

Review

Advances in Enantioselective C–H Activation/Mizoroki-Heck Reaction and Suzuki Reaction

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Abstract: Traditional cross-coupling reactions, like Mizoroki-Heck Reaction and Suzuki Reaction, have revolutionized organic chemistry and are widely applied in modern organic synthesis. With the rapid development of C–H activation and asymmetric catalysis in recent years, enantioselective C–H activation/cross-coupling reactions have drawn much attention from researchers. This review summarizes recent advances in enantioselective C–H activation/Mizoroki-Heck Reaction and Suzuki Reaction, with emphasis on the structures and functions of chiral ligands utilized in different reactions.

Keywords: enantioselective C–H activation; C–C cross-coupling; Suzuki reaction; Mizoroki-Heck reaction

1. Introduction

Over the past few decades, C–H bond activation was established as a credible and viable strategy in organic synthesis [1–18]. On the basis of previous work, C–H activation/functionalization is employed as a dynamic strategy for the synthesis of a great deal of highly valuable natural products and other classes of compounds for pharmaceuticals or research interests [19–22]. Chemists have long been captivated by such synthetic techniques, owing to the obvious merits. From a philosophical point of view, chemists regard C–H bonds as dormant equivalents of various pre-functionalized groups. Moreover, the direct modification of ubiquitously-existing C–H bonds successfully live up to the criteria of one perfect catalytic reaction that ought to be atom-economic and environmental-friendly [23]. Thus, it provides new synthetic disconnections in retrosynthetic analysis [24–28].

It is widely acknowledged that carbon-carbon (C–C) bond formation is fundamental and essential in organic chemistry. Numerous methods have been well developed to enable such C–C bond formation to proceed smoothly. Among these reactions, transition-metals (Pd, Rh, Ru, Cu, Zn, Sn, Mg, etc.) catalyzed cross-coupling reactions are efficient techniques to realize C–C bond formation, which can be well exemplified by Suzuki [29], Mizoroki-Heck [30], Sonogashira [31], Negishi [32], Stille [33], Kumada [34] coupling reaction, etc. These coupling reactions are renowned for their extraordinary utility, practicality, and reliability, and have been broadly utilized in many syntheses, involving pharmaceuticals, fine chemicals, agrochemicals, etc. Consequently, Richard Mizoroki-Heck, Ei-ichi Negishi, and Akira Suzuki jointly won the Nobel Prize in Chemistry 2010 for their excellent work of “palladium-catalyzed cross-coupling reactions in organic synthesis”, which furnished a novel way to achieve C–C bond formation that substantially accelerated the development of pharmaceuticals and electronics industries [35]. Although lots of outstanding achievements in this field have been made, from an atom-economic and environmental-harmoniously perspective, there are still shortcomings

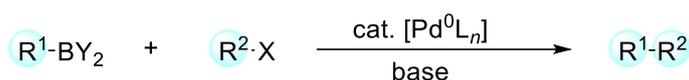
in these known and powerful traditional cross-coupling reactions. For instance, the substrates must be pre-functionalized, such as using organic (pseudo) halides or organometallic reagents, to gain reactivity during cross-coupling processes. Subsequently, it would result in metal (pseudo) halide wastes, which are supposed to be evaded for atom-economic purpose. Therefore, it is a brilliant notion to develop new methods replacing the pre-functionalized substrates with raw arenes or hydrocarbons, which can achieve the C–H activation and C–C cross-coupling simultaneously. When compared with traditional cross-coupling reactions, the C–H activation/C–C cross coupling reactions have obvious superiority in the aspect of atom-economy and environmental benignity.

With the rapid development of C–H activation/C–C cross-coupling reactions and the emerging of asymmetric catalysis, the enantioselective C–H activation/C–C cross-coupling reactions drew much more attention from researchers. It is a dynamic research frontier to achieve C–H activation/C–C cross-coupling reactions in a stereoselective manner. However, the direct asymmetric functionalizations of inert C–H bonds still remain challenging in current organic synthesis because of the poor reaction selectivity (regioselectivity and enantioselectivity). This is not odd due to the properties of C–H bond: (1) Substrates commonly contain diverse C–H bonds, which usually have high but comparable bond dissociation energy (BDE of C–H bonds are typically 90–110 kcal·mol⁻¹) within one molecular, rather than bearing a single targeted C–H bond [36–40]; (2) Higher reaction temperature is required for most of the reactions that are related to C–H activation in order to meet the high energy for the cleavage of C–H bonds, which would undoubtedly impose a detrimental effect on the asymmetric induction or coordination between the chiral ligands and the transition metals. Despite the difficulty in controlling stereoselectivity of C–H cleavage, tremendous progresses have been made in transition-metal catalyzed enantioselective C–H activation in the past few decades [41–46]. Among these highly efficient synthetic methodologies, complex chiral ligands or neighboring directing groups are usually needed. For instance, the Pd-catalyzed desymmetrization of prochiral C–H bonds has emerged as a promising strategy that can lead to a wide range of corresponding coupling products.

To our knowledge, numerous articles and reviews have been reported previously [30,36,39–41,46–52], particularly in the field of enantioselective coupling via asymmetric cross-dehydrogenative-coupling (CDC) [40,51] and enantioselective metal carbenoid/nitrenoid insertion into unactivated C–H bonds [40,46,53,54]. As such, this review is meant to briefly highlight, discuss, and illustrate the latest progresses and encountered challenges on enantioselective C–H activation/Mizoroki-Heck reaction and Suzuki reaction with a focus on the origin of chirality. The corresponding mechanism and characteristic features of each part will be discussed in detail, meanwhile, emphasizing the structures and functions of chiral ligands utilized in different reactions.

2. Enantioselective C–H Activation/Suzuki Reaction

Among different cross-coupling strategies, the Suzuki reaction between a C(sp²/sp³)-halide or C(sp²/sp³)-triflate with a C(sp²/sp³)-boronic acid or ester manifests remarkable performance in realizing C–C bond formation (Scheme 1). It has fascinated enormous attention since its first disclosure in 1979 and become a dynamic and powerful tool [29].



R¹=alkyl, alkynyl, aryl, vinyl

R²=alkyl, alkynyl, aryl, benzyl, vinyl

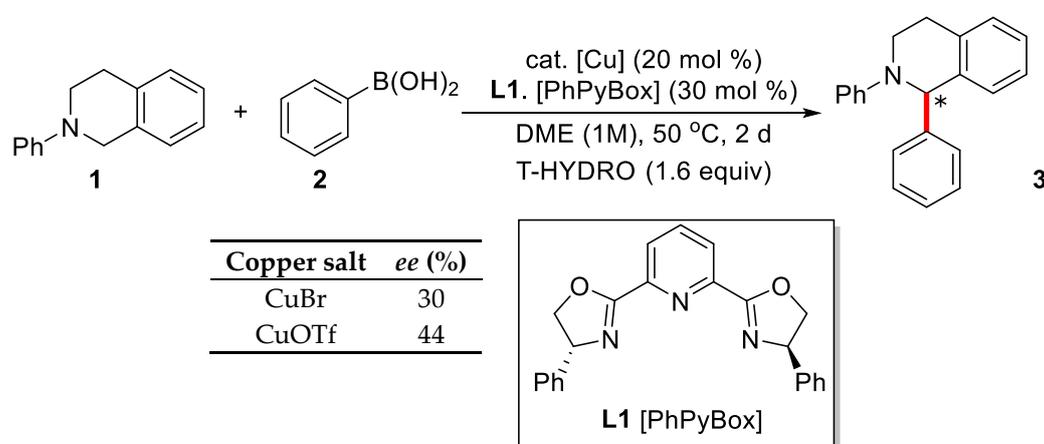
X=Br, Cl, I, OAc, OP(=O)(OR)₂, OTf

Scheme 1. Traditional Suzuki coupling reaction.

The great influences of Suzuki reaction are attributed to its high tolerance of different functional groups and extraordinary efficiency under facile reaction conditions in various media. In addition, its prominent compatibility to diverse processes, including microwave [55] and continuous flow conditions [56,57], and the easy accessibility of organic boronic acid or ester coupling partners, which are usually stable to oxygen, water, as well as harsh reaction conditions, are also attractive to scientists.

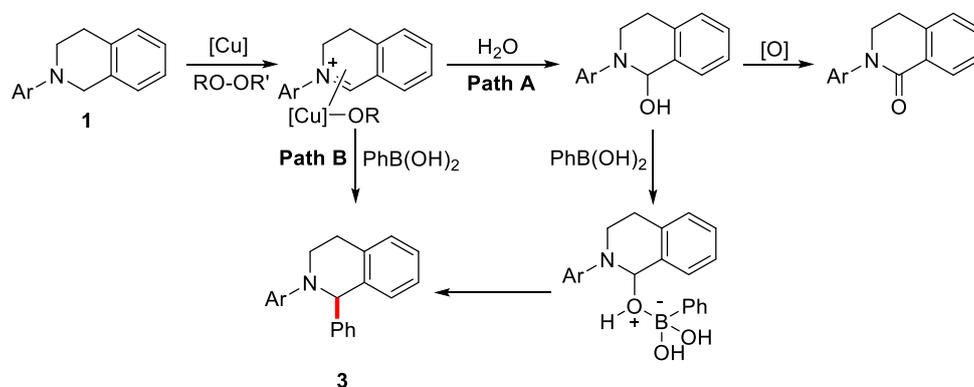
In recent years, the direct asymmetric C–H activation/Suzuki cross-coupling reactions have substantially attracted the attention of synthetic chemists. Herein, we review the recent progresses on enantioselective C–H activation/Suzuki cross-coupling reactions of prochiral substrates.

In 2008, Li et al., developed the asymmetric C(sp³)–H arylation reactions of tetrahydroisoquinolines with aryl boronic acids [58]. The reaction proceeded smoothly with CuBr as the catalyst and T-HYDRO as the oxidant in DME. Interestingly, when chiral PhPyBox was added as the ligand, the desired product was obtained with 30% *ee* (Scheme 2). The addition of CuOTf instead of CuBr further increased the enantioselectivity to 44%.



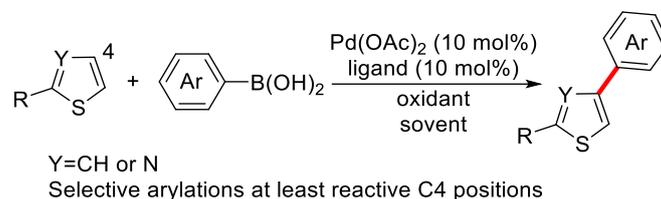
Scheme 2. Copper-catalyzed oxidative C(sp³)–H bond arylation with aryl boronic acids. Reproduced from Reference [58].

There were two proposed mechanism pathways (Scheme 3) and path B is preferred. In pathway B, the copper-iminium ion intermediate is generated and the subsequent coupling with aryl boronic acids gives access to the desired product. Meanwhile, the introduction of chiral ligands could induce the enantioselective C–H activation process. However, the enantioselectivity still remains to be further improved for practical applications.



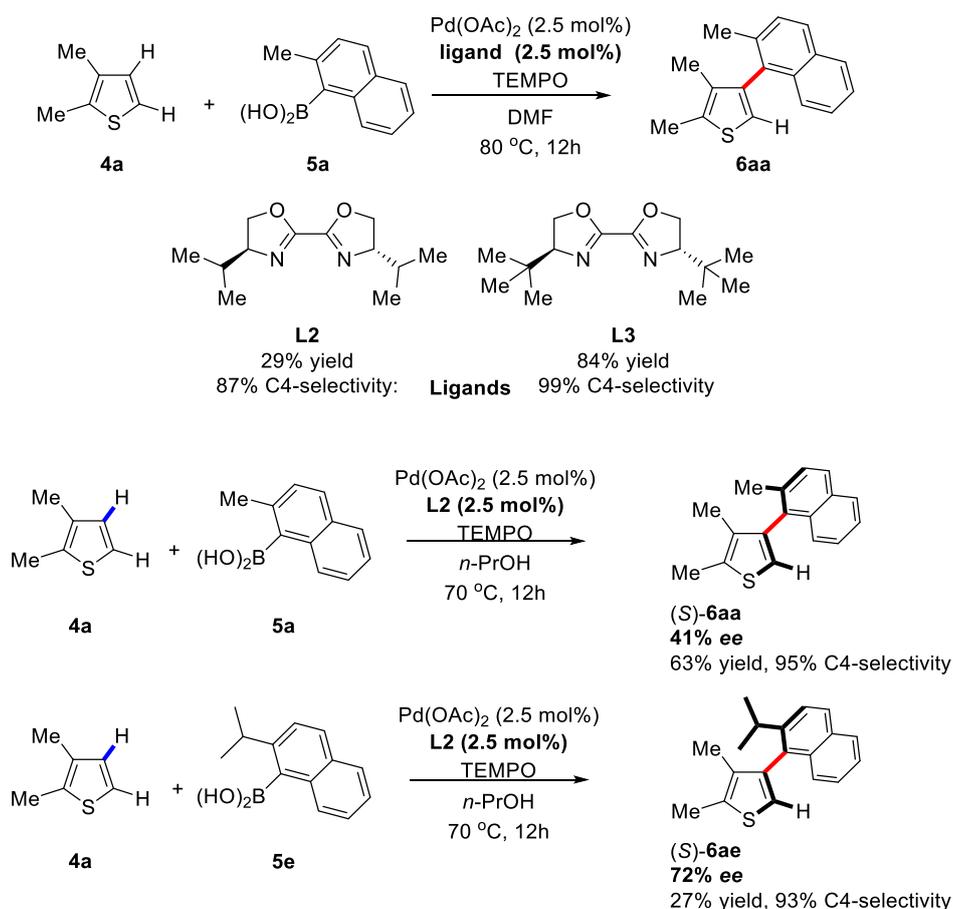
Scheme 3. Proposed mechanism of the oxidative arylation reaction. Reproduced from Reference [58].

Since 2009, the direct arylation of inert C–H of heteroarenes catalyzed by Pd-catalysts has rapidly evolved as a reliable and practical method. In 2011, Itami et al., developed the Pd-catalyzed oxidative C4-selective C–H arylation of thiophenes and thiazoles enabled by boronic acids (Scheme 4) [59].



Scheme 4. Selective arylation of heteroarenes via C–H activation [59].

This approach was further improved by Itami group in 2012 [60]. In order to access the hindered heterobiaryls, the screening of ligands was executed employing **4a** and **5a** (2,3-dimethylthiophene and 2-methylnaphthalenyl-1-boronic acid respectively) as substrates and Pd^{II} as the catalyst. Consequently, the desired coupling product was obtained with bisoxazolines ligands in the presence of Pd(OAc)₂, and **L3** was proved to be the most effective ligand (Scheme 5). Under the optimized reaction conditions, the scope of the substrates (thiophenes and arylboronic acids) was examined. A variety of different substrates were amenable for this system, delivering moderate yields of up to 84% and excellent C4 regioselectivities up to 99%. The successful synthesis of the tetra-*ortho*-substituted heterobiaryl **6aa** manifested the high efficiency of this bisoxazoline-Pd catalytic system.



Scheme 5. Generation of axially chiral biaryls via C–H activation/Suzuki reaction [60].

As the ligands delivering excellent performance (**L2** and **L3**) are chiral, the enantioselective synthesis of axially chiral heterobiaryls was predicted to be possible. To have a better understanding of the axial chirality of the substituted heterobiaryls, the rotation energy of 3-methyl-4-(2-methylnaphthalen-1-yl)-thiophene (**6ba**) between two conformations was investigated by DFT calculations (Figure 1). It was found that the rotation energy was high enough for the two atropisomers to exist stably at room temperature.

