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Authors
Su, Bo
Hartwig, John F

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Development of Chiral Ligands for the Transition-Metal-Catalyzed Enantioselective Silylation and Borylation of C–H Bonds

Bo Su[*],

State Key Laboratory of Medical Chemical Biology, College of Pharmacy, Nankai University, 38 Tongyan Road, Jinnan District, Tianjin, 300350 (P. R. China)

John F. Hartwig[*]

Department of Chemistry, University of California, Berkeley, Berkeley, CA 94720 (USA)

Abstract

Enantioselective reactions that install functional groups at the positions of unactivated C–H bonds can be envisioned to produce intermediates for the synthesis of the active ingredients in pharmaceuticals and agrochemicals directly from simple feedstocks. Among these C–H bond functionalization reactions, those that form carbon–silicon (C–Si) and carbon–boron (C–B) bonds have been pursued because the products of these reactions can be converted to those containing a wide range of functional groups and because compounds containing silicon and boron possess unique properties that can be valuable for medicinal and materials chemistry. Although the silylation and borylation of C–H bonds have undergone extensive development during the past two decades, enantioselective versions of these reactions were not known until a few years ago. In this Minireview, we present the rapid development of enantioselective silylation and borylation of C–H bonds, with an emphasis on the design and development of the types of chiral ligands needed to achieve these reactions and an intention to inspire an expansion of these types of transformations.

Graphical Abstract

[*] subo@nankai.edu.cn; jhartwig@berkeley.edu.

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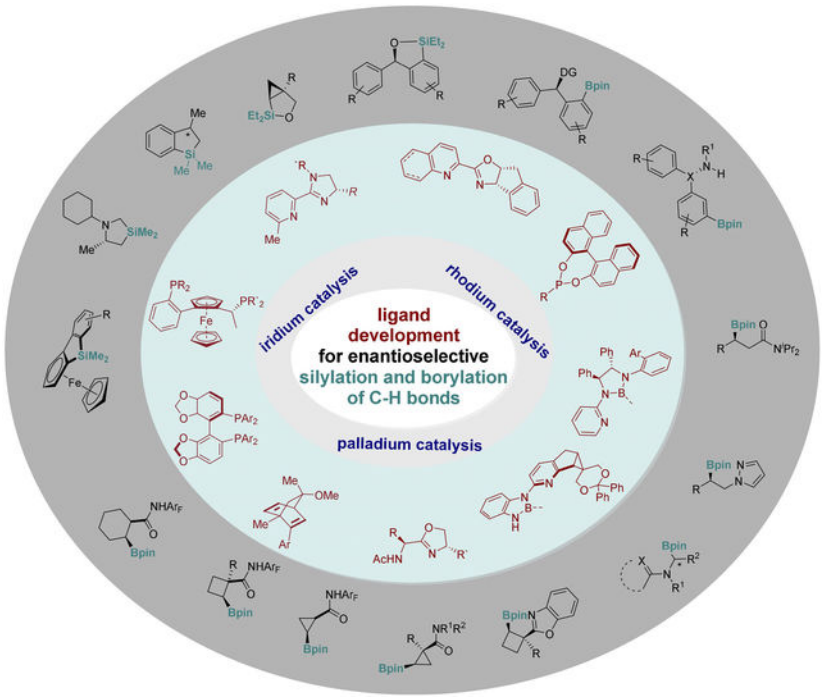
Conflict of Interest

The authors declare no conflict of interest.



Keywords

borylation; C–H bond functionalization; enantioselective C–H activation; ligand design; silylation

1. Introduction

The functionalization of C–H bonds has become a powerful tool for synthetic chemists.[1] These reactions can reduce the number of steps of synthetic sequences and have begun to change the way chemists synthesize organic molecules.[2] Among various reactions that lead to the functionalization of C–H bonds, the silylation and borylation of C–H bonds have been pursued with particular intensity by chemists during the past two decades.[3] This interest is high because silicon- and boron-containing compounds are unique building blocks in material science, agrochemicals, and pharmaceuticals (Figure 1),[4] and the newly formed C–Si and C–B bonds can be readily transformed to other bonds, including C–C, C–N, C–O, and C–X (X = F, Cl, Br, I) bonds.[3b,c,e] In addition, these reactions usually occur under mild conditions, making them compatible with a broad range of functional groups. This tolerance of functional groups is useful for the late-stage modification of natural products and drug molecules.

