were formed in ^{i}PrCN.



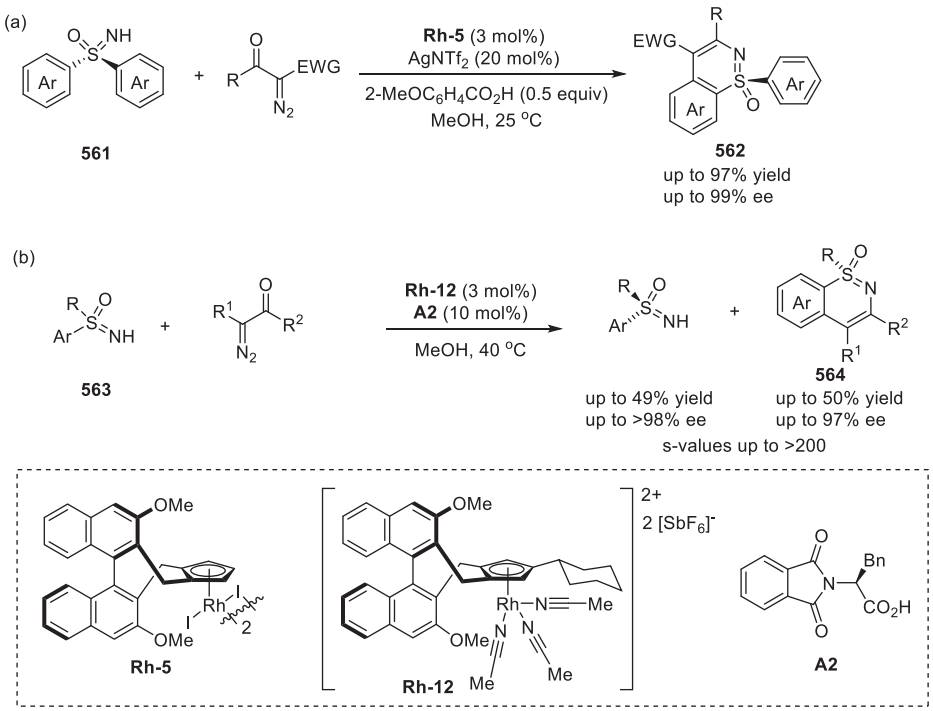
Scheme 138 Asymmetric synthesis of isoindolinones by C-H activation.

The [4 + 2] annulation reactions have attracted much attention since the pioneering works by the groups of Rovis and Ward, and Cramer.[174] In 2017, Cramer and coworkers presented a Rh(III)-catalyzed asymmetric [4 + 2] annulation for the synthesis of P-chiral compounds from easily accessible diaryl phosphinamides (Scheme 139A).[179a] The use of Rh(III) complex (**Rh-3**) was shown to enable an enantio-determining C-H activation step. Upon trapping with alkynes, a broad range of cyclic phosphinamides (**559**) with a stereogenic phosphorus(V) atom were generated in up to 86% yield with 92% ee. In 2018, Perekalin and coworkers developed a class of novel planar chiral rhodium catalyst $[(C_5H^t_2Bu_2CH^t_2Bu)RhI_2]_2$ in two steps from $[Rh(cod)Cl]_2$ and *tert*-butylacetylene. Pure enantiomers of the catalyst were obtained by separation of its diastereomeric adducts with (*S*)-proline. This Rh catalyst (**Rh-11**) promoted enantioselective reaction of aryl hydroxamic acids with strained alkenes to give dihydroisoquinolones (**560**) in up to 97% yield with 95% ee (Scheme 139B).[179b]