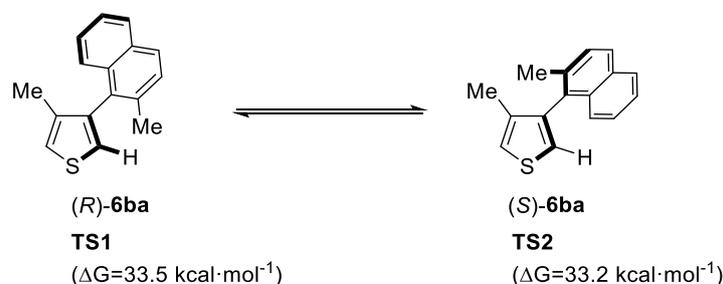
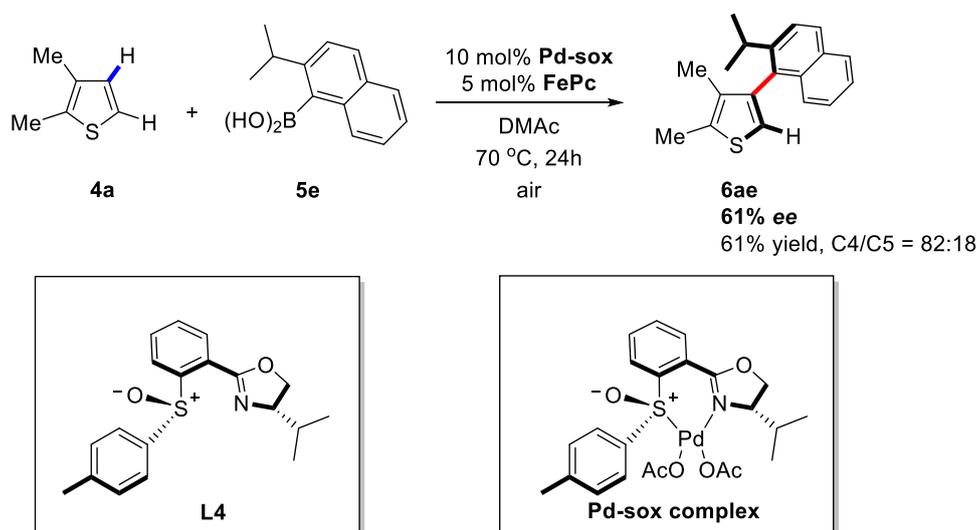


Figure 1. Rotation energy of **6ba** calculated at B3LYP/6-31G(d) level. Reproduced from Reference [60].

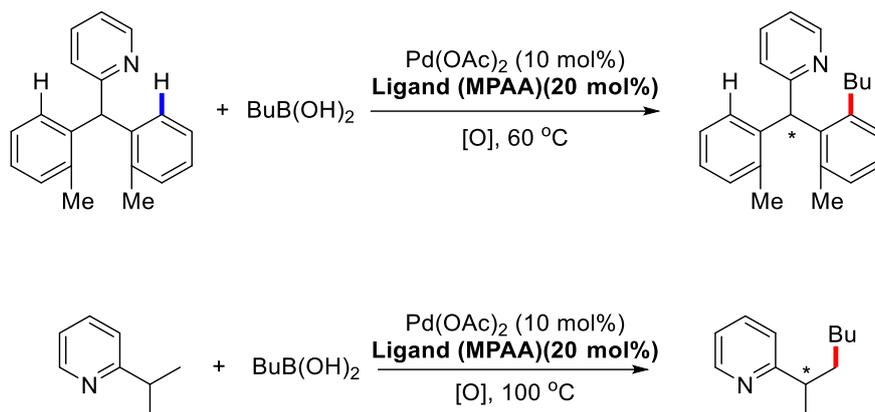
After investigating various conditions, impressively, the asymmetric induction truly occurred (Scheme 5). When the *n*-PrOH solution of **4a** and **5a** was exposed to Pd(OAc)₂/**L2** and TEMPO at 70 °C for 12 h under air, the product (*S*)-**6aa** was obtained with 41% *ee* and 63% yield. When a more sterically encumbered arylboronic acid **5e** was used, the enantiometric excess of the corresponding product was improved to 72%, albeit with a lower yield. The absolute stereo-configuration of the asymmetric products was determined by X-ray crystallography.

In 2013, the same group revealed another version of this reaction [61]. In this paper, they utilized a Pd^{II}-sulfoxide-oxazoline/iron-phthalocyanine (**FePc**) dual catalyst system for the syntheses of sterically hindered heterobiaryls with air as the oxidant instead of using TEMPO as the stoichiometric co-oxidant (Scheme 6). It was proposed that the ligands (e.g., **L4**) took effect in the form of a Pd-sox complex, which exhibited higher reactivity in coupling hindered partners.



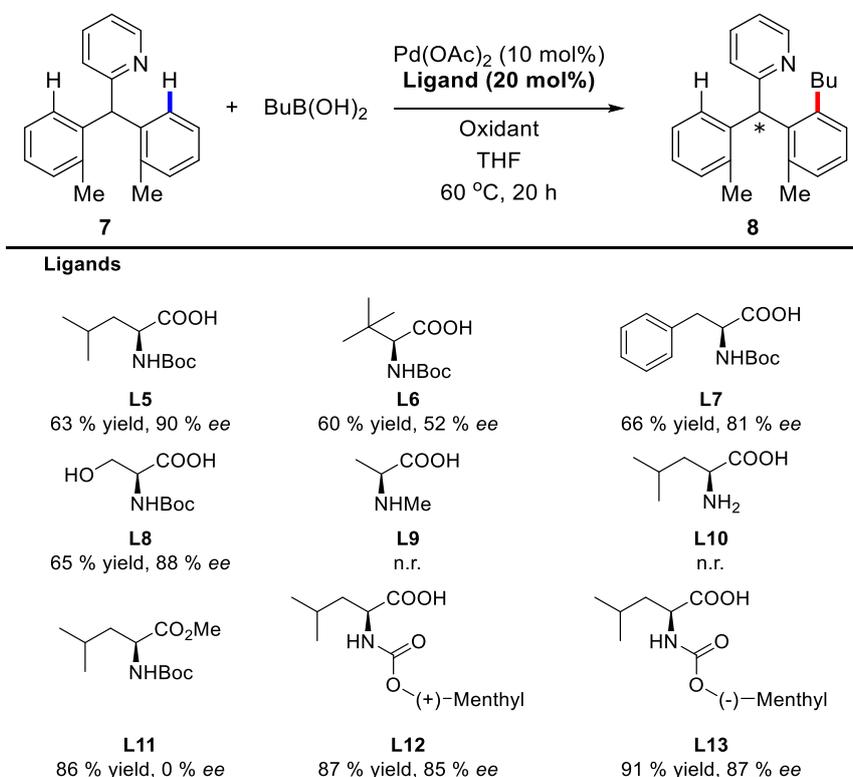
Scheme 6. Enantioselective C–H activation/C–C coupling between heteroarenes and arylboronic acids [61].

In 2008, a huge advance was made by Yu and coworkers [62]. They developed the Pd^{II}/chiral mono-*N*-protected amino acid (**MPAA**) system and applied it in the desymmetrization reaction of prochiral substrates (Scheme 7).



Scheme 7. Desymmetrization of prochiral C(sp²)-H and C(sp³)-H bonds [62].

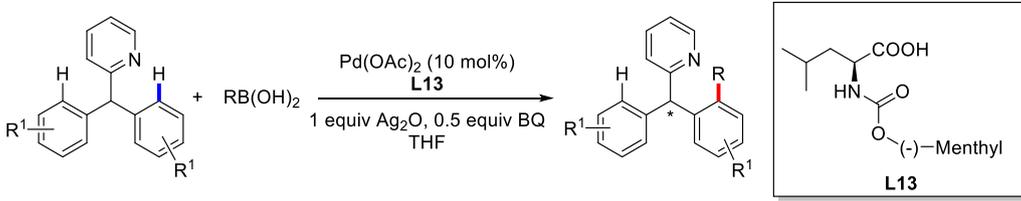
Detailed mechanism studies by Yu and coworkers suggested that using conformationally rigid chiral carboxylic acids as ligands as well as Pd^{II} catalyst might induce the enantioselective C-H activation process. Indeed, when Boc-protected chiral amino acids were used, the asymmetric induction took place. With compound **7** and butylboronic acid as model substrates, Boc-L-leucine afforded the corresponding product with 63% yield and 90% *ee* (Scheme 8). Intriguingly, when the Boc protecting group was removed or substituted by methyl group, the reactions failed to occur, which indicates that an electron-withdrawing group on the nitrogen atom is essential in maintaining the electrophilicity of Pd^{II} towards the C-H bond. Moreover, the esterification of the amino acid or the decrease of the nitrogen protecting group size resulted in significant declines of enantioselectivities. Thus, the bulkier menthoxycarbonyl protecting groups were introduced and ligand **L13** was found to give the best results.



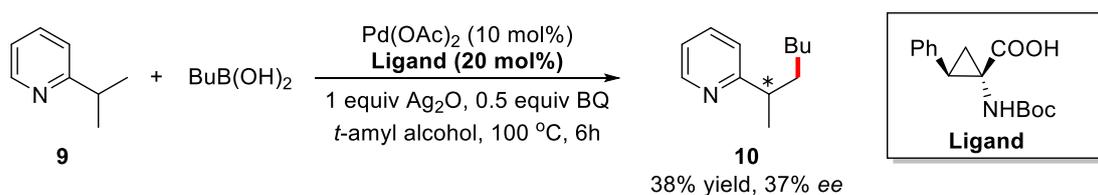
Scheme 8. Influence of ligands on the enantioselectivities [62].

With the optimized condition in hand, different substrates and boronic acids were investigated and the products were obtained in good yields and moderate to excellent *ee* (Table 1). Furthermore, enantioselective alkylation of C(sp³)-H bonds, such as substrate **9**, was also executed and the desired product was obtained with 38% yield and 37% *ee* (Scheme 9).

Table 1. Investigation on substrate scope [62].



R ¹	R	T [°C]	L [mol %]	Yield (%)	<i>ee</i> (%)
<i>o</i> -Me	<i>n</i> -Bu	50	20	50	95
<i>o</i> -Me	<i>n</i> -Bu	60	10	96	88
H	<i>n</i> -Bu	80	20	47	79
<i>o</i> -Me	Et	60	10	81	84
<i>o</i> -Me	Cy	60	10	61	89
<i>m</i> -Me	<i>n</i> -Bu	60	10	58	84
<i>m</i> -OMe	<i>n</i> -Bu	80	10	55	54
<i>m</i> -OAc	<i>n</i> -Bu	80	10	43	72
<i>p</i> -Me	<i>n</i> -Bu	80	10	61	78



Scheme 9. Enantioselective alkylation of C(sp³)-H bond [62].

In the proposed transition state, both the nitrogen atom and the carboxylate group of the amino acid ligand coordinate with the Pd^{II} center in a bidentate way, providing a chiral environment. Transition state **11a** rather than **11b** is preferred, in that the steric repulsion between the substituent on the newly generated chiral center (*o*-Tol) and the Boc group on the nitrogen center is minimized (Figure 2).

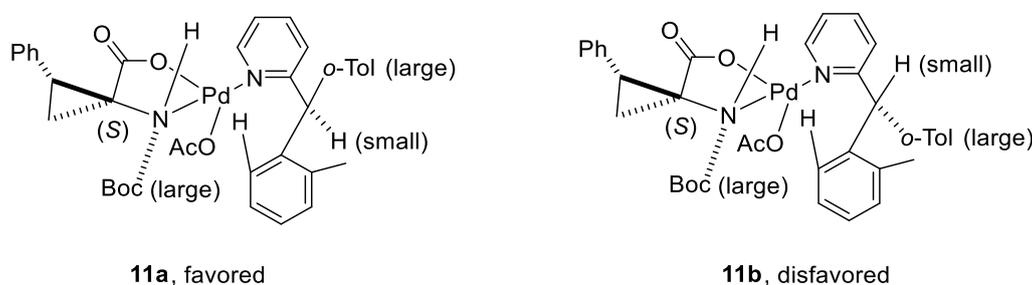
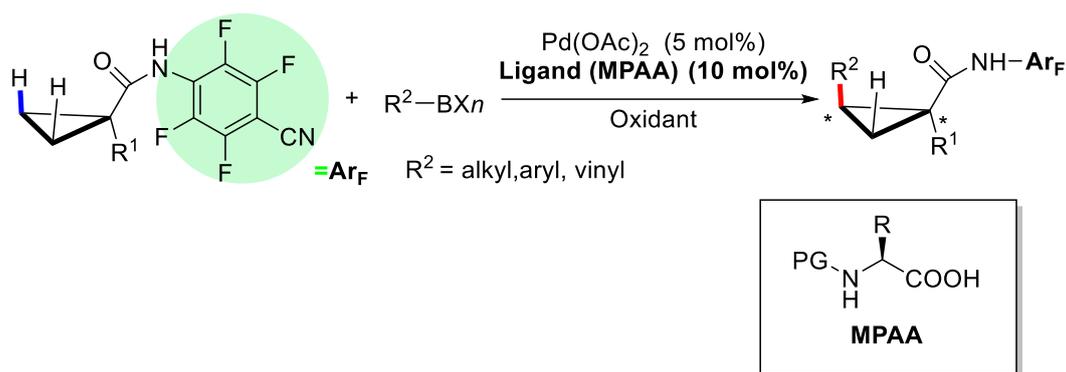


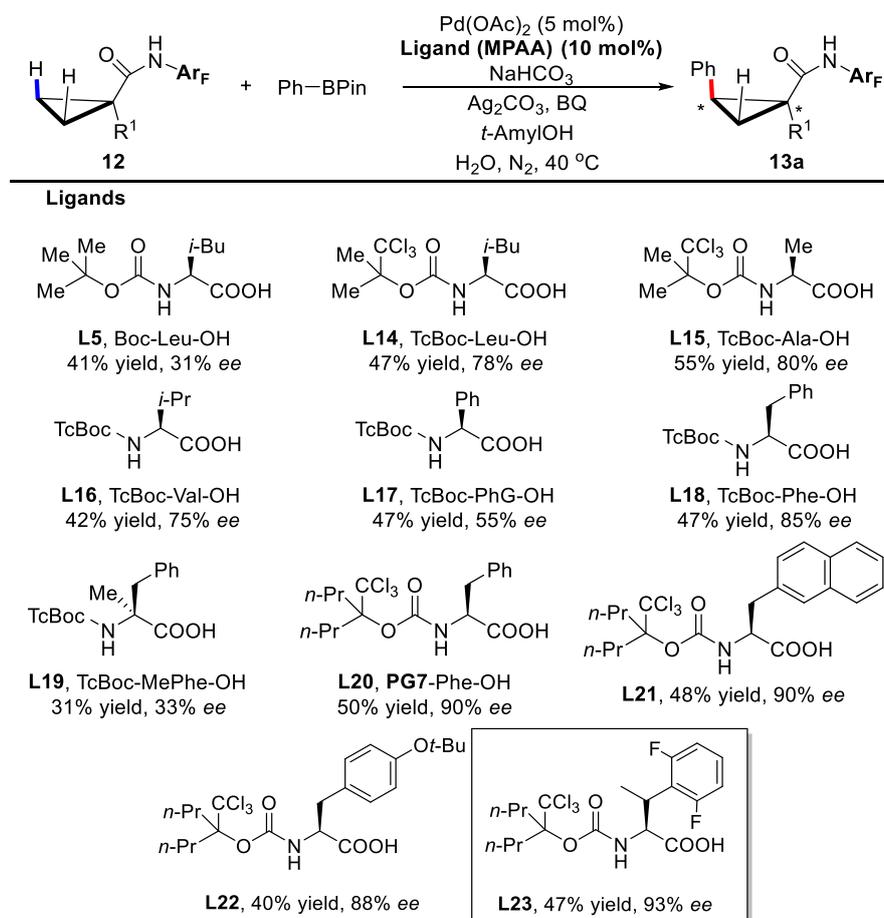
Figure 2. Key intermediates in the proposed mechanistic model. Reproduced from Reference [62].