Although various metal catalysts have been developed for the silylation and borylation of C–H bonds,[3b,d, 5] chiral catalysts suitable for enantioselective silylation and borylation were not known until 2013. This late development contrasts the rapid development of enantioselective C–H bond functionalizations that lead to the installation of other functionalities at C–H bonds.[6] One of the major challenges facing the development of enantioselective silylation and borylation of C–H bonds was the common use of iridium

catalysts containing nitrogen-donor ligands and the lack of suitable chiral nitrogen-donor ligands that possess the steric and electronic properties to generate active catalysts. More specifically, the activity and functional-group tolerance of iridium catalysts is highest when ligated by dinitrogen ligands, such as bipyridines and phenanthrolines, but chiral analogues of bipyridine and phenanthroline are difficult to develop because these ligands are planar. Nevertheless, recent efforts have led to the design of several systems—mainly based on iridium with chiral nitrogen ligands and rhodium with chiral bisphosphine ligands—that catalyze enantioselective silylation and borylation of C–H bonds.

This Minireview presents the recent development of such enantioselective silylations and borylations of C–H bonds. The first section covers enantioselective silylation, and the second part, enantioselective borylation of C–H bonds. In each part, reactions are presented based on the type of the catalyst. Where appropriate, a general background and discussion of the reaction mechanisms is included. The intention of this review is to present an overview of the rapid progress of these catalysts and transformations and to reveal the limitations and challenges that will inspire continued development of this synthetic method for the synthesis of enantioenriched molecules.[7]

2. Enantioselective Silylation of C–H Bonds

Seminal reports on the dehydrogenative silylation of C–H bonds catalyzed by transition-metal complexes first appeared in the 1980s,[8] and significant progress has been made in the last decade.[5, 9] Yet, enantioselective silylation reactions have been published only in recent years.

2.1. Rhodium-Catalyzed Enantioselective Silylation of C–H bonds

The first enantioselective silylation of C–H bonds was reported by Kuninobu, Takai, and co-workers in 2013.[10] With $[RhCl(cod)]_2$ (cod = cyclooctadiene) as precatalyst, they examined various chiral bisphosphine ligands for the enantioselective synthesis of a spirosilabifluorene by two aryl C–H silylation processes (Figure 2). Among the ligands examined, (*R*)-BINAP led to the most enantioselective rhodium catalysts for this reaction (81% *ee*). In part because a high temperature (135 °C) was needed for the reactions to occur in reasonable yield, the scope of the substrates was limited, and only moderate to good enantiomeric excess of the spirosilabifluorene products was obtained.

Although detailed mechanistic investigations were not conducted, a catalytic cycle based on the previously reported rhodium-catalyzed silylation of aryl C–H bonds was proposed (Figure 3).[11] This proposed mechanism begins with an oxidative addition of the [Si]–H bond of the bis-(biphenyl)silane to a Rh^{I} center to afford a Rh^{III} intermediate **A**, which cleaves an aryl C–H bond to form a Rh^{V} species **B** that undergoes reductive elimination of H_2 to produce an aryl Rh^{III} intermediate **C** (path a); intermediate **C** also could be formed by σ-bond metathesis involving intermediate **A** (path b). Intermediate **C** would afford the final silylation product **D** by reductive elimination to form the C–Si bond. Following a second silylation of an aryl C–H bond in product **D**, the spirosilabifluorene product would be obtained. Although there are no experimental data provided, the enantio-determining step in this mechanism would be the first aryl C–H bond silylation because the configuration of

the chiral silicon center of intermediate **D** should be retained in the oxidative addition and reductive elimination steps of the second dehydrogenative silylation.

Following this use of rhodium catalysts containing BINAP for the enantioselective silylation of aryl C–H bonds, Shibata and co-workers explored rhodium catalysts bearing other chiral bisphosphine ligands and diene ligands for the construction of planar chiral benzosiloloferrocenes by the silylation of a ferrocenyl C–H bond (Figure 4).[12] The reaction of the hydridodimethylsilyl-substituted ferrocenes catalyzed by the combination of a rhodium precursor and (*S*)-BINAP led to the benzosiloloferrocene product in acceptable yield (78%) but with poor enantioselectivity (27% *ee*). However, the same reaction catalyzed by a rhodium catalyst ligated by a chiral diene (**diene-1** to **diene-8**), including Carreira's diene (**diene-3**), afforded the benzosiloloferrocene product with enantiomeric excess up to 65% *ee*.