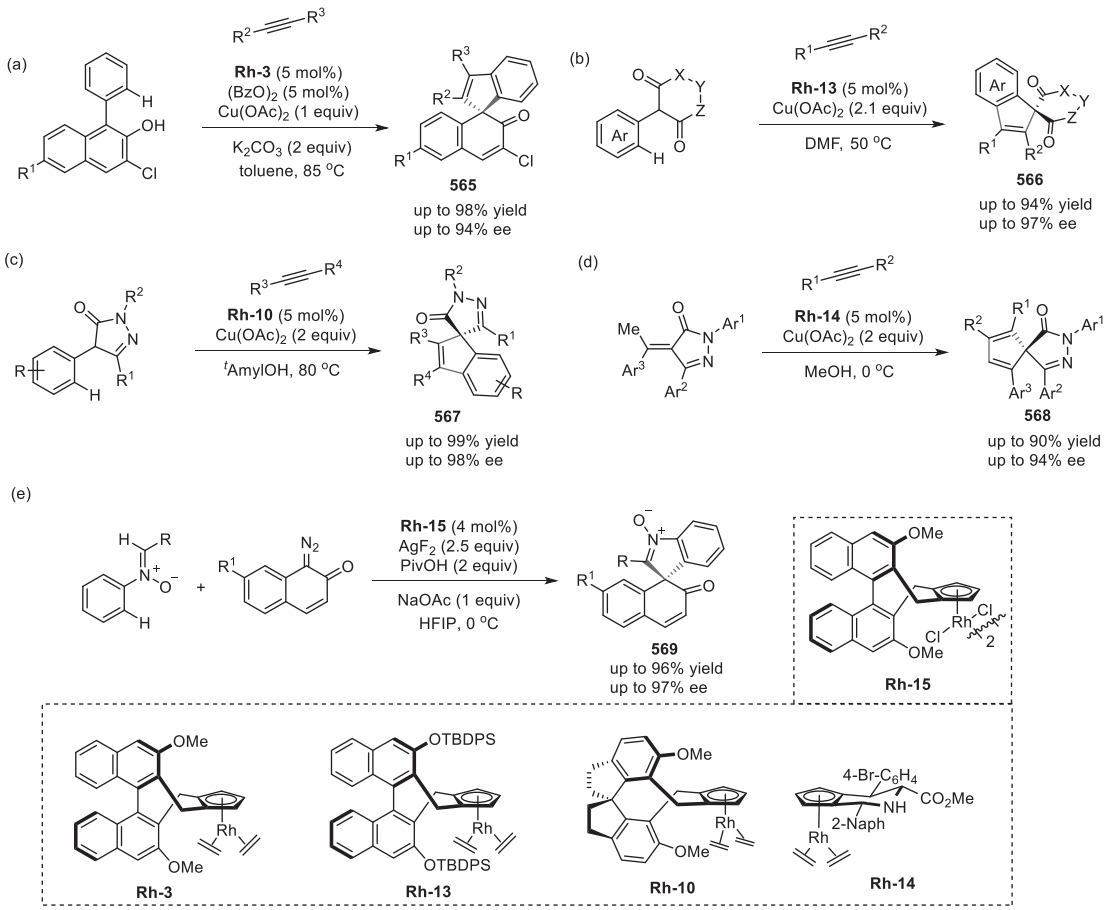
Scheme 139 Rh(III)-catalyzed asymmetric [4 + 2] annulation.

In 2018, Li and coworkers realized an enantiodivergent [4 + 2] annulative coupling of sulfoximines and diazo compounds by Rh(III)-catalyzed desymmetrizing C-H activation (Scheme 140A).[180a] The reaction proceeded with a broad scope of sulfoximines and several classes of diazo compounds in good to excellent enantioselectivity. The enantioselectivity of the reaction seems to be correlated to the steric bias between the benzoic acid additive and the arene substrate. A similar work was reported by the Cramer group in 2019. They developed an efficient kinetic resolution of racemic sulfoximines via Rh(III)-catalyzed asymmetric C-H annulation reaction (Scheme 140B).[180b] This kinetic resolution gave a very impressive *s* value (up to >200).



Scheme 140 [4 + 2] annulative coupling of sulfoximines with diazo compounds.