In 2011, Yu and coworkers reported the enantioselective C(sp³)-H activation of cyclopropanes catalyzed by Pd^{II}/MPAA (Scheme 10) [44].



Scheme 10. Asymmetric C–H activation/C–C coupling reaction of cyclopropane [44].

In this reaction, the amide derivative of 1-methylcyclopropanecarboxylic acid was utilized as the substrate and the electron-deficient arylamide group plays as a directing group. In the process of screening the chiral **MPAA** ligands, it was discovered that both the protecting group of the amine and the backbone of the amino acid were crucial for the enantioselectivities (Scheme 11). When the protecting group Boc was changed into TcBoc, the enantioselectivity increased dramatically to 78% from 31%, indicating that CCl_3 might serve as a bulkier group and an electron-withdrawing group (EWG) simultaneously. Further screening revealed that phenylalanine derivative **L23** was the best ligand, and up to 93% *ee* was achieved.



Scheme 11. Screening of chiral mono-protected amino acid ligands [44].

With the optimized conditions, different cyclopropanes and organoboronic compounds were investigated and the products were obtained in good yields and good to excellent *ee* (Figure 3).

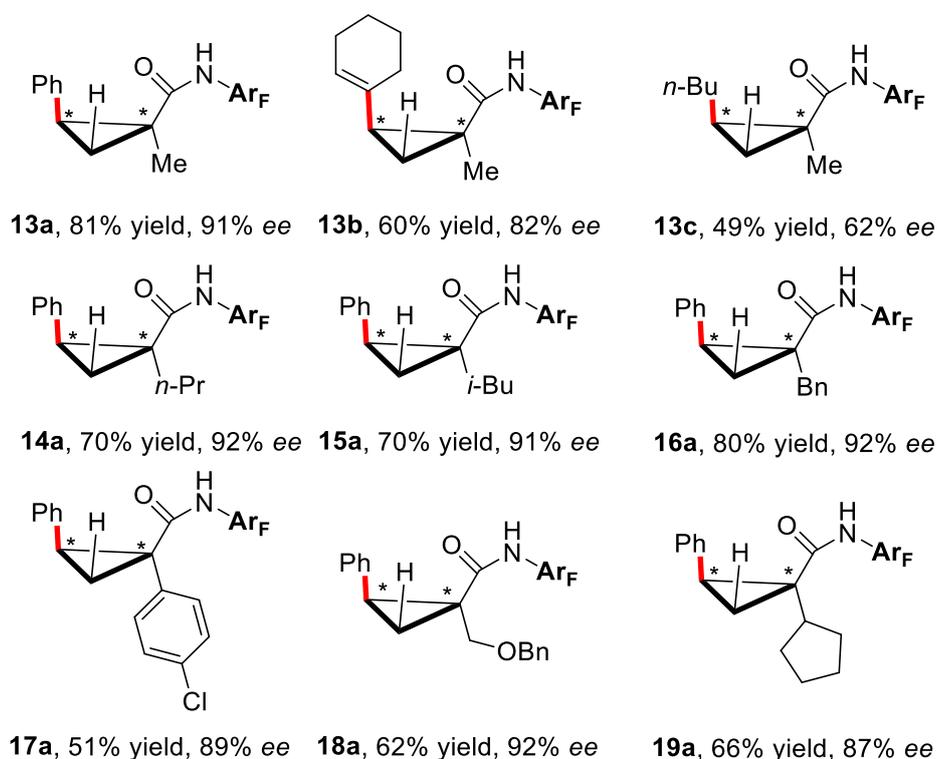
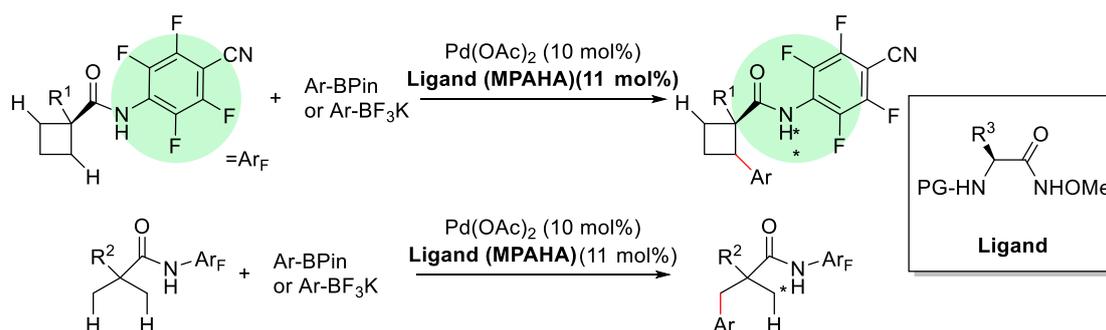


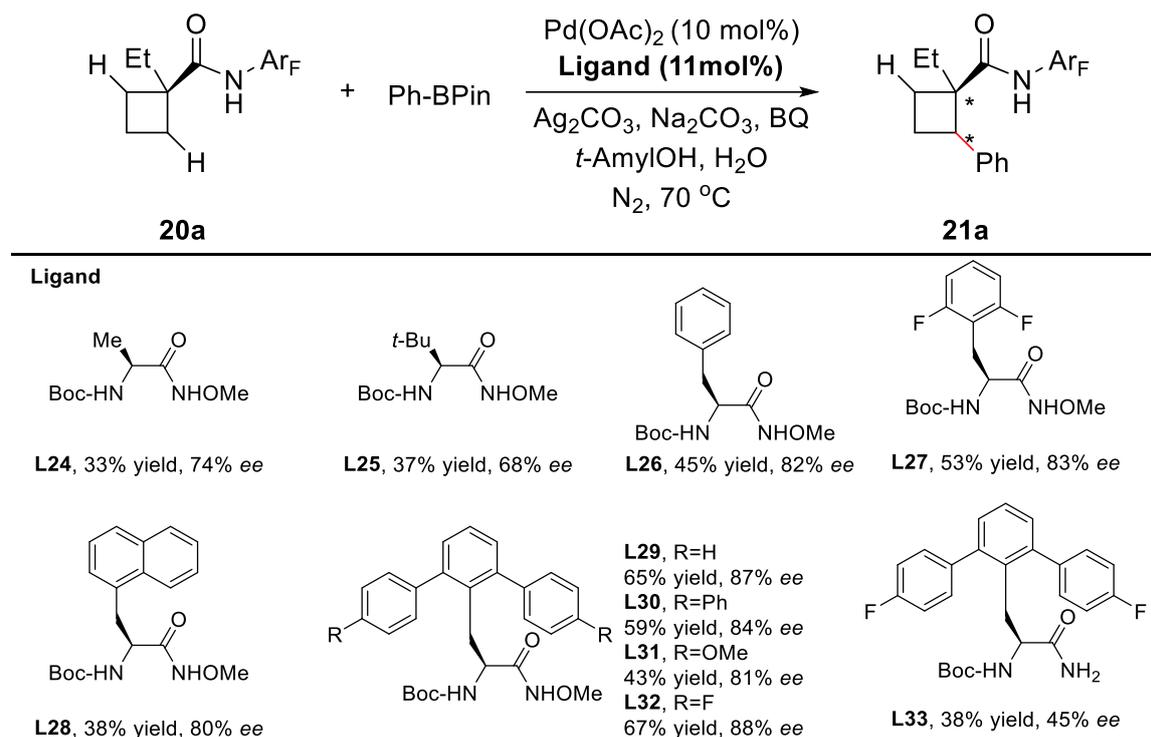
Figure 3. The substrate scope of asymmetric cyclopropane C–H functionalization [44].

In 2014, the same group reported a further research for the arylation of methylene β -C(sp³)–H bonds of cyclobutanecarboxylic acid derivatives with arylboron reagents using palladium(II) catalyst with chiral mono-*N*-protected α -amino-*O*-methylhydroxamic acid (MPAHA) as the ligand (Scheme 12) [63]. This method provided a complementary protocol for the syntheses of enantioenriched cyclobutanes containing chiral quaternary stereocenters [64,65].



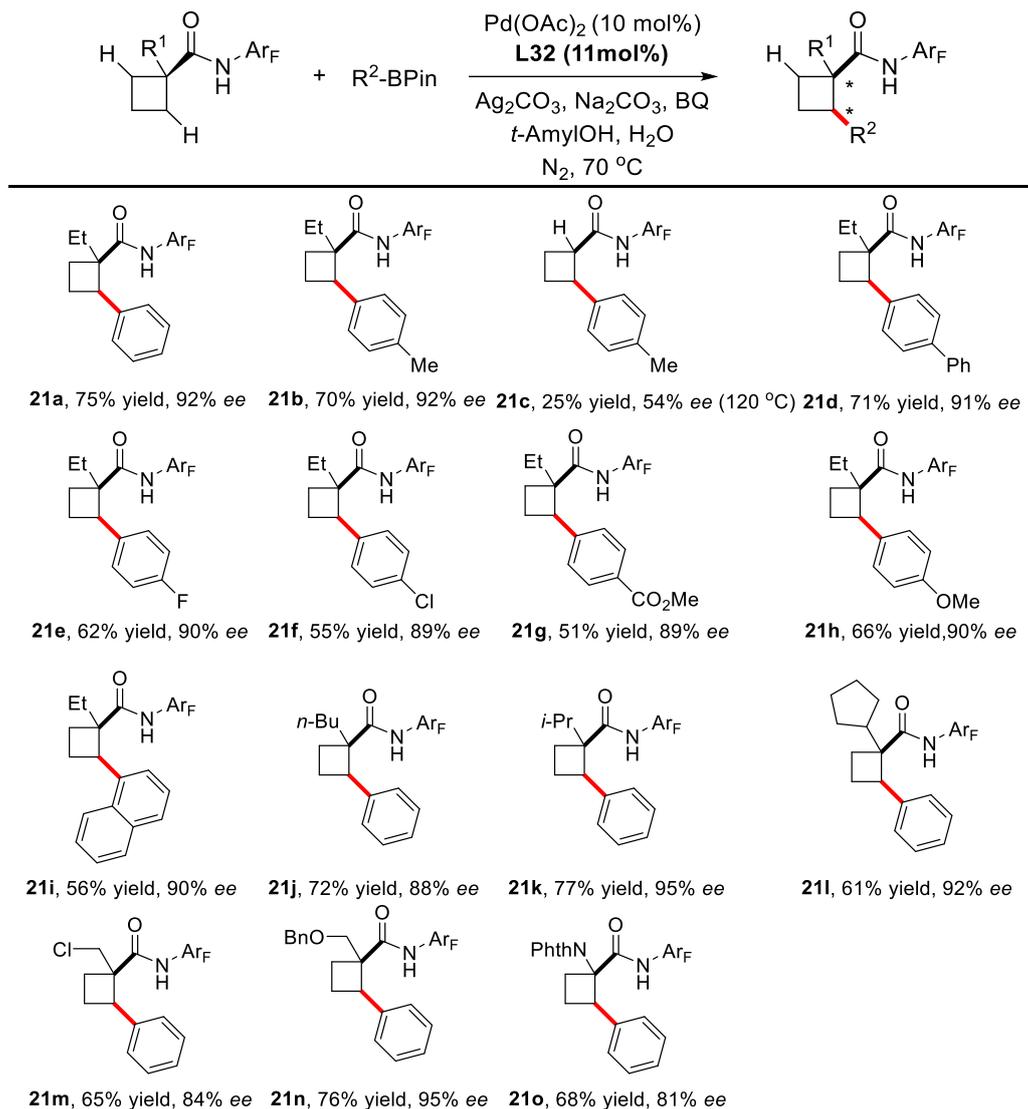
Scheme 12. Enantioselective C(sp³)–H activation of cyclobutanes [63].

Similar to the precedent studies, **MPAHA** can generate a chiral complex with Pd^{II} catalyst and is the key to obtain appreciable yield and enantioselectivity. When *O*-methylhydroxamic acids were used as ligands instead of the previously used mono-protected amino acids, a significant boost of enantioselectivity was observed, which might derive from the stronger coordination between the ligand and the Pd^{II} center. Further evaluation revealed that the Boc protecting group and an aromatic side chain within the ligand were prone to elevate the enantioselectivities. Of the various ligands that were tested, **L32** gave the best results (Scheme 13). Further optimization of the solvents, bases and catalysts eventually led to the desired product with 75% yield and 92% *ee*.



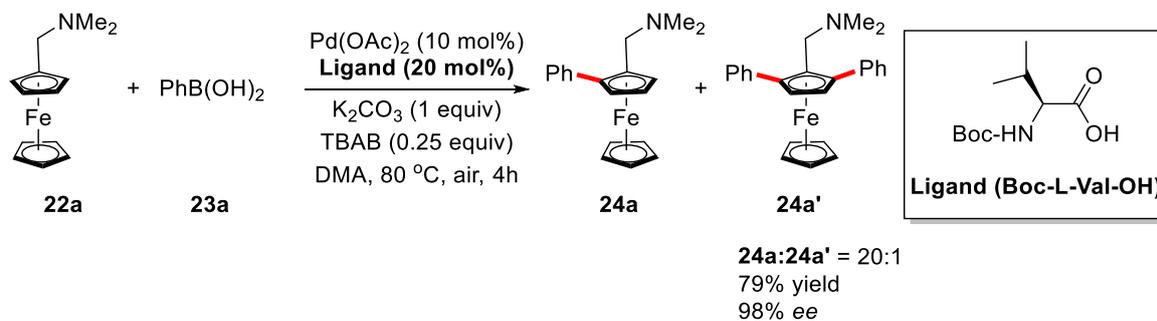
Scheme 13. Designs of chiral ligands [63].

Under the optimized condition, the reaction was found to work well between a variety of arylboronic acid pinacol esters and various 1-substituted 1-cyclobutanecarboxylic acid derivatives (Scheme 14).



Scheme 14. Substrates scope for C(sp³)-H activation of cyclobutanes [63].