Further investigations showed that the presence or absence of alkene as hydrogen acceptor also strongly influenced both yield and *ee* of the product (Figure 5). For example, the reaction with added 4-vinylcyclohexene formed the product in almost quantitative yield, but with only 40% *ee*; the reaction with 3,3-dimethylbut-1-ene afforded the product with a higher *ee* (85%), but the yield of the product was comparable to that obtained from reaction without the addition of hydrogen acceptor. Like the first enantioselective silylation of aryl C–H bonds catalyzed by rhodium bearing BINAP as ligand, reactions with the rhodium catalyst containing a chiral diene ligand required high reaction temperatures, thereby limiting the scope of the reaction and affording the benzosiloloferrocene derivatives with only moderate to good enantioselectivity.

To improve the enantioselectivity of the rhodium catalysts for the synthesis of benzosiloloferrocenes, He and co-workers investigated the effect of the ligand and the substituent of the silyl group on the enantioselectivity (Figure 6a).[13] They examined a wide range of chiral bisphosphine ligands, including BINAP, phosphines with substituted biphenyl backbones, and Spirophos derivatives for the reaction of hydridodimethylsilyl-substituted ferrocenes and found that rhodium catalysts containing (*S*)-TMS-Segphos led to the benzosiloloferrocene product with the highest enantioselectivity. Using this rhodium catalyst, reactions with hydridodiethylsilyl- and hydridodipropylsilyl-substituted ferrocenes gave the corresponding silylation products with higher enantioselectivity than those with hydridodimethylsilyl- and hydridodiphenylsilyl-substituted ferrocenes; when the silicon was substituted with bulkier *i*-Pr groups, the silylation reaction did not occur under the same conditions. Contemporaneously, Takai and Murai reported results that are similar to those of He. In their studies, (*R*)-DTBM-Segphos was used as the ligand (Figure 6b).[14]

Rhodium catalysts were further applied to the synthesis of six-membered rings fused to ferrocenes (Figure 7).[15] Zhao and co-workers reported that rhodium catalysts containing a Josiphos ligand led to the silylation products with good *ee* values. The reactions required a higher temperature (120 °C) than those leading to five-membered rings fused to ferrocenes, probably because the barrier to C–H bond cleavage that forms a seven-membered rhodacycle intermediate is higher than that to form a six-membered analogue.

In addition to compounds with planar chirality, compounds with point chirality have been prepared by enantioselective silylation of aryl C–H bonds. In 2015, Hartwig, Ryberg, and co-workers reported the desymmetrization of diarylmethoxy diethylsilanes by a rhodium-catalyzed intramolecular silylation of aryl C–H bonds. This reaction represented the first enantioselective silylation that set a stereogenic center at carbon (Figure 8).[16] After extensive investigation of ligands, including bisphosphine ligands, nitrogen phosphine ligands (N,P-ligands), and a Pybox ligand (N,N-ligand), they found that the selectivity of the rhodium catalysts for the desymmetrization of the diarylmethanol derivatives was highly dependent on the structure of the ligands. More specifically, slight variation of the substituent of the substrates led to significant changes in the enantioselectivity of the reaction. Thus, five ligands (**P-1** to **P-5**) were used to form products with high enantiomeric excess.

To gain insight into the enantioselective silylation of aryl C–H bonds catalyzed by rhodium complexes, Hartwig and co-workers conducted detailed mechanistic studies by experiment and computation.[17] The proposed catalytic cycle is depicted in Figure 9. The catalyst resting state was shown to be the rhodium silyl dihydride or rhodium-norboryl complexes **II** or **III**, both of which were formed from Rh-H species **I**, depending on the relative concentration of the diarylmethoxysilane ([Si]-H) and norbornene (nbe). The oxidative addition of [Si]-H to rhodium complex **III** generates a rhodium(III) intermediate **IV** (path a), which also could be formed by the insertion of nbe into rhodium dihydride species **II** (path b); DFT calculations of the barriers for each path disfavors the formation of **IV** from the insertion of nbe into **II** because the barrier for this path b is 7.1 kcalmol^{-1} higher than that for path a. The formation of intermediate **IV** through either path a or b is likely to be reversible, as revealed by the observation of the deuterium incorporation into the hydrogen acceptor (nbe) when the [Si]-D was used as the reactant. Intermediate **IV** undergoes reductive elimination to form intermediate **V** through path c; compound **V** also could form by reductive elimination of H_2 from intermediate **II** through path d. Selective oxidative addition of the aryl C–H bond by intermediate **V** generates species **VI**, which leads to the silylation product by reductive elimination to form the C–Si bond and regenerate the rhodium hydride species **I**. Measurements of the intermolecular kinetic isotope effect (KIE) (1.1 ± 0.1) and intramolecular KIE (3.0 ± 0.1) indicated that the C–H bond cleavage step is not rate-determining and is partially reversible; these results, together with DFT calculations of the oxidative addition of the C–H bond and reductive elimination to form the C–Si bond, indicated that the transition-state energies for these two reactions are similar, and both steps, therefore, are likely to affect the enantioselectivity of the silylation process. DFT calculations also showed that the high level of enantioselectivity results from the steric interaction between the alkyl substituent on the silicon of the reactant and the aryl group on the bisphosphine ligand.