The development of efficient access to chiral spirocycles has been the subject of intensive research. In 2015, You and coworkers achieved an asymmetric C-H activation/dearomatization reaction of *β*-naphthol derivatives by a chiral Rh catalyst (**Rh-3**) (Scheme 141A).[181a] The reaction allowed a dearomative transformation of naphthol derivatives into chiral spirocyclic



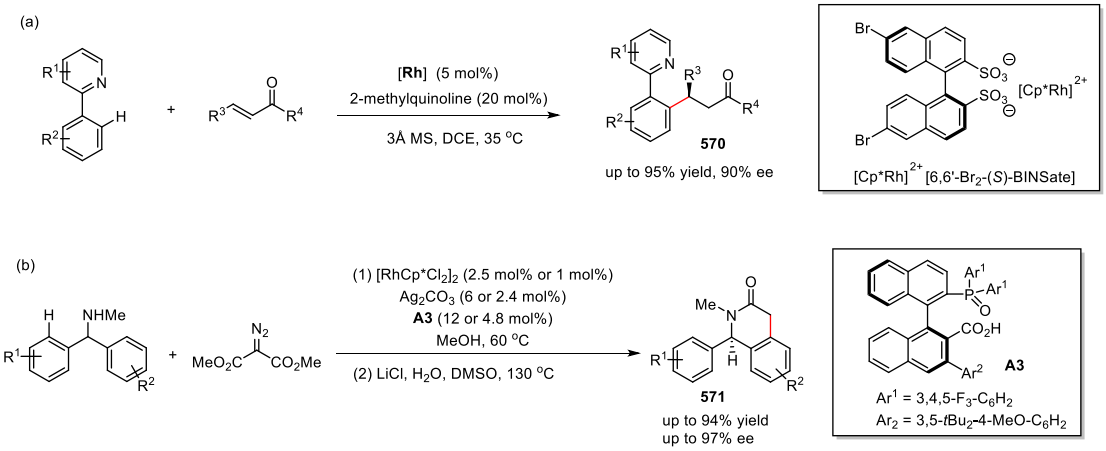
Scheme 141 Chiral spirocyclic compounds through Rh(III)-catalyzed C-H functionalizations.

β-naphthalenones (**565**) bearing an all-carbon quaternary stereogenic center in 98% yield with 94% ee. Interestingly, Lam and coworkers developed an enantioselective synthesis of spiroindenes (**566**) from the oxidative annulation of aryl cyclic 1,3-dicarbonyl compounds (or their enol tautomers) with alkynes, in the presence of chiral cyclopentadienyl rhodium catalyst (**Rh-10**) (Scheme 141B).[181b] This process tolerated a wide range of substrates to give diverse products containing an all carbon-quaternary stereocenter with up to 97% ee.

In 2017, You and coworkers described an asymmetric synthesis of spiropyrazolones from pyrazolones and alkynes by Rh(III)-catalyzed C(sp^2-H) activation/annulation (Scheme 141C).[181c] The use of chiral SCpRh catalyst (**Rh-7**) provided excellent enantioselectivity, reactivity, and regioselectivity. This method enabled the transformation of a wide range of simple substrates into highly enantioenriched spiropyrazolones (**567**) containing an all-carbon quaternary stereogenic center. Later, the Waldmann group reported the annulation of α-arylidene pyrazolones through formal C(sp^3)-H activation in the presence of Rh(III)-Cp^x catalyst (**Rh-11**) (Scheme 141D).[181d] This method gave access to a class of structurally diverse spiropyrazolones (**568**) in up to 90% yield with 94% ee. The synthetic utility of this method was demonstrated by the late-stage functionalization of drugs and natural products as well as the preparation of enantioenriched [3]dendralenes.