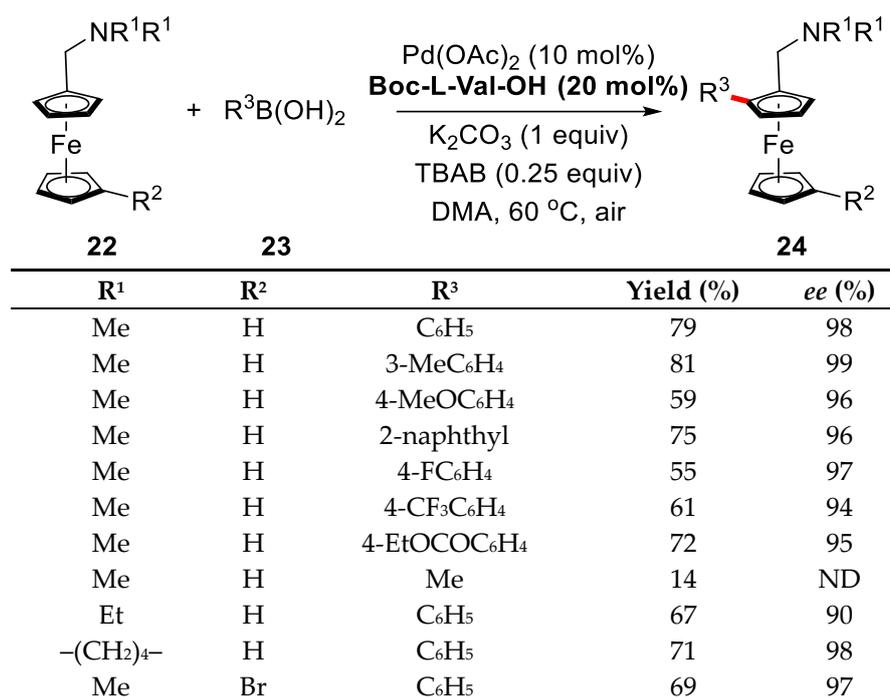
It is well known that planar chiral ferrocenes are frequently applied as highly efficient catalysts or ligands in asymmetric synthesis [66–71]. Inspired by previous studies from Yu group [44,62], You et al., developed an enantioselective syntheses of planar chiral ferrocenes via palladium-catalyzed direct coupling with arylboronic acids in 2013 (Scheme 15) [72].



Scheme 15. Synthesis of planar-Chiral Ferrocenes via enantioselective C–H activation [72].

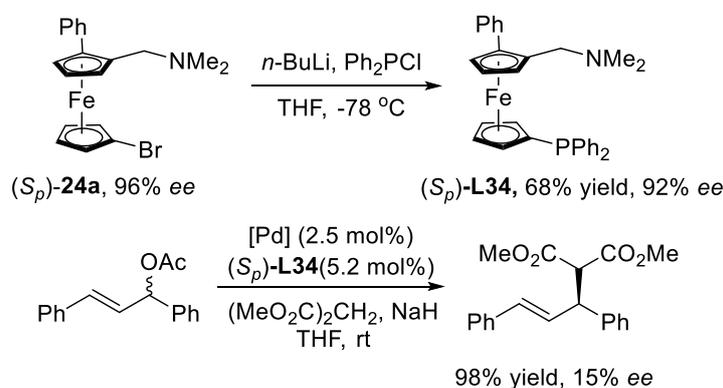
In this work, dimethylaminomethylferrocene **22a** and phenylboronic acid **23a** were chosen as model substrates. The reaction proceeded smoothly in the presence of 10 mol % Pd(OAc)₂, 20 mol % Boc-L-Val-OH, and 1 equiv of K₂CO₃ in DMA (Dimethylacetamide) at 80 °C under air, providing the desired product with 58% yield and 97% *ee*. The yield was further improved to 79% with 25 mol % TBAB as the additive when the reaction was performed at 60 °C.

With the optimized condition, various aminomethylferrocene derivatives and boronic acids were examined. Substituted arylboronic acids bearing either an electron-donating group or an electron-withdrawing group were well-tolerated and afforded the corresponding products in good yields and excellent enantioselectivities. Moreover, the reaction was also general for aminomethylferrocenes with different alkyl groups on the nitrogen atom (Scheme 16). In addition, a large scale reaction was executed smoothly, which further confirmed the practicality of this method.



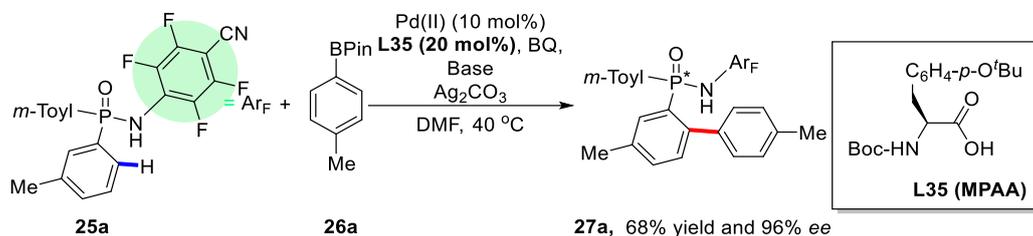
Scheme 16. Investigation of substrate scope [72].

At last, the planar-chiral *P,N*-ligand **L34** prepared from compound **24** was successfully utilized in the palladium-catalyzed allylic alkylation reaction (Scheme 17), which fully demonstrated the potential application of this novel protocol.



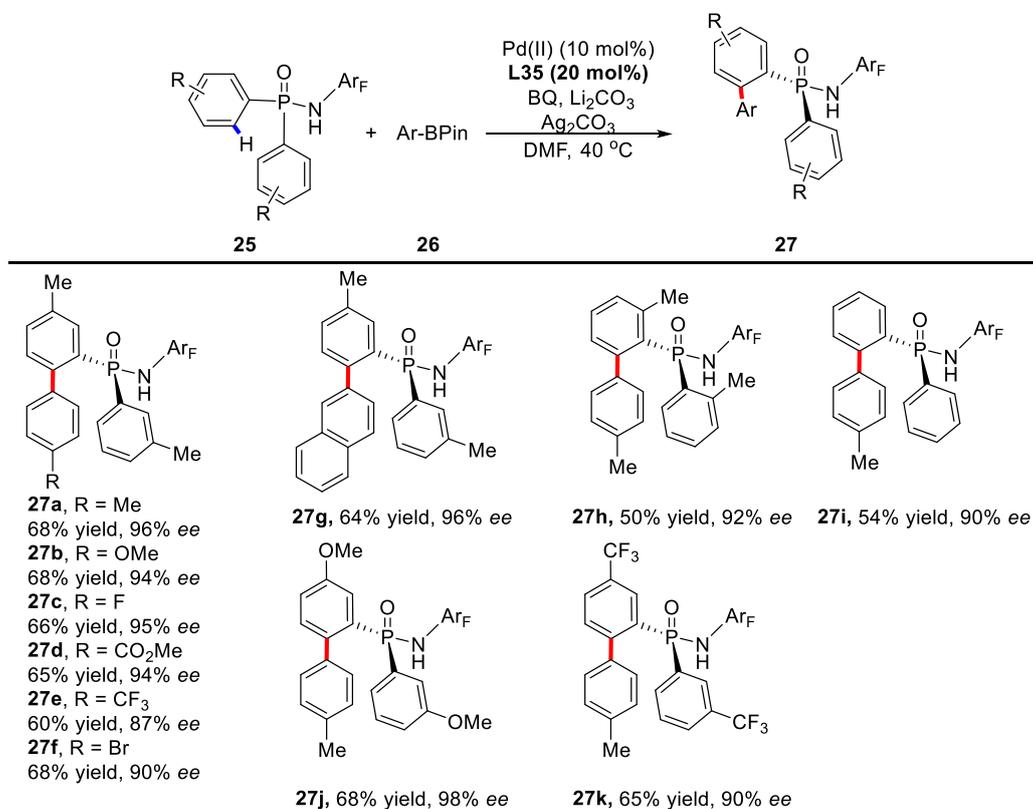
Scheme 17. Application of the synthesized planar-chiral ferrocenes. Reproduced from Reference [72].

It is well known that chiral phosphorus compounds play important roles as ligands or organocatalysts in asymmetric synthesis [73–76]. In 2015, Han group reported the asymmetric syntheses of traditionally inaccessible *P*-stereogenic phosphinamides via Pd-catalyzed enantioselective C(sp²)-H functionalization (Scheme 18) [77].



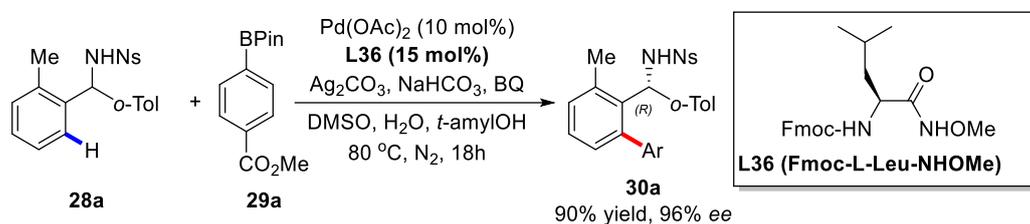
Scheme 18. Enantioselective synthesis of *P*-stereogenic phosphinamides via asymmetric C–H arylation [77].

Similarly, chiral mono-*N*-protected amino acids (MPAA) were used as ligands in this reaction. The presence of the carbamate moiety employed as the *N*-protecting group and the carboxylic acid group within the ligand were essential to deliver the desired products with good enantioselectivities. Of the various chiral ligands tested, ligand **L35** was found to be the optimal ligand, affording 68% yield and 96% *ee* (Scheme 18). The best reaction condition was found to be 10 mol % Pd(OAc)₂, 20 mol % **L35**, 0.5 equiv of BQ, 1.5 equiv of Ag₂CO₃, 3.0 equiv of Li₂CO₃, and 40.0 equiv of H₂O in anhydrous DMF at 40 °C under air. In addition, an array of substrates, including arylboronic esters decorated with different groups and different diarylphosphinamides, were subjected to this protocol and most of the reactions occurred efficiently (Scheme 19). Practically, this novel approach could be carried out in the gram scale with consistent efficiency.



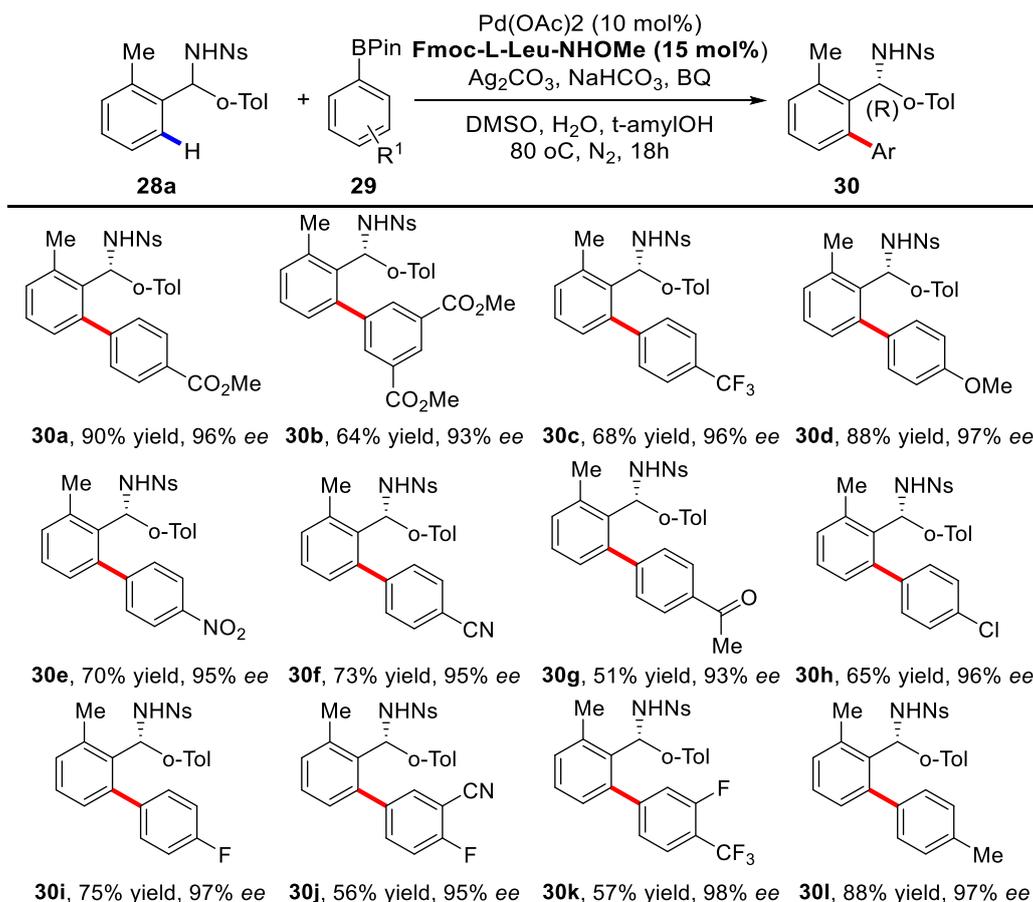
Scheme 19. Evaluation of substrate scope [77].

Recently, the enantioselective *ortho*-C(sp²)-H coupling between *para*-nitrobenzenesulfonyl (nosyl) protected diarylmethylamines and arylboronic acid pinacol esters was established by Yu and coworkers (Scheme 20) [78].

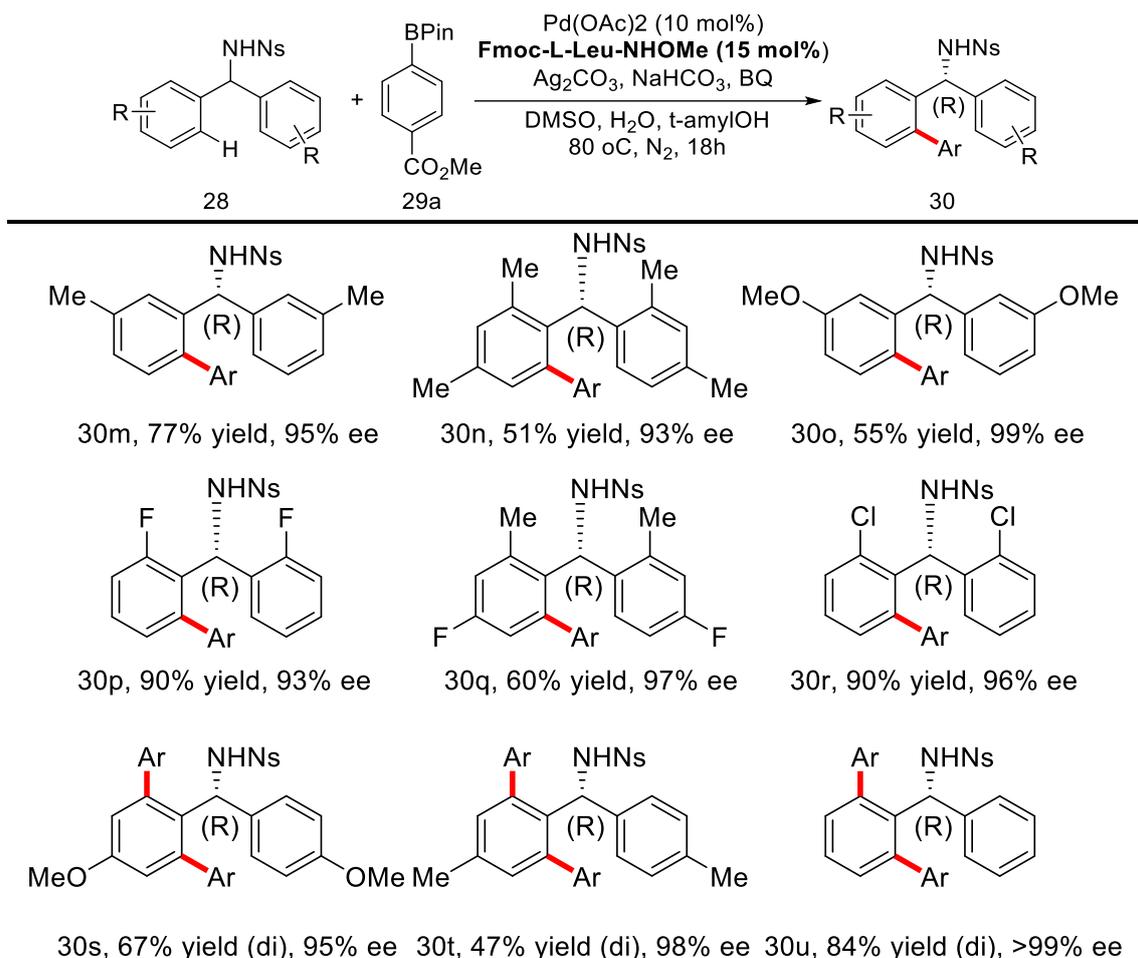


Scheme 20. Enantioselective *ortho*-C-H activation of diarylmethylamines [78].