With the successful application of chiral rhodium catalysts for the silylation of C(sp^2)–H bonds, enantioselective silylation of C(sp^3)–H bonds was explored. Hartwig and co-workers reported the enantioselective intramolecular silylation of C–H bonds in cyclopropylmethanol derivatives catalyzed by rhodium catalysts bearing an (*S*)-DTBM-Segphos ligand. The reaction occurred at 50°C and tolerated a wide range of functionalities (e.g. esters, amines,

ethers, etc.), leading to the silylation products with modest to excellent enantioselectivity (Figure 10).[18] A kinetic isotope effect of 2.1 showed that cleavage of the C–H bond could be the turnover-limiting and enantioselectivity-determining step, but the low value of the KIE suggests this step could be partially reversible.

Takai, Murai, and co-workers investigated the silylation of methyl C–H bonds catalyzed by rhodium complexes. However, the enantioselectivity of the silylation of the methyl C(sp^3)–H bonds in an isopropyl group was not highly enantioselective (less than 40% *ee*) when catalyzed by rhodium complexes of various chiral bisphosphine ligands (Figure 11).[19] Greater success was achieved with iridium catalysts for this class of transformation, as described in the next section.

2.2. Iridium-Catalyzed Enantioselective Silylation of C–H Bonds

In parallel with chiral rhodium catalysts for the enantioselective silylation of C–H bonds, chiral iridium catalysts for related enantioselective silylations have been sought. However, the combination of an iridium precatalyst and a bisphosphine ligand reacted with poor enantioselectivity or limited scope, or both (Figure 12). For example, when Shibata attempted to apply the iridium catalyst bound by (*S*)-BINAP to the intramolecular silylation of the C–H bonds in ferrocenes, the product was obtained with only 7% *ee* (Figure 12, top).[12] Attempts to achieve the desymmetrization of diarylmethanol derivatives by the silylation of aryl C–H bonds reported by Hartwig and Ryberg[16] led to high enantioselectivity, but substrates that reacted with this high selectivity were were limited to the silyl ether from an unsubstituted diarylmethanol (90% *ee*); reactions with those from substituted diarylmethanols led to low yields (Figure 12, bottom).[20] For this reason, their study focused on rhodium catalysts, as described in Section 2.1.

Dinitrogen ligands, such as bipyridine and phenanthroline, were commonly used in the iridium-catalyzed silylation of C–H bonds, but the planar structure of these ligands hindered the development of chiral analogues. Nevertheless, chiral nitrogen ligands for iridium-catalyzed silylations of C–H bonds are appealing because iridium complexes containing dinitrogen ligands catalyze the silylation of C–H bonds with the most favorable combination of rate and functional-group tolerance.

Hartwig, Shi, and co-workers systematically investigated the performance of a wide range of dinitrogen ligands for the iridium-catalyzed enantioselective silylation of aryl C–H bonds in diarylmethyl silyl ethers (Figure 13).[21] Iridium complexes containing chiral C_2-symmetric PyBOX, bipyridine, and BOX ligands did not catalyze the silylation of aryl C–H bonds. Iridium catalysts containing an unsymmetrical pyridyl oxazoline ligand were more reactive, but they were poorly enantioselective. Further modification of the pyridyl oxazoline ligand led to a new chiral tetrahydroquinyl oxazoline ligand, which was highly reactive and highly enantioselective for the silylation reaction.