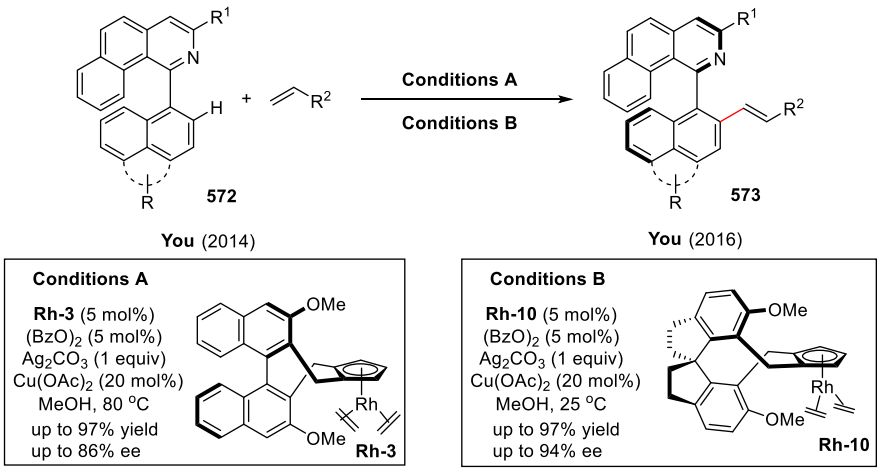
Axial-to-central chirality transfer is an important strategy to construct chiral centers. Recently, Li and coworkers realized a Rh(III)-catalyzed enantioselective spiroannulative synthesis of nitrones (Scheme 141E).[181e] The annulation proceeded via C-H arylation to give an atropomerically metastable biaryl, followed by intramolecular dearomative trapping under oxidative conditions with high degree of chirality transfer.

C-H activation steps often proceed through a carboxylate-assisted CMD mechanism, and thus in principle, in such a process a chiral carboxylic acid or a chiral carboxylate base can enable the selective cleavage of enantiotopic C—H bonds, even in the absence of a chiral Cp^x ligand. In 2018, Yoshino, Matsunaga and coworkers ingeniously developed an enantioselective conjugate addition of aromatic C—H bond to α, β-unsaturated ketones catalyzed by Cp^*Rh(III)/BINSate (BINSate = 1,1′-binaphthyl-2,2′-disulfonate) (**Rh-16**), which was readily prepared by treatment of (*S*)-1,1′-binaphthyl-2,2′-disulfonic acid ((*S*)-BINSA) with Ag_2CO_3, followed by $[Cp^*RhCl_2]_2$ in CH_3CN. Various addition products (**570**) were obtained with good enantioselectivity (up to 95:5 er) in the presence of a catalytic amount of 2-methylquinoline (Scheme 142A).[182a] Lin, Yoshino, Matsunaga and coworkers reported an achiral Cp^xRh(III)/chiral carboxylic acid (**A3**) catalyzed asymmetric C-H alkylation of diarylmethanamines with a diazomalonate, followed by cyclization and decarboxylation to afford 1,4-dihydroisoquinolin-3(2*H*)-ones (**571**) (Scheme 142B).[182b] The transformation of secondary alkylamines as well as nonprotected primary alkylamines underwent with high enantioselectivity by using a newly developed chiral carboxylic acid as the sole source of chirality.