Herein, chiral mono-*N*-protected amino acids (MPAA) were adopted as chiral ligands at first. Further screening revealed that carbamate-protected, *N*-methoxyamide-substituted aliphatic amino acids were the best choice. When Fmoc-L-Leu-NHOMe was used, the desired product could be obtained in 90% yield and 96% ee. This method was further applied to a variety of different diarylmethylamines with arylboronic acid pinacol esters as coupling partners. Under the optimized condition, most of the reactions proceeded smoothly with good yields and excellent enantioselectivities (Schemes 21 and 22).



Scheme 21. Reactions with different arylboronic acid pinacol esters [78].



Scheme 22. Reactions with different diarylmethylamines [78].

A stereochemical model was proposed (Figure 4). It was assumed that the coordination between the imine moiety of the deprotonated anionic sulfonamide and Pd^{II} center promoted the stereoselective C–H activation followed by arylation.

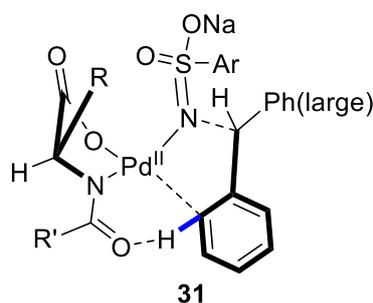
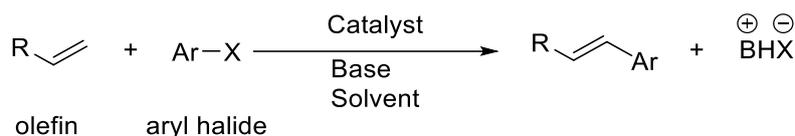


Figure 4. Proposed transition state. Reproduced from Reference [78].

3. Enantioselective C–H Activation/Mizoroki-Heck Type Reaction

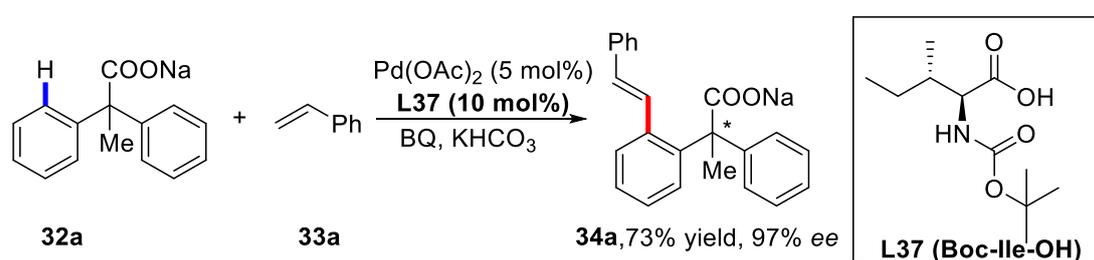
Another important type of cross coupling reaction is the Mizoroki-Heck reaction (Scheme 23), which exhibits extraordinary performance with high efficiency in assembling C–C bonds [79,80]. Herein, we will highlight the recent progresses in the field of enantioselective C–H activation concerning Mizoroki-Heck type reaction.



Scheme 23. Mizoroki-Heck reaction.

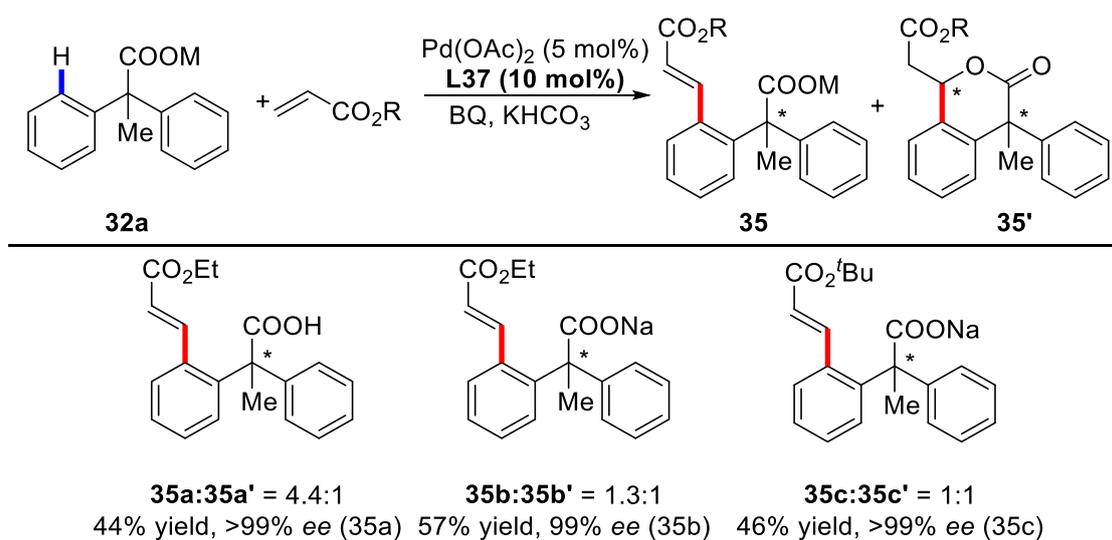
Inspired by the excellent performances of monoprotected amino acids (MPAA) as ligands for enantioselective C–H activation [62], Yu and coworkers developed an enantioselective C–H olefination reaction of diphenylacetic acids using MPAA as chiral ligands [81].

Among the various chiral monoprotected α -amino acids examined, Boc-Ile-OH proved to be the best one. The yield could be improved to 73% (97% *ee*) with the preformed sodium salt of the starting material and KHCO_3 as the base (Scheme 24).



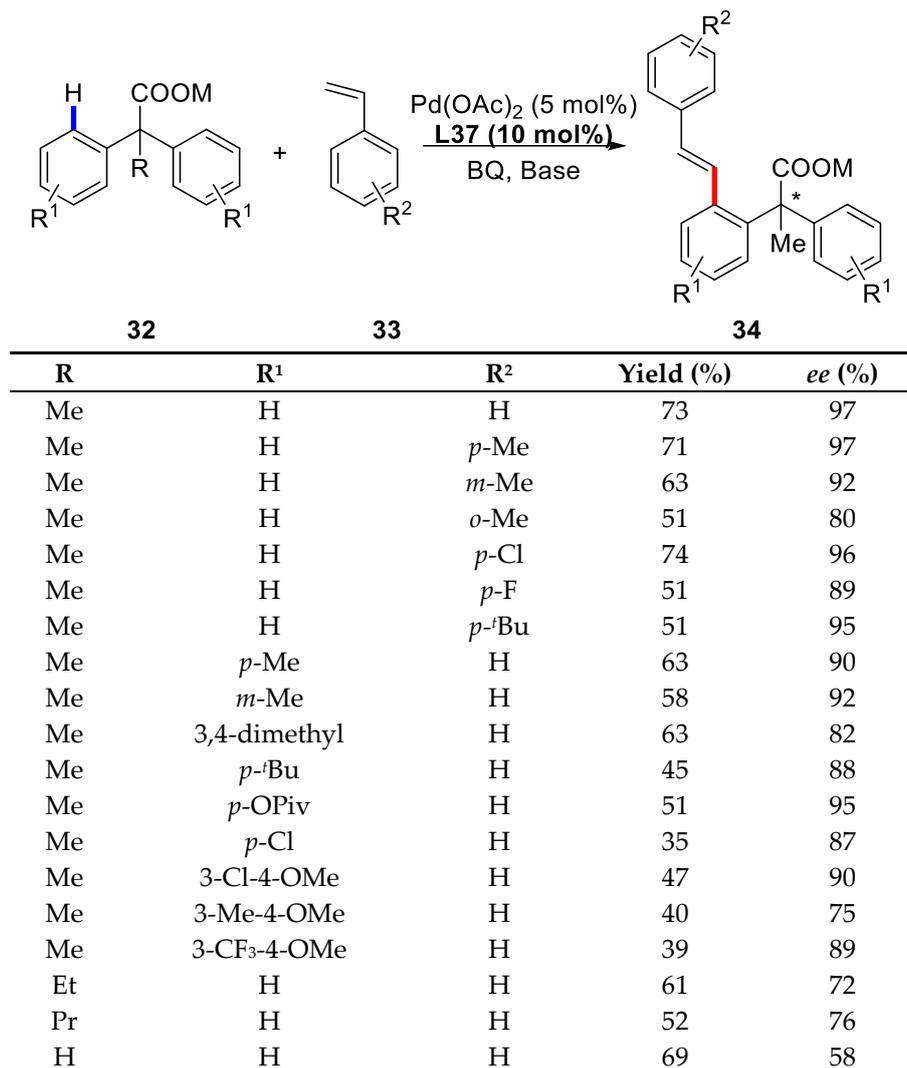
Scheme 24. Enantioselective C–H olefination of diphenylacetic acids [81].

A broad range of styrenes with different substituents were inspected and it was found that styrenes with *para* and *meta* alkyl substituents gave higher enantioselectivities (92–97% *ee*). In addition, acrylate coupling partners were also tolerant to such condition, affording 99% *ee*. However, a mixture of the desired olefination product and the corresponding conjugated addition product was isolated (Scheme 25).



Scheme 25. Acrylates employed as the coupling partners [81].

Different carboxylic acids were also treated with this strategy and most of them proceeded efficiently except for α -hydrogen containing substrate (58% *ee*). Besides, substrates containing electron-donating groups and moderately electron-withdrawing groups were well compatible to this procedure, although olefination of the latter gave lower yields (Scheme 26).



Scheme 26. Enantioselective C–H olefination with substituted styrenes as coupling partners [81].

Yu also proposed a possible transition state for this enantioselective C–H olefination (Figure 5). A chiral carbon–Pd intermediate could be formed, followed by olefination to give the corresponding chiral product.

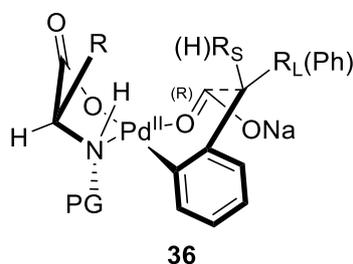
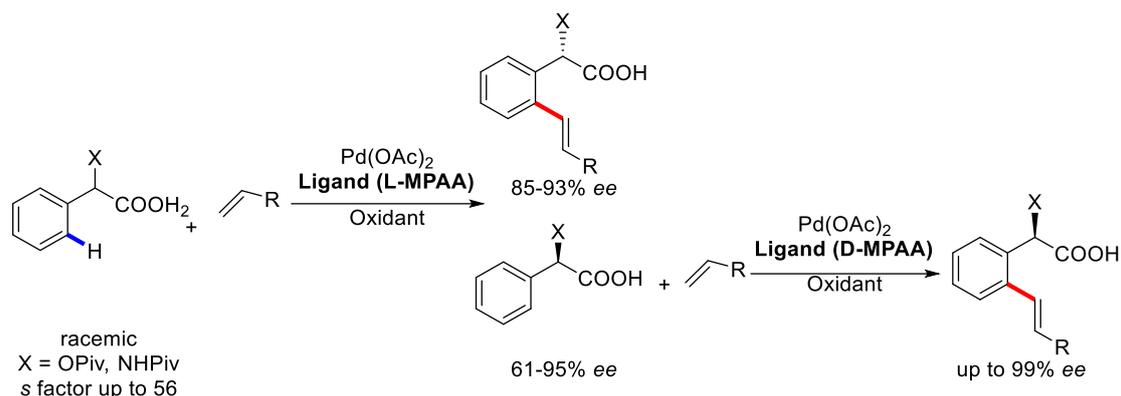


Figure 5. The proposed transition state. Reproduced from Reference [81].

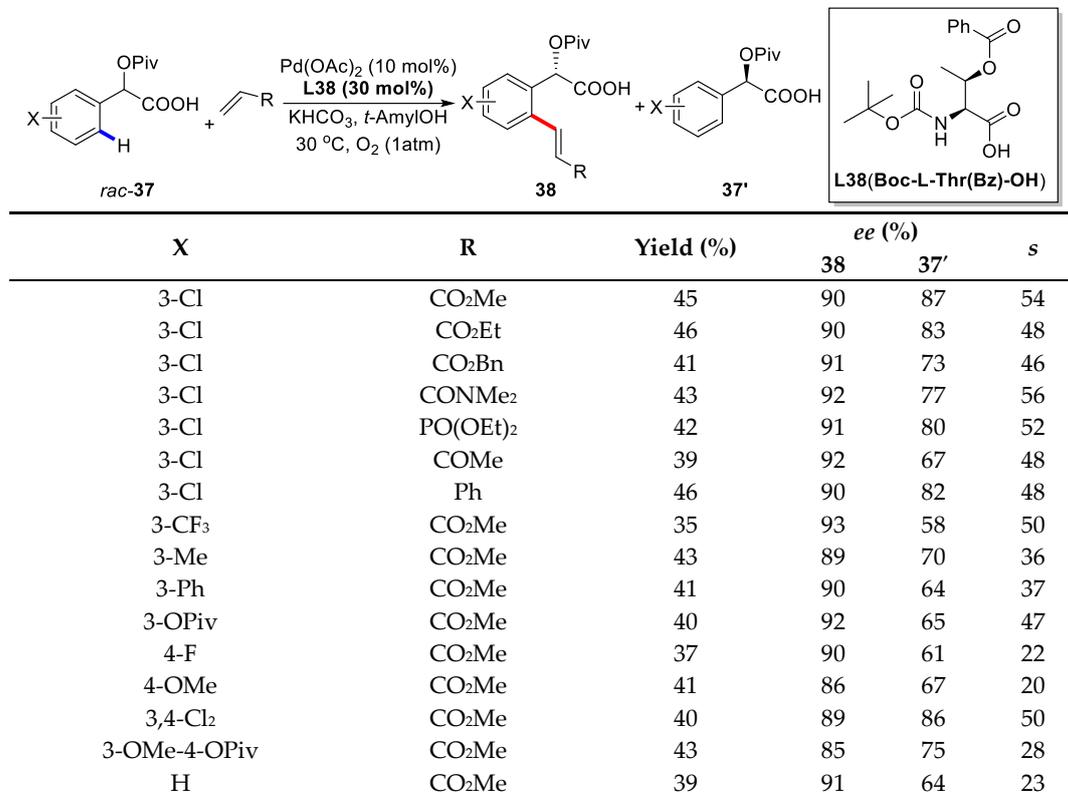
Based on the recent development of enantioselective C–H iodination using Pd^{II}/MPAA catalysts for kinetic resolution through C–H hydroxylation and iodination [82,83], Yu and coworkers developed a kinetic resolution method to achieve enantioselective C–H olefinations of α -hydroxy and α -amino phenylacetic acids utilizing Pd^{II}-catalyzed system in 2016 (Scheme 27) [84].



Scheme 27. Enantioselective C–H olefination by kinetic resolution. Reproduced from Reference [84].