The enantioselective silylation of aryl C–H bonds with iridium catalysts containing tetrahydroquinyl oxazolidines as the N,N-ligand proceeded under milder conditions (40–45 °C) and with compatibility toward a broader range of functional groups than those with rhodium catalysts (Figure 14, top). *Para*- and *meta*-substituted diarylmethanol derivatives

reacted efficiently to form the silylation products with good to excellent enantioselectivity (> 90% *ee*); in contrast, *ortho*-substituted diaryl methanols did not react, even at elevated temperature (80 °C). Based on the significantly lower reactivity of the *ortho*-substituted aryls, a kinetic resolution of unsymmetrical diarylmethanol derivatives was designed that led to regio- and enantioselective silylation of aryl C–H bonds; the selectivity factor reached 120 (Figure 14, bottom).

Iridium catalysts containing chiral N,N-ligands also were more reactive and enantioselective for the silylation of unactivated C(sp^3)–H bonds. Using these catalysts, Hartwig and co-workers disclosed the first highly enantioselective silylation of unactivated C(sp^3)–H bonds. The reactions occurred under mild conditions (50 °C) and tolerated a wide range of functionalities, including a tertiary amine, an amide, silyl ethers, carbonates, a carbamate, a ketal, an aryl chloride, and an aryl nitrile, leading to the silylation products with up to 96% *ee* (Figure 15).[22] In stark contrast, rhodium catalysts bound by bisphosphine ligands gave the analogous products in less than 40% enantioselectivity.[19] Computational studies by Huang and co-workers indicated that C–H bond cleavage is likely the rate- and enantioselectivity-determining step of the reaction.[23]

To expand the application of iridium catalysts containing N,N-ligands to the silylation of C(sp^3)–H bonds in alkyl amine derivatives, Hartwig and co-workers examined reactions of the enantiotopic methyl groups in isopropyl amino silylmethanes catalyzed by iridium complexes with pyridyl oxazoline ligands. They found iridium catalysts containing these ligands displayed moderate enantioselectivity and poor reactivity, possibly because of the competing coordinating effect of the alkylamine unit to the catalyst (Figure 16). To increase the reactivity of the catalyst, they designed more electron-donating imidazoline ligands. Reactions with pyridyl imidazoline ligands occurred even below ambient temperatures to afford the silylation product in good yields with moderate to good enantioselectivity.[24] This silylation reaction catalyzed by the iridium-imidazoline catalyst system is currently the most rapid silylation of a C–H bond reported.

3. Enantioselective Borylation of C–H Bonds

Since the discovery of stoichiometric reactions of Cp*Fe-$(CO)_2BR_2$ and Cp*$W(CO)_3BR_2$ with C–H bonds under photochemical conditions by Hartwig in the 1990s (Figure 17a),[25] much effort has been made to develop the borylation of C–H bonds into synthetically valuable catalytic processes. To enable the borylation of C–H bonds to occur catalytically, Hartwig first reported the photochemical borylation of primary alkyl C–H bonds with B_2pin_2 catalyzed by [Cp*$Re(CO)_3$] (Figure 17b).[26] Soon after, Hartwig disclosed that the rhodium complex (Cp*Rh(η^4-C_6Me_6)) catalyzes the borylation of primary alkyl C–H bonds under thermal conditions,[27] (Figure 17c) and Smith used this catalyst for the borylation of arenes with HBpin.[28] Although the borylation of alkyl and aryl C–H bonds occurred with these catalyst, and chiral Cp ligands are known,[29] the development of enantioselective versions of these reactions was challenging because of the high reaction temperatures, need for substrate as solvent, and poor functional group compatibility.

Iridium catalysts containing phosphine- and nitrogen-based ligands enabled the borylation of aryl C–H bonds with high rate and functional group tolerance (Figure 17d). Smith, Maleczka, and co-workers reported iridium complexes having monophosphine or bisphosphine ligands for the borylation of arenes with HBpin at high temperatures (100–150°C).[30] In parallel, Hartwig, Ishiyama, and Miyaura developed iridium catalysts containing bipyridine ligands[31] that made the borylation of C–H bonds more efficient and increased the functional group compatibility. These results paved the way for the development of enantioselective borylations.[32]