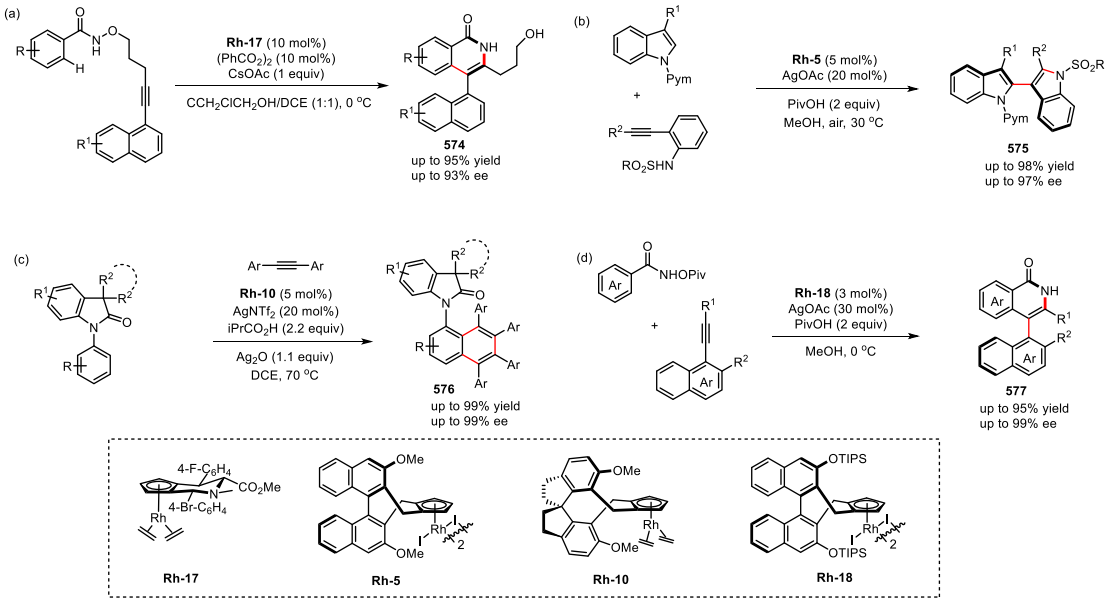
Scheme 142 Enantioselective C-H functionalizations by achiral Rh(III) with chiral acid.

Chiral binaphthyl-derived Cp^xRh complexes could be employed to induce good enantioselective control for the synthesis of axially chiral biaryls. In 2014, You and coworkers developed an asymmetric C-H oxidative alkenylation of biaryl derivatives (**572**) with olefins by using chiral binaphthyl-derived Cp^xRh catalyst (**Rh-3**), affording axially chiral biaryls (**573**) in 97% yield with 86% ee (Scheme 143A).[183a] In 2016, You and coworkers reported a series of novel cyclopentadienyl ligands (SCps) based on 1,1′-spirobiindane scaffold. One of the Rh complexes derived from SCp behaved as a superior catalyst in asymmetric oxidative C–H alkenylation of biaryl derivatives with olefins (Scheme 143B).[183b] Comparison of the X-ray crystal structures of binaphthyl-based Cp^xRh (**Rh-3**) and 3,3′-dimethoxy substituted SCpRh complex (**Rh-10**) revealed that the two methoxy groups as side walls are closer to the Rh center creating a better chiral environment in the SCpRh complex.



Scheme 143 Axially chiral biaryls by Rh(III)-catalyzed asymmetric oxidative C–H alkenylation.

Axially chiral 4-arylisoquinolones are endowed with pronounced bioactivity, and methods for their efficient synthesis have gained widespread attention. In 2018, Antonchick, Waldmann and co-workers realized a Rh(III)-catalyzed C-H intramolecular annulation reaction for the synthesis of axially chiral 4-arylisoquinolones (Scheme 144A).[184a] The use of chiral cyclopentadienyl ligand bearing a piperidine ring backbone afforded the atropisomers (**574**) in up to 95% yield with 93% ee. In 2019, Li and coworkers realized oxidative coupling of indoles with *o*-alkynylanilines/phenols employing binaphthyl-derived Cp^{x}Rh catalyst (**Rh-5**) (Scheme 144B).[184b] The reaction proceeded via initial C–H activation, followed by alkyne cyclization, affording 2,3′-biindolyls (**575**). Importantly, the chiral rhodacyclic intermediate was isolated and its crystal structure revealed that the bulky iodide group is disposed distal to the methoxy group of the Cp ligand.