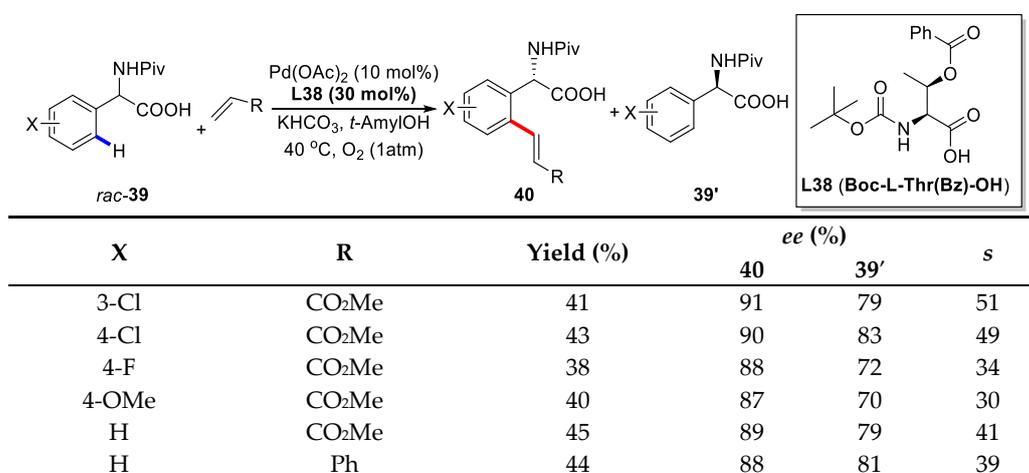
In this paper, Yu also employed mono-*N*-protected amino acid (MPAA) as ligands to enable enantioselective C–H bond olefinations. Of different MPAA ligands screened, Boc-*L*-Thr(Bz)-OH (**L38**) gave the best selectivity factor (*s*) [85] of 54 (90% *ee* and 45% yield). Notably, the loading of Pd(OAc)₂ could be reduced to 5 mol % without a pronounced erosion of the selectivity, and the addition of 0.4 equivalent of olefin increased the enantioselectivity to 93%.

With the optimized reaction condition, a series of olefin coupling partners were subjected to this transformation and a broad range of electron-deficient olefins were well tolerated. Of note, acrylates were a good coupling partner affording *s* factors ranging from 46 to 54. Vinyl amides and vinyl phosphates also proceeded smoothly. A wide range of different substituted mandelic acid substrates were also successfully olefinated with reasonable *s* factors (Scheme 28).



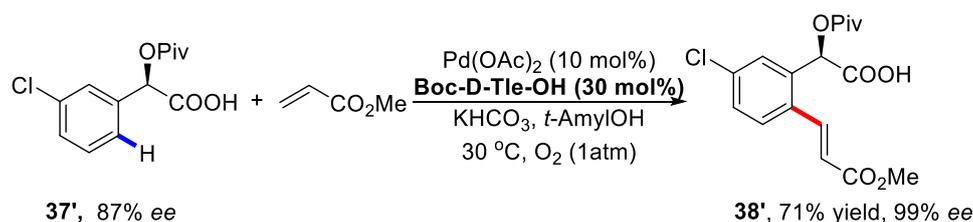
Scheme 28. Enantioselective C–H olefination/kinetic resolution of mandelic acids [84].

Moreover, the scope of different substituted racemic phenylglycine substrates was investigated and most of them furnished the products with synthetically useful *s* factors (Scheme 29).



Scheme 29. Enantioselective C–H olefination/kinetic resolution of phenylglycines [84].

Furthermore, for the remaining starting materials **37'** with 87% *ee*, a following olefination protocol using the opposite configuration ligand could afford the corresponding chiral product with 99% *ee* (Scheme 30).



Scheme 30. Enantioselective C–H olefination of the remaining starting material [84].

In analogy to previously mentioned mechanism, there are two proposed intermediates (Figure 6), **TS_S** and **TS_R**, respectively, and **TS_S** is the favored configuration due to the less steric repulsion between the Boc group and larger OPiv moiety. This stereomodel can well rationalize the origin of the enantioselectivity.

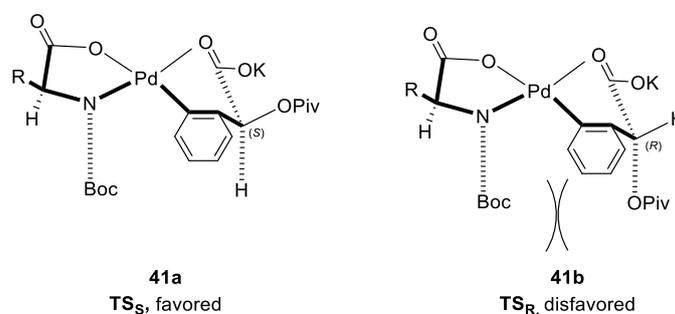
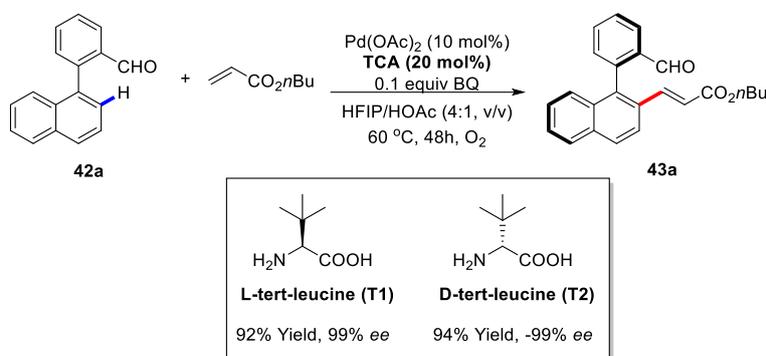


Figure 6. The proposed intermediate state. Reproduced from Reference [84].

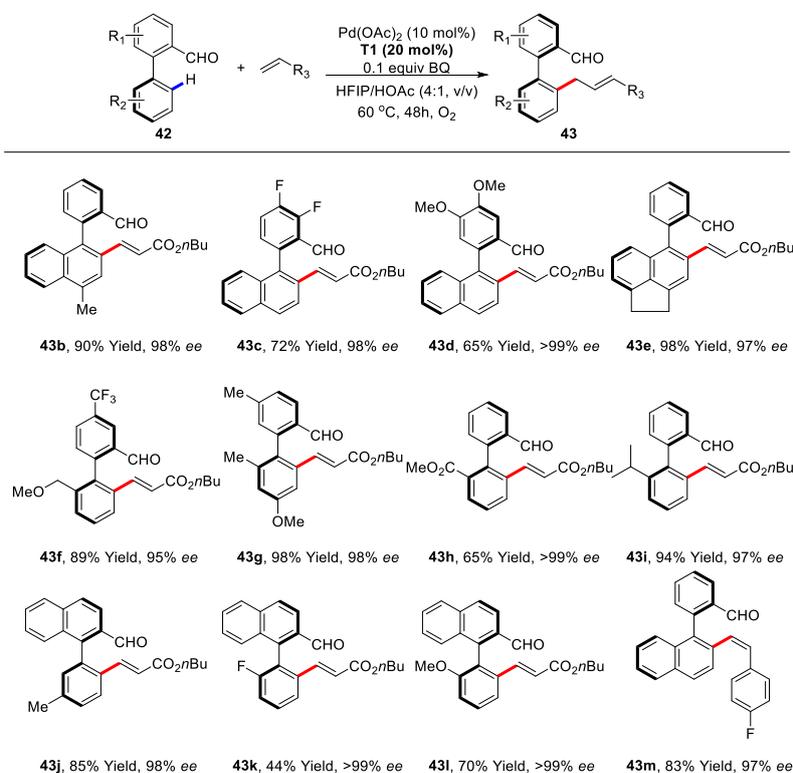
Another interesting finding on enantioselective C–H activation/Heck reaction was provided by Shi and coworkers in 2017 [86]. In this article, atroposelective synthesis of axially chiral biaryls by C–H

olefination, utilizing the Pd^{II}/transient chiral auxiliary (TCA) as the catalytic system, was achieved. Of note, in this asymmetric C–H olefination reaction, the chiral free amino acid played as a transient chiral auxiliary (TCA), which promoted the C–H activation process instead of only serving as a simple chiral ligand. Of the various TCA examined, the *L*-*tert*-leucine (T1) was found to be the optimal. As expected, the other atropisomer was obtained, while the opposite TCA (*D*-*tert*-leucine) was employed (Scheme 31).



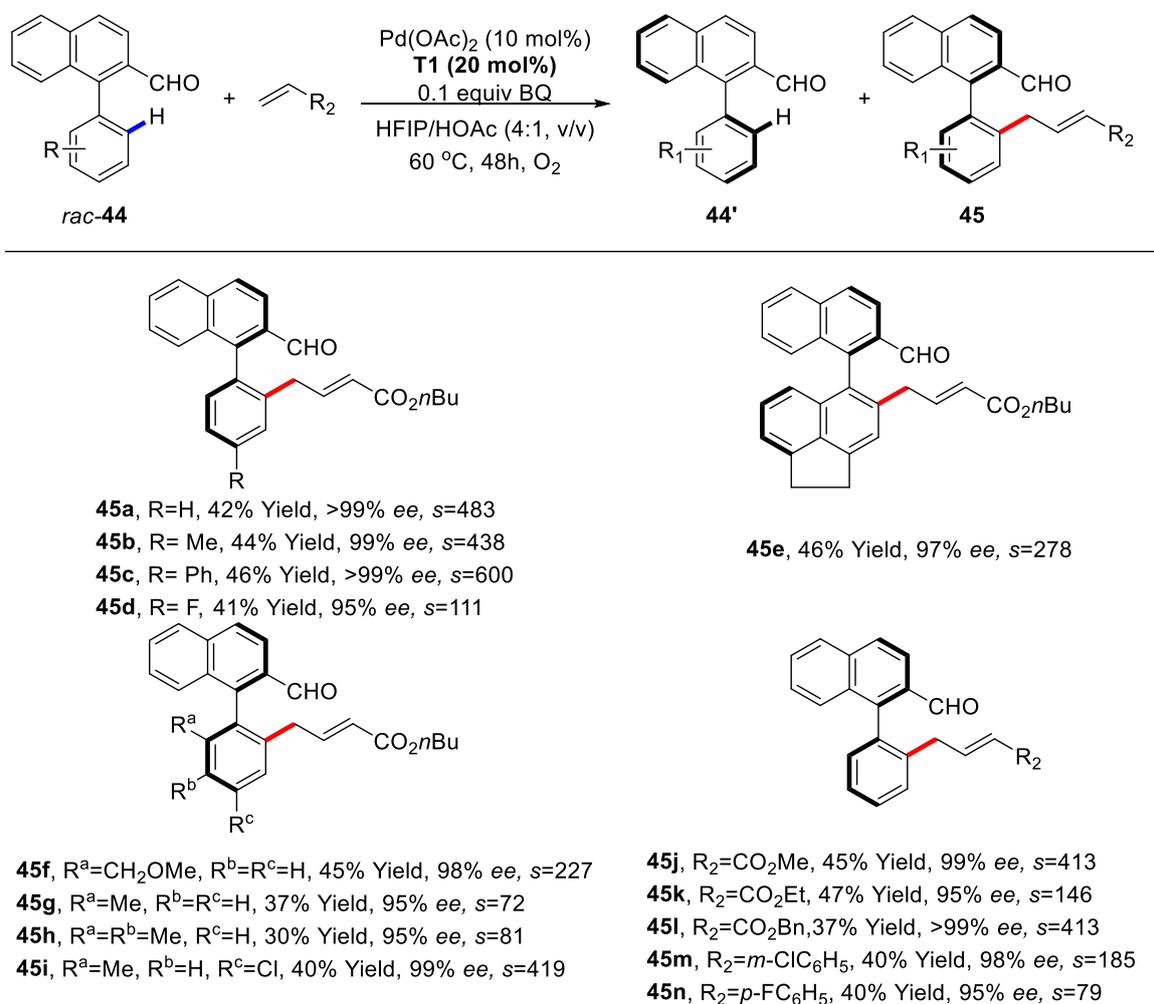
Scheme 31. Optimization of the reaction [86].

With the optimized reaction condition, the substrate generality was inspected. A broad range of biaryls with different substituents were tolerated to this protocol. It ought to be noted that C–H olefination of biaryls with substituents at either 6- or 2'-position or less hindered substituents at both 6- and 2'-position proceeded successfully in a dynamic kinetic resolution (DKR) manner, giving enantioenriched products in good to excellent yields and excellent enantioselectivities (95 to >99% *ee*) (Scheme 32).



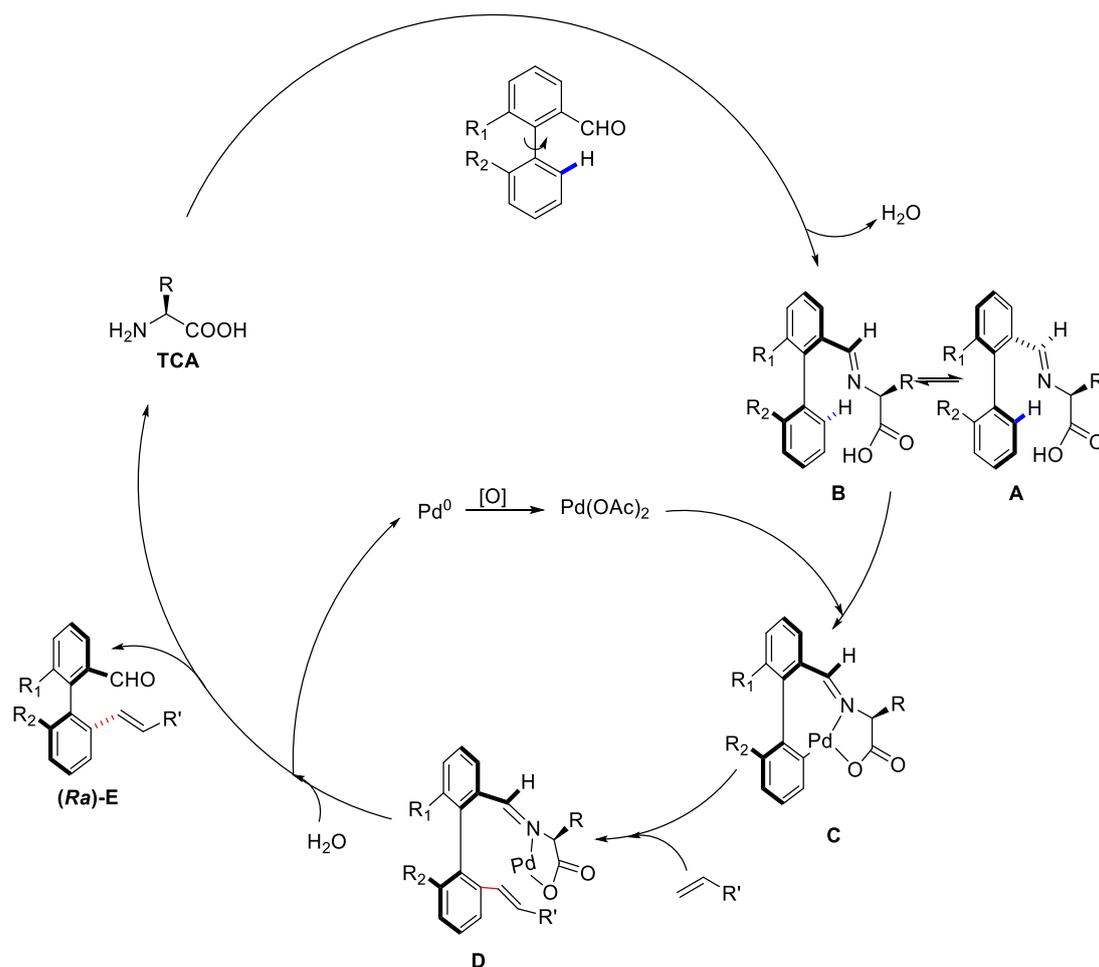
Scheme 32. Substrate scope of biaryls concerning C–H olefination/DKR [86].