Detailed mechanistic investigations of the borylation of C–H bonds have been reported in several papers.[33] Before the presentation of recent progress on the enantioselective borylation of C–H bonds, mechanistic aspects of the reaction and key intermediates will be presented. A general catalytic cycle for the borylation of aryl C–H bonds with an iridium catalyst bearing a dinitrogen ligand (dtbpy) is shown in Figure 18.[33a] Reversible dissociation of cyclooctene (coe) from the precatalyst [Ir(dtbpy)$(Bpin)_3$(coe)] forms the active 16-electron species [Ir(dtbpy)$(Bpin)_3$], which reacts with the aryl C–H bond to afford the Ir^V intermediate [Ir(dtbpy)$(Bpin)_3$(H)Ar] by oxidative addition. The Ir^V species leads to an arylboronate ester and an Ir^{III} hydride species by reductive elimination to form the C–B bond. The Ir^{III} hydride reacts with B_2pin_2 to form HBpin and regenerate the 16-electron triboryl-iridium complex. The proposed catalytic cycle was supported by DFT calculations reported by Sakaki et al.[33b] The 16-electron species [Ir(dtbpy)$(Bpin)_3$] containing two dative nitrogen ligands and three covalent boryl ligands was the intermediate that cleaved the C–H bond; the identity of this intermediate guided development of chiral ligands for the enantioselective borylation of C–H bonds (vide infra).

3.1. Iridium-Catalyzed Enantioselective Borylation of C–H Bonds

The enantioselective borylation of C–H bonds was first reported in 2017. The iridium catalyst containing a novel tetrahydroquinolyl oxazoline ligand like that used for the enantioselective silylation of C–H bonds led to the development of the first enantioselective borylation of aryl C–H bonds.[34] The iridium-catalyzed desymmetrization of diarylmethyl silanes by silyl-directed borylation of aryl C–H bonds occurred at 0°C, affording the borylated products with good to excellent *ee* values (Figure 19). Recently, Hong and co-workers also reported an iridium catalyst that contains a pyridyl dihydroisoquinoline ligand for the same reaction, but the enantioselectivity of the reactions catalyzed by this newly developed catalyst was highly dependent on the steric and electronic properties of the substrates; diarylmethyl silanes containing electron-poor substituents on the arene led to the borylation products with low to moderate enantioselectivity.[35]

After the discovery of iridium catalysts containing chiral N,N-ligands for the enantioselective borylation of C–H bonds, Sawamura and co-workers reported iridium complexes of chiral monophosphoramidite ligands for the enantioselective borylation of 2-alkylpyridines. The reaction occurred selectively at the β-C–H bonds of the pyridyl group, but the enantioselectivity of the borylated products was low (Figure 20).[36] The pyridyl group on the substrate played two roles. It functioned as the directing group to control the

site-selectivity of the borylation, and it acted as an auxiliary ligand that, together with the monophosphoramidite ligand, accelerated the borylation process.

To increase the enantioselectivity of the iridium catalysts for the borylation of 2-alkylpyridines, Sawamura conducted further studies with monophosphite ligands. The combination of $[Ir(cod)(OMe)]_2$ and a phosphite ligand containing two chiral BINOL moieties reacted with the highest enantioselectivity for the borylation of 2-alkylpyridines and 2-alkyl-1,3-azoles (Figure 21).[37] DFT calculations suggested that a monophosphite-Ir-tris(boryl) complex is the catalytic intermediate that cleaves the C–H bond and that the ligand generates a narrow chiral reaction pocket for cleavage of one of two enantiotopic methylene C–H bonds with enantioselectivity controlled by the combination of multiple noncovalent interactions. The monophosphite-Ir-tris(boryl) complex contains two open coordinating sites, one to coordinate with the pyridyl group on the substrate and the other to bind and cleave the C–H bond.

In the above two examples reported by Sawamura, the borylations occurred through a five-membered iridacycle intermediate formed by selective activation of methylene C–H bonds β to the chelating functional group on the substrate. Using a similar iridium catalyst, the same group achieved the challenging enantioselective borylation of γ-methylene C–H bonds of amides and esters, which occurs through six-membered iridacycles (Figure 22).[38] In addition to the chiral monophosphite ligand, an achiral pyridyl-urea ligand was used. These two ligands, together with the iridium precatalyst, form a cavity containing additional attractive noncovalent interactions with the reactant that place the substrate in position for the activation of one methylene C–H bond γ to the amide group. Among the multiple noncovalent interactions in the enzyme-like pocket, hydrogen-bonding interactions between the urea unit on the urea-pyridine ligand and the carbonyl group on the amide and ester likely account for this γ-selectivity.