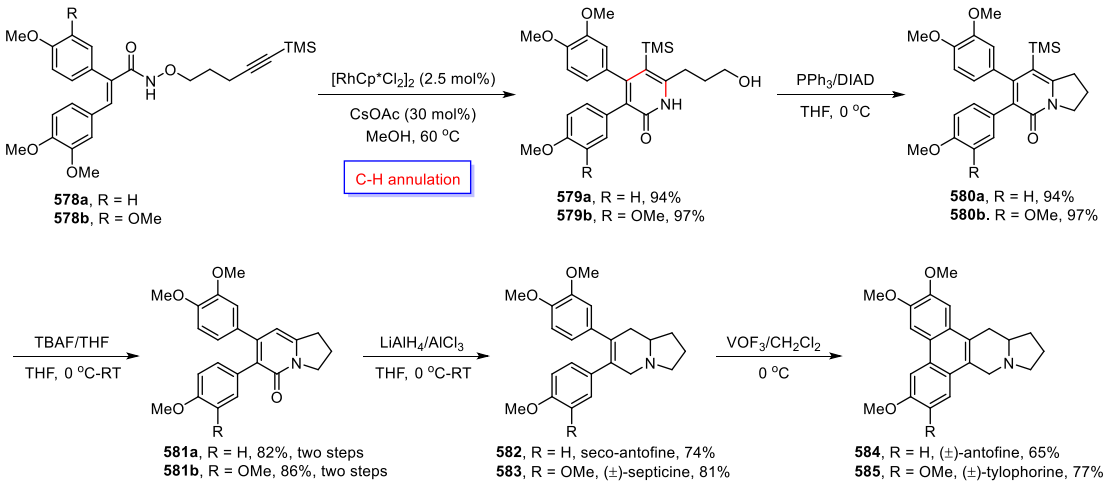
Scheme 144 Axially chiral biaryls by Rh(III)-catalyzed asymmetric C-H annulations.

The C-N axial chirality is less studied than C-C axial chirality. In 2019, Wang and coworkers developed an asymmetric Rh(III)-catalyzed dual C-H activation reaction of *N*-aryloxindoles and alkynes for the synthesis of a variety of C-N axially chiral *N*-aryloxindoles (**576**) in up to 99% yield with 99% ee (Scheme 144C).[184c] Recently, the atroposelective synthesis of biaryl isoquinolones (**577**) by Rh(III)-catalyzed C-H [4 + 2] annulation of benzamides and 2-substituted 1-alkynylnaphthalenes was reported by the Li group (Scheme 144D).[184d] Both benzamides and heteroaryl carboxamides were found to be suitable substrates in this reaction, and excellent regioselectivity and enantioselectivity were obtained. The enantiomerically and diastereomerically pure

rhodacyclic complex was prepared and offered insights into enantiomeric control of this annulation reaction, wherein the steric interactions between the amide directing group and the alkyne substrate dictated both the regio- and enantioselectivity.

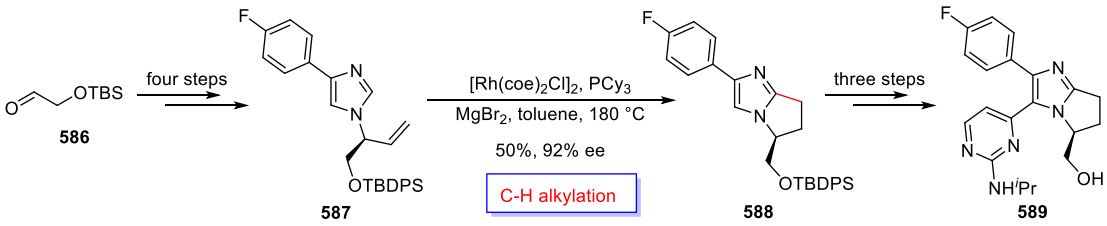
12.05.3.7 Applications in organic synthesis