Nonetheless, for the biaryls bearing sterically more hindered substituents at both 6- and 2'-position, C–H olefination would occur through a kinetic resolution (KR) manner in excellent selectivities (Scheme 33). Moreover, various acrylates and styrenes were investigated and most of them were compatible to this method, except that electronrich styrenes were determined as inert coupling partners (Schemes 32 and 33).



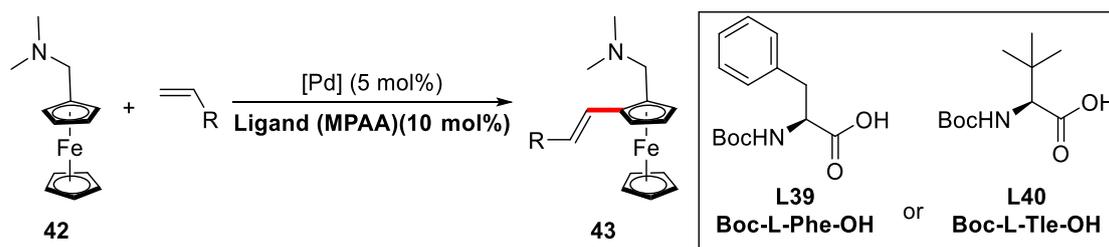
Scheme 33. Substrate scope of biaryls concerning C–H olefination/KR [86].

As far as the mechanism was concerned, it was proposed that the chiral amino acid would react with the racemic substrate to give the imine intermediates **A** and **B** reversibly. Then, C–H cleavage of **B** took place selectively due to the minor steric repulsion, resulting in intermediate **C** with axially stereo-enriched biaryl palladacycle. Then, intermediate **C** underwent a typical Heck reaction with olefin to afford intermediate **D**, which would be hydrolyzed to furnish the desired chiral biaryls (**Ra**)-**E**. Meanwhile, the Pd⁰ was reoxidised into Pd^{II} to close the catalytic cycle (Scheme 34).



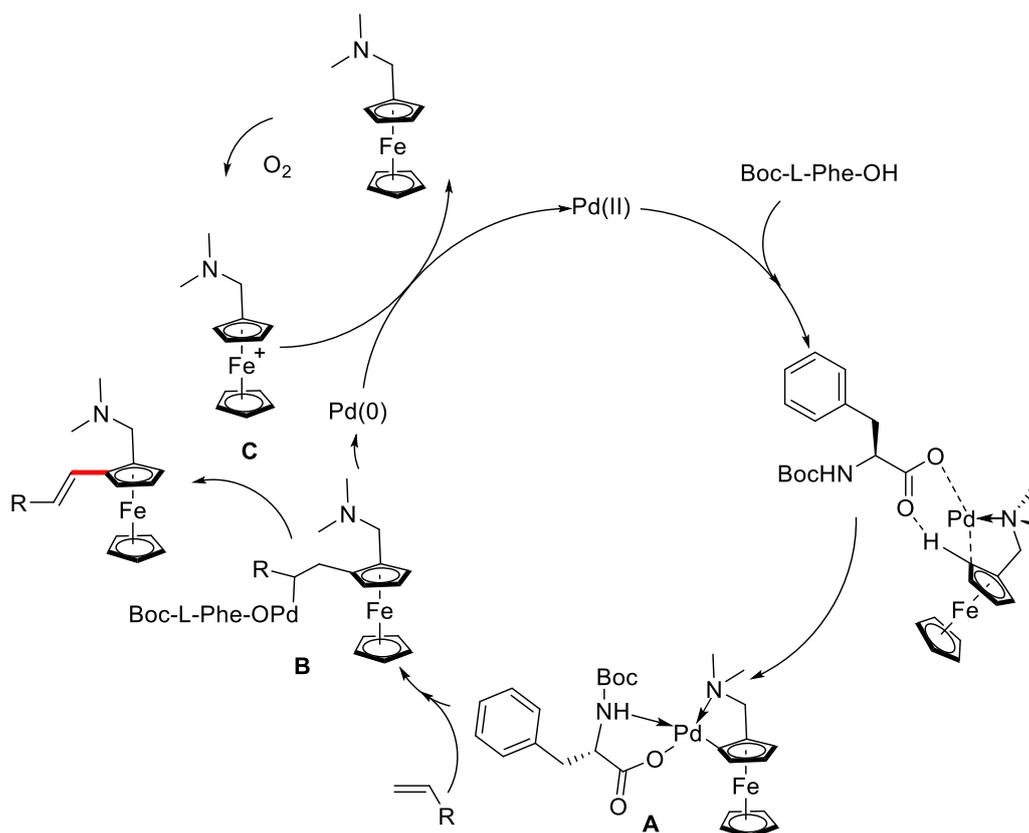
Scheme 34. Hypothesis on the mechanism for the C–H olefination/DKR [86].

The Pd^{II} /MPAA catalysts were also applied in the enantioselective olefinations of *N,N*-dimethylaminomethylferrocene by Wu group (Scheme 35) [87].



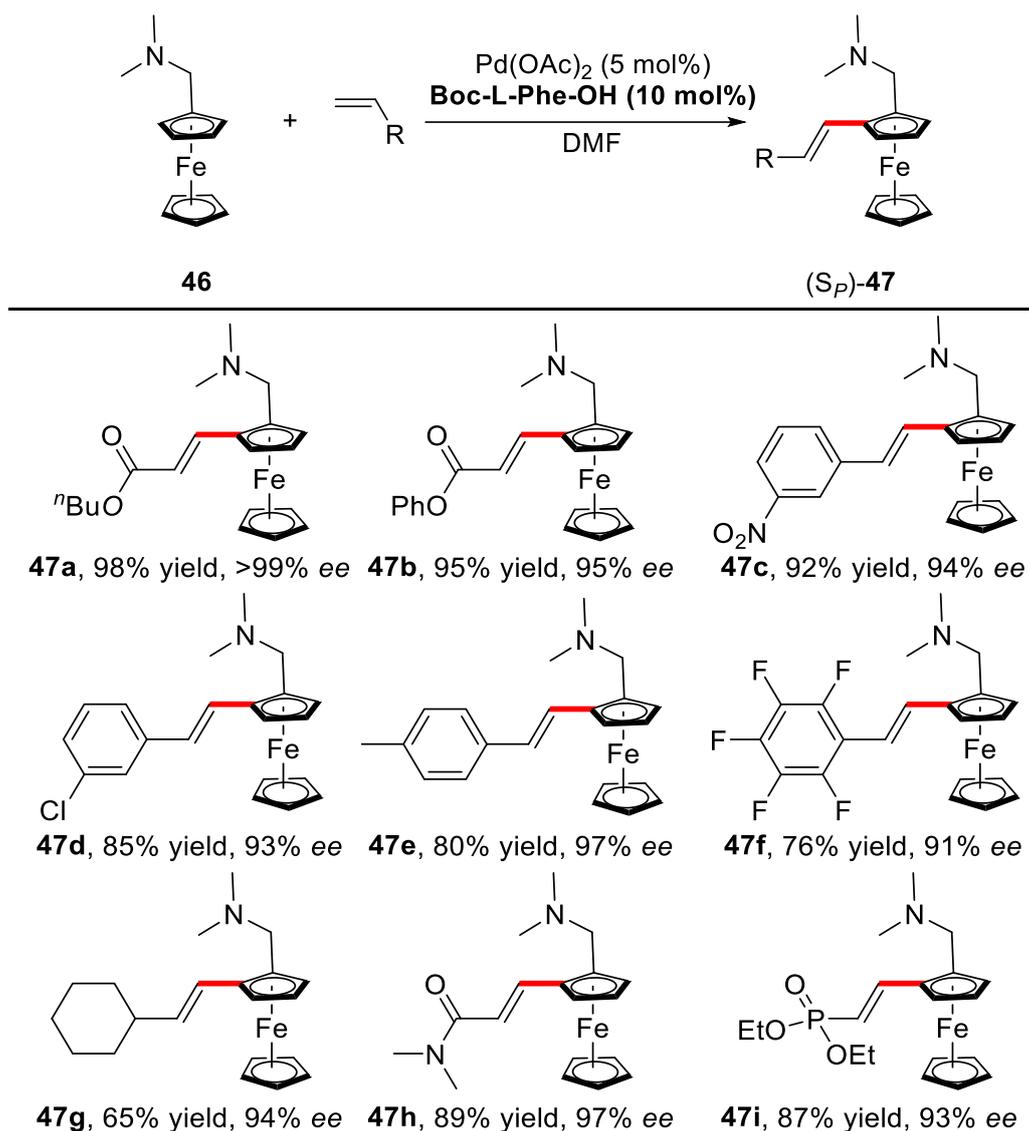
Scheme 35. Pd-catalyzed direct C–H olefination of *N,N*-dimethylaminomethylferrocene [87].

In the proposed mechanism, the cyclopalladated complex **A** was first generated by palladium species through coordination with the substrate and the ligand. Then, intermediate **A** underwent a typical Heck reaction to furnish the desired product. It is worth noting that in this catalytic system, the *N,N*-dimethylaminomethylferrocenium **C** was generated in situ by air and served as a terminal oxidant to regenerate active Pd^{II} from the reduced Pd⁰ species, completing the catalytic cycle. Therefore, no external oxidant was needed (Scheme 36).



Scheme 36. The proposed mechanism for the reaction. Reproduced from Reference [87].

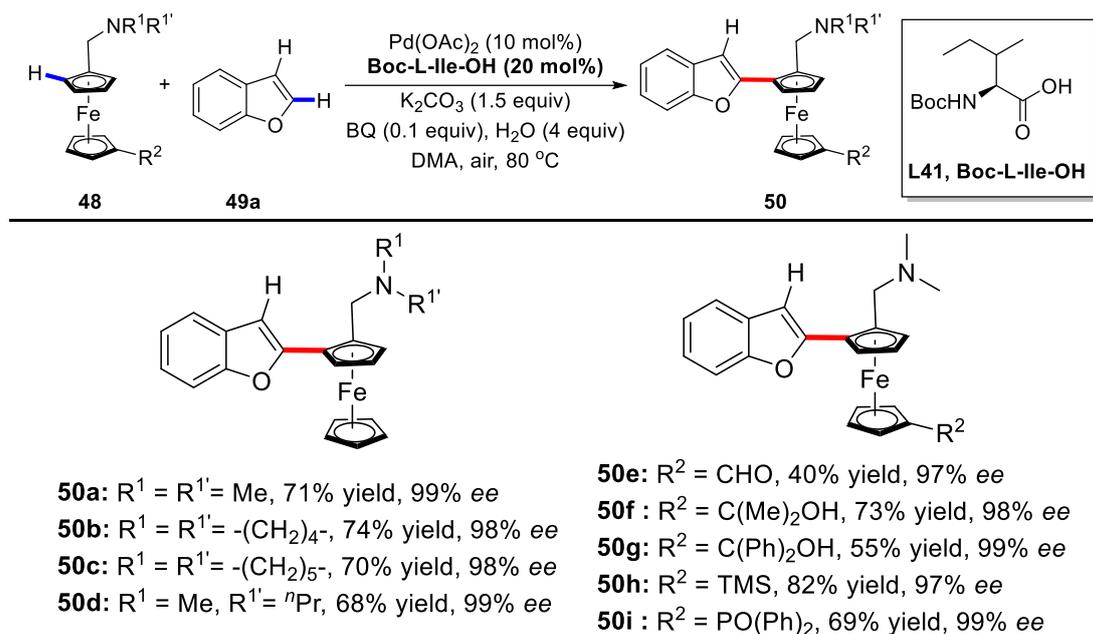
N,N-dimethylaminomethylferrocene and butyl acrylate were chosen as the model substrates. It was found the introduction of mono-*N*-protected amino acids (MPAA) as ligands to Pd^{II}, not just induced the high enantioselectivities, but also dramatically increased the reaction yields. Both Boc-L-Phe-OH (**L39**) and Boc-L-Tle-OH (**L40**) gave excellent yields and enantioselectivities for the model reaction (Scheme 35). Under the optimized condition, various acrylates, styrenes, and even aliphatic olefins were tested (Scheme 37). All of them worked well with excellent enantioselectivities (up to 99%) and yields (up to 98%).



Scheme 37. Substrate scope for the enantioselective C–H olefination reaction [87].

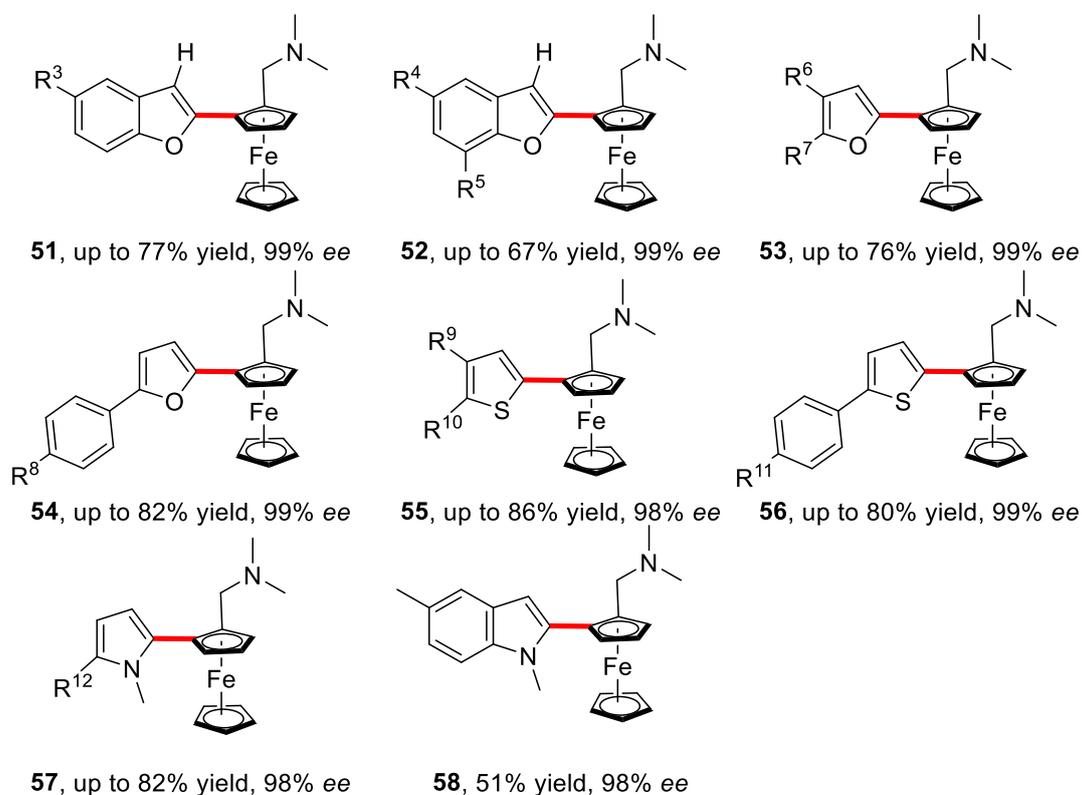
Another impressive development was revealed by You and coworkers [88]. They also employed the $\text{Pd}^{\text{II}}/\text{MPAA}$ catalyst system in the enantioselective oxidative C–H/C–H cross-coupling of ferrocenes with heteroarenes to prepare planar chiral ferrocenes.