Iridium catalysts ligated by a bidentate N,B-ligand also were reported for the borylation of C–H bonds. In 2017, Li and co-workers reported the preparation of an achiral N,B-ligand precursor that contains a pyridyl unit and a silylborane unit, and this precursor reacted with $[Ir(cod)Cl]_2$ to form iridium catalysts containing an N,B-ligand. The iridium catalysts led to high *ortho*-selectivity for the borylation of C–H bonds with a wide range of arenes that bear a coordinating functionality, including an ester, amide, pyridyl, hydrazone, or oxime ether (Figure 23).[39]

Inspired by the high reactivity of iridium catalysts ligated by N,B-ligands for the borylation of aryl C–H bonds, Xu and co-workers developed chiral N,B-ligands, the chiral environment of which was introduced by the substituents on the boron-containing five-membered ring. The chiral N,B-ligand was applied to the desymmetrization of diarylmethylamines by iridium-catalyzed borylation of aryl C–H bonds (Figure 24).[40] The borylated products were obtained in good yields and with good-to-excellent enantioselectivity and regioselectivity.

This catalyst was extended to the borylation of C–H bonds of cyclopropanes, cyclobutanes, and azacycles by Xu and co-workers.[41] To obtain good reactivity and enantioselectivity, modification of the N-aryl group on the N,B-ligand was required. For example, the ligand

containing an N-aryl group substituted with 2-aryl and 5-*t*Bu substituents formed a catalyst that was both active and highly enantioselective for the borylation of cyclopropyl C–H bonds (Figure 25),[41a] while the catalyst containing the ligands bearing N-aryl groups substituted with 2,6-dimethyl or 2,6-diethyl substituents reacted with higher enantioselectivity for the borylation of cyclobutyl C–H bonds (Figure 26).[41b] By further modification of the N,B-ligand on the pyridinyl and N-aryl units, the same group also reported highly enantioselective borylations of the α-C–H bonds in five- to nine-membered azacycles.[41c]

The N,B-ligands were also applied to the iridium-catalyzed borylation of unactivated methylene C–H bonds of linear substrates, such as amides and pyrazoles. In this case, the bulkier N,B-ligand containing cyclohexyl groups at the 2, 4, and 6-positions of the N-aryl group was required for the iridium catalysts to react in high yield and enantioselectivity (Figures 27 and 28).[42] The borylation of both pyrazoles and amides occurred at the β-position of the coordinating functional group through five-membered iridacycle intermediates.

The N,B-ligands just described contain a planar pyridyl unit and a chiral boron-containing five-membered ring. Very recently, another type of N,B-ligand that contains a chiral pyridyl unit and a planar boron-containing scaffold was developed by Li, Xu, and co-workers (Figure 29).[43] Desymmetrization of 2-pyridinyl-substituted diarylmethane derivatives with iridium catalysts bearing this new N,B-ligand led to the borylated products with high enantioselectivity and in good yields.

Directed C–H bond functionalization of arenes usually occurs at the *ortho*-position of the directing group; the functionalization of remote aryl C–H bonds, particularly enantioselective functionalization of remote aryl C–H bonds, is more challenging.[44] Phipps and co-workers reported this type of desymmetrization of geminal diaryl motifs by iridium-catalyzed, *meta*-selective borylation of C–H bonds (Figure 30).[45] Asymmetric induction in the long-range borylation of aryl C–H bonds was achieved by a strategy involving chiral cations. A bipyridine ligand containing an anionic sulfonate group and an iridium precatalyst assemble to generate an anionic iridium catalyst, which, together with the chiral cationic dihydroquinine ligand, catalyzes the enantioselective borylation of C–H bonds *meta* to the directing group. The *meta* selectivity was attributed to the hydrogen-bonding interaction between the sulfonate group on the bipyridine ligand and the directing group on the substrate, and the enantioselectivity was induced by the chiral, cationic dihydroquinine ligand. This work provided an approach for the synthesis of P-stereogenic phosphorus compounds through enantioselective borylation of *meta*-aryl C–H bonds. Very recently, Xu and co-workers reported the synthesis of this type of compound through enantioselective borylation of *ortho*-aryl C–H bonds, in which iridium catalysts containing an N,B-ligand were used.[46]

3.2. Rhodium-Catalyzed Borylation of C–H bonds

In contrast to the rapid development of iridium catalysts for the enantioselective borylation of C–H bonds, highly enantioselective rhodium catalysts for the borylation of C–H bonds are rare. The first enantioselective borylation of C–H bonds catalyzed by rhodium was reported by Sawamura in 2017 (Figure 31).[36] They showed that the combination of

a rhodium precursor and a phosphoramidite ligand led to enantioselective borylation at methylene C–H bonds of saturated nitrogen heterocycles bearing a pyridyl group on nitrogen. However, the borylated products formed with low to moderate enantioselectivity.