Because of their remarkable biological profiles and unusual pentacyclic architectures, phenanthroindolizidine alkaloids, such as antofine (**584**) and tylophorine (**585**), are attractive synthetic targets. Alkaloids **583**, **584**, and **585** could be readily prepared from amides **578a** and **578b** (Scheme 145). In the presence of $[(Cp^*RhCl_2)_2]$ (2.5 mol%), the intramolecular C-H annulation reaction of **578a** and **578b** produced 2-pyridones **579a** and **579b** in excellent yields, respectively. Under Mitsunobu conditions, **579a** and **579b** were converted to indolizidines. Removal of the TMS group gave **581a** and **581b** in 82% and 86% yields, respectively. After reduction of **581a** and **581b**, seco-antofine (**582**) and alkaloid septicine (**583**) were provided in high yields. Finally, synthesis of antofine (**584**) and tylophorine (**585**) was achieved by oxidative coupling of secoantofine (**582**) and septicine (**583**). [185]



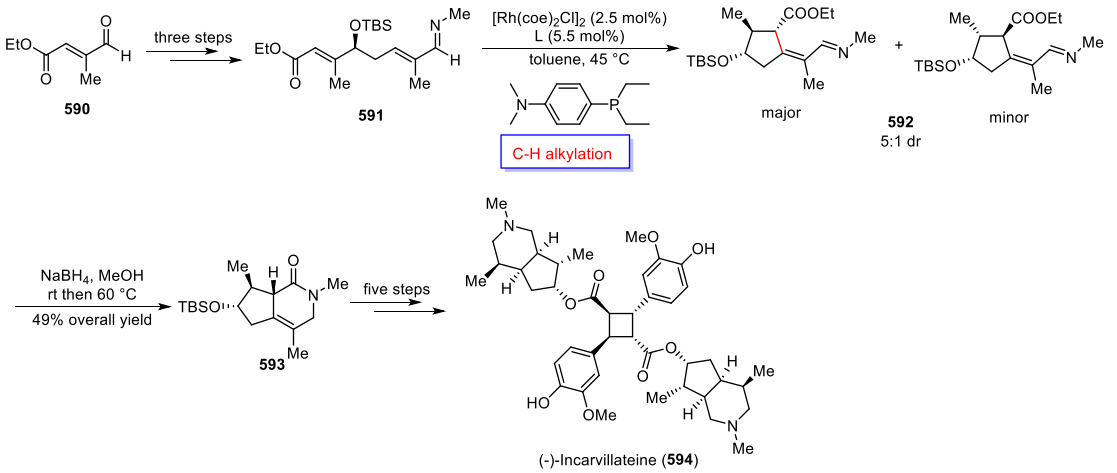
Scheme 145 Total synthesis of alkaloids **583**, **584**, and **585**.

In 2007, Bergman, Ellman and coworkers developed an effective and flexible route to synthesize potent kinase inhibitor **589**, the key transformation of which is an intramolecular alkylation via Rh-catalyzed C-H functionalization (Scheme 146). Compound **587** was synthesized from commercially available tertbutyldimethylsiloxyacetaldehyde **586** over 4 steps. Ultimately, the cyclization of **588** proceeded in 50% yield and 92% ee in the presence of 5 mol% $[RhCl(coe)_2]_2$, 15 mol% PCy_3, and 5% $MgBr_2$ as an additive at 180 °C. The subsequent three-step reactions efficiently afforded the final product **589**.[186]