The Boc-L-Ile-OH proved to be the best ligand, affording the desired product in a C2 regioselective manner with 71% yield and nearly perfect 99% ee under the optimal reaction conditions with air as the oxidant. Subsequently, various ferrocene derivatives were evaluated and the reaction exhibited excellent tolerance towards different functional groups (Scheme 38).



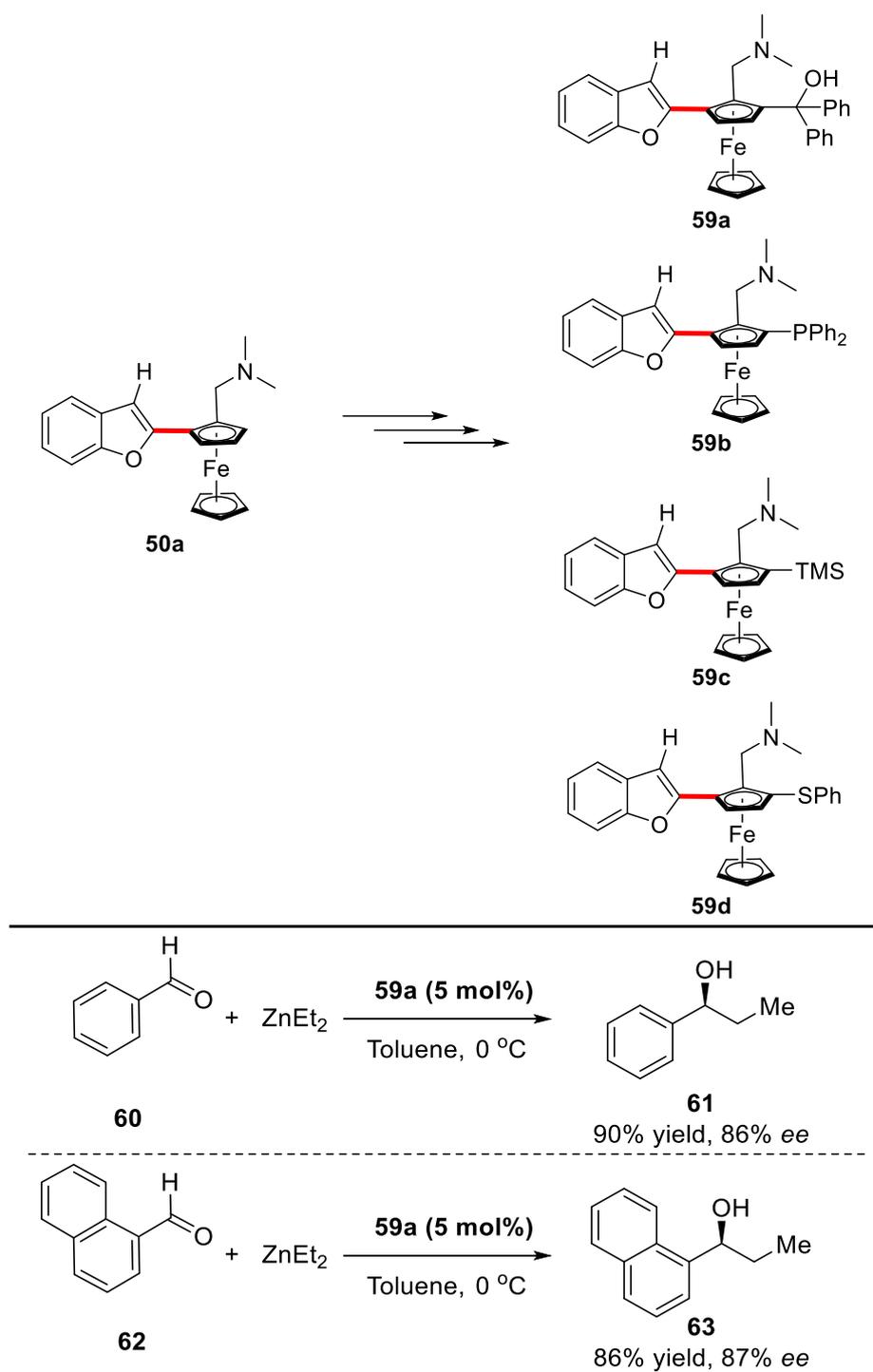
Scheme 38. Enantioselective cross-coupling reactions of benzofurans [88].

Moreover, the scope of heteroarenes was explored as well. Various substituted benzofurans, furans, thiophenes, pyrroles, and indoles worked smoothly under this condition, providing impressive yields and enantioselectivities (up to 99%) (Scheme 39).



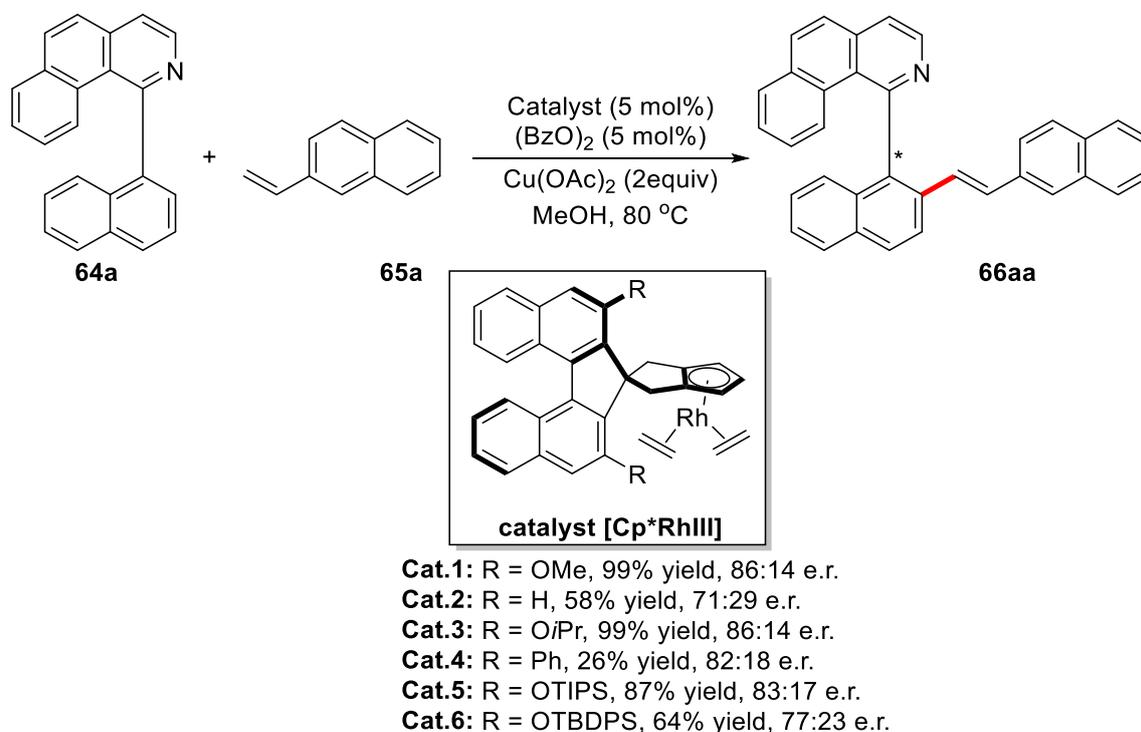
Scheme 39. Enantioselective cross-coupling reactions with different heteroarenes [88].

Besides, the newly synthesized planar chiral ferrocenes could be further elaborated into useful ligands for asymmetric transformations (Scheme 40).



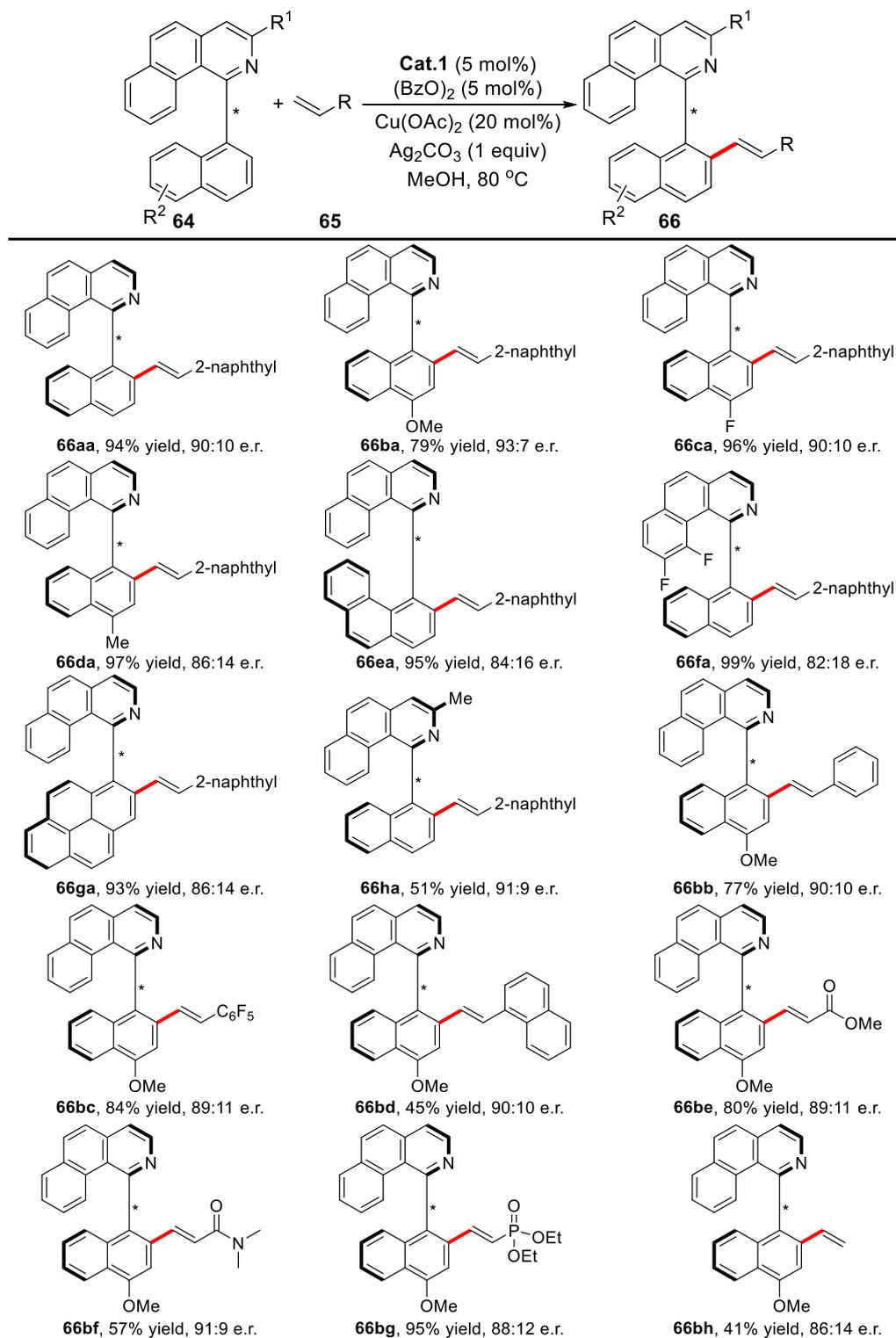
Scheme 40. Applications of the protocol [88].

Another excellent work on synthesizing novel axially chiral biaryls by direct C–H bond olefination was fulfilled by You and coworkers [89]. This dehydrogenative coupling reaction was catalyzed by chiral Cp/rhodium complexes. Further screening revealed that catalysts with bulky substituents usually led to diminished yield and e.r. value (Scheme 41). Finally, the combination of the **Cat.1**, Ag_2CO_3 (1.0 equiv), and $\text{Cu}(\text{OAc})_2$ (20 mol %) in methanol was determined to be the optimal condition, affording the desired product with 94% yield and 90:10 e.r.



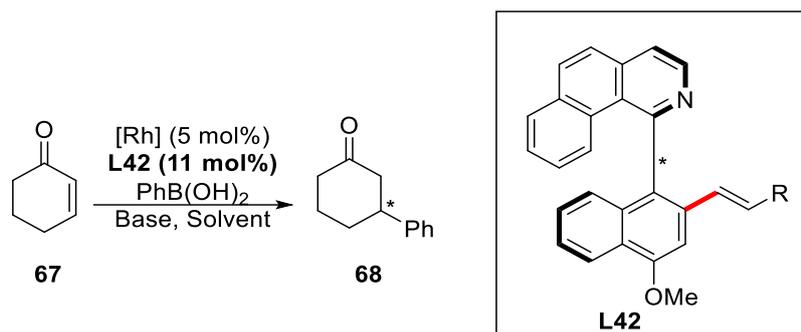
Scheme 41. Catalyst screening for the enantioselective oxidative Heck coupling reaction [89].

Under the optimized condition, biaryl substrates bearing different EDG or EWG proceeded efficiently to generate the desired alkenylated products in moderate to excellent yields and enantioselectivities, with up to 97% conversion and 93:7 e.r. Additionally, different olefins were well tolerated to this reaction, including styrenes, acrylates, acrylamides, and vinyl phosphonate esters. Notably, ethylene was also introduced, which gave the desired product with 86:14 e.r. Moreover, the gram-scale reaction also worked well (Scheme 42).



Scheme 42. The investigation of substrate scope [89].

Finally, the product was successfully utilized as ligands in the rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone reaction (Scheme 43), which sufficiently demonstrated the potential of this method.



Scheme 43. The application of enantioenriched biaryl products [89].

4. Summary

Although traditional cross-coupling reactions have revolutionized organic chemistry and are widely applied in modern organic synthesis, the need for prefunctionalized starting materials has prompted chemists to investigate more atom and step economic alternatives. Therefore, C–H activation has emerged as a powerful tool to achieve C–C bond formation, allowing for the transformation of otherwise unreactive C–H bonds, thus maximizing the overall operational efficiency and decreasing the amount of stoichiometric metallic waste. The combinations of C–H activation/C–C cross-coupling reactions provide unlimited possibilities for synthetic chemists to access complex molecules.

This review summarizes the recent development on enantioselective C–H activation/Mizoroki-Heck reaction and Suzuki reaction. Due to the low reactivity of the C–H bonds, and the selectivity problem rooted in the abundance of C–H bonds, these transformations are extremely difficult to achieve. However, thanks to the increased mechanistic studies, chemists continually develop a better understanding of the mechanical aspects ruling these transformations. The Pd^{II}/MPAA systems developed by Yu group have been utilized successfully and represents one of the most important progresses.

It should also be pointed out that the concept of toxic heavy metals and benign lighter metals should not be taken for granted. Recently, studies revealed that some palladium, rhodium compounds, which were often considered heavy and toxic, might be less toxic than lighter metals [90]. This may change our traditional views on the toxic effects of metal salts in favor of Pd-catalyzed C–H activation.

Even though apparent advancements in this area have been made, more general protocols are highly demanded. Much research efforts as far as to design new chiral catalysts and chiral ligands, expand the substrate scope, and improve the efficiency of these transformations are still needed before a more general, atom-economical, and more environmentally friendly process become the method of choice for chemists in industrial or academic settings.

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Conflicts of Interest: The author declares no conflicts of interest.

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