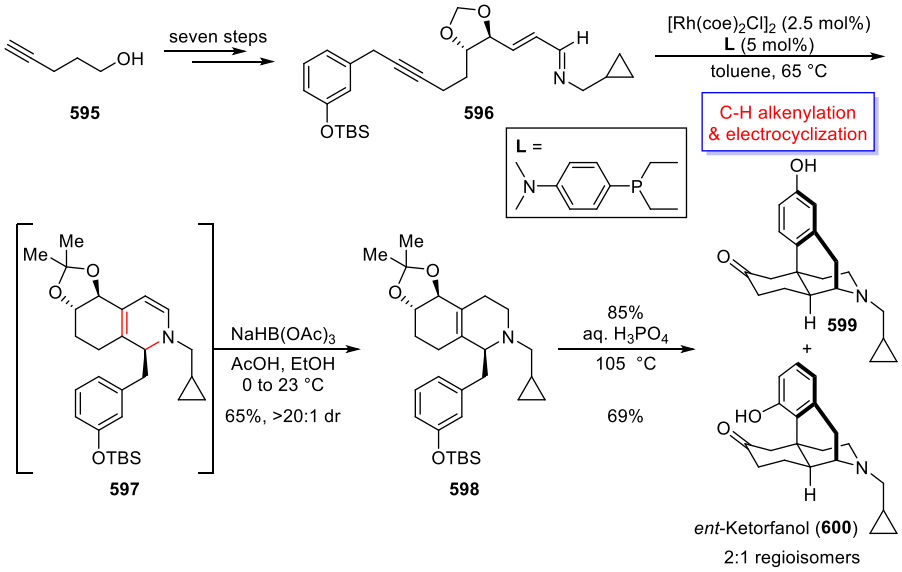
Scheme 146 Enantioselective synthesis of potent kinase inhibitor **589**.

Bergman, Ellman and coworkers accomplished the concise asymmetric synthesis of (−)-incarvillateine (**594**) in 11 total steps, with 15.4% overall yield, which was significantly improved compared with the previously reported synthesis (Scheme 147). Rh-catalyzed diastereoselective C-H alkylation of **591** simultaneously installed two of the five necessary stereocenters in the bicylic piperidine **592** while stereospecifically generating the tetrasubstituted, exocyclic alkene that enabled the rapid synthesis of (−)-incarvillateine (**594**).[187]



Scheme 147 Asymmetric total synthesis of (–)-incarvillateine (**594**).

Then, Houk, Ellman and coworkers reported an efficient synthesis of *ent*-ketorfanol (**600**) starting from simple and commercially available materials (Scheme 148). The fused bicyclic 1,2-dihydropyridine as a key intermediate (**597**) was generated by Rh(I)-catalyzed intramolecular C-H alkenylation/6π electrocyclization cascade reaction. The ketone functional group and the final ring were introduced in one-step by redox-neutral acid catalyzed rearrangement of the vicinal diol to obtain the desired carbonyl group, and then followed by an intramolecular Friedel-Crafts alkylation.[188]



Scheme 148 Asymmetric total synthesis of *ent*-ketorfanol.

12.05.4 Concluding remarks

Great progresses on Pd- and Rh-catalyzed carbon-carbon bond forming reactions such as arylation, alkylation, olefination and annulation via C-H functionalization have been made in the past decades. These methods have significant advantages over traditional methods for the construction of C—C bond in terms of step and atom economies. These newly developed C-H functionalization reactions offer straightforward and distinct retrosynthetic approaches for the synthesis of complex molecules, which display remarkably high efficiency. Notably, the development of enantioselective variants of these C-H functionalization reactions provides a new avenue for the field of asymmetric catalysis. Deep mechanistic understandings of the C-H functionalization processes have enabled rational design of ligand, catalyst, and transformations. Despite the impressive achievements, the C-H functionalization field is still far from mature. More transformations based on novel C-H activation modes are still underdeveloped.

The site-selective reactions rely heavily on the introduction of directing groups, which often require pre-installation and subsequent removal. Directing group free C-H functionalization processes are rare and will likely to be the future research topic. Catalytic systems that enable highly enantioselective C—H bond activation are limited, and the design and synthesis of chiral ligands and catalysts will play a key role here. In terms of practicality, catalysts with higher efficiency or those based on cheap metals will be explored and ultimately have a better chance for application in the production of pharmaceutical intermediates and fine chemicals. Therefore, the development of highly efficient and selective (regio-, chemo- and enantioselective) C-H functionalizations will continue and more applications of C-H functionalization reactions in the synthesis of functional molecules will be expected in future.

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