The enantioselectivity of the rhodium catalysts for this reaction was significantly increased by the same group by using a monophosphite as the ligand (Figure 32), and this complex led to the only rhodium-catalyzed, highly enantioselective borylation of C–H bonds.[47] Reactions with a broad range of substrates containing coordinating groups, such as pyridine, isoquinoline, benzooxazoline, and benzimidazole, led to the borylated products in good yields and with high enantiomeric excesses. This rhodium catalyst is highly reactive and enantioselective for the borylation of C–H bonds adjacent to the basic nitrogen of *N*-benzyl amides derived from benzoic acid and pivalic acid but was less reactive for the borylation of less sterically hindered amides (e.g. those from acetic acid and cyclohexanecarboxylic acid).

3.3. Palladium-Catalyzed Enantioselective Borylation of C–H Bonds

Palladium-catalyzed enantioselective functionalization of C–H bonds has been investigated extensively in the last decade,[6] but the enantioselective borylation of C–H bonds catalyzed by palladium is not common.[48] In 2017, Yu and co-workers reported the only palladium-catalyzed enantioselective borylation of C–H bonds (Figure 33).[49] Chiral, acetyl-protected aminomethyl oxazolines were used as ligands with a Pd^{II} precatalyst for the enantioselective borylation of carbocyclic amides. Reactions with cyclobutyl carboxamides occurred with the highest combination of yield and enantioselectivity. Reactions of a cyclopropyl carboxamide, and 4-substituted cyclohexyl carboxamides led to the borylated products with good to excellent enantioselectivity and diastereoselectivity, although in lower yield, and the reaction with the unsubstituted cyclohexyl carboxamide gave an approximately 2:1 mixture of two diastereomers.

4. Summary and Outlook

Enantioselective silylation and borylation of C–H bonds catalyzed by transition metals are appealing strategies for the construction of chiral molecules because the newly formed C–Si and C–B bonds can be easily transformed to a wide range of carbon–carbon and carbon–heteroatom bonds attached to hydrocarbyl and functional groups, thereby enabling the increase of the structural diversity and complexity of chiral intermediates during a synthetic sequence. Through extensive investigations of chiral ligands, several catalyst systems, especially those containing iridium and rhodium, were developed for enantioselective C–H bond functionalization. Rhodium catalysts containing bisphosphine ligands and iridium catalysts with pyridyl oxazolidine (N,N-) ligands led to highly enantioselective intramolecular silylation of aryl and alkyl C–H bonds; iridium catalysts containing quinolinyl oxazoline (N,N-) ligands, N,B-ligands, or monophosphite ligands enabled enantioselective borylation of $C(sp^2)$–H and $C(sp^3)$–H bonds.

Despite the significant progress made, many limitations and challenges exist. First, all the enantioselective silylations of C–H bonds occurred intramolecularly; intermolecular reactions are not known. Second, enantioselective silylation focused mainly on aryl and primary alkyl C–H bonds; there are no reactions in which enantioselective silylation occurs

at secondary alkyl C–H bonds. Third, the enantioselective reactions focused mainly on rhodium and iridium catalysts, although catalysts based on several transition metals (e.g. Pd, Co, Ni, and Pt) are known to be capable of catalyzing the borylation of C–H bonds, and enantioselective borylations catalyzed by palladium complexes are now known. Finally, undirected enantioselective borylation of C–H bonds is underexplored. To overcome these limitations and to make these reactions synthetically more valuable, development of more reactive and selective metal catalysts is required, and this development relies on the design of new classes of ligands and a deeper understanding of the factors controlling the reaction rates and selectivities.

Acknowledgements

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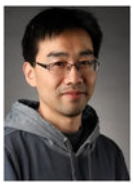
Biographies



Bo Su graduated in Chemistry from Zhengzhou University (China) and obtained his Ph.D. from Nankai University (Tianjin, China). After postdoctoral research at Peking University and then at UC Berkeley (USA), he returned to Nankai University and started his independent career as a professor in 2020. His research focuses on the development of new chemical reactions catalyzed by transition metal complexes and synthesis of molecules that are of interest in medicinal chemistry and organic chemistry.

John F. Hartwig obtained his A.B. from Princeton University (USA) and his Ph.D. from UC Berkeley. After a postdoctoral position at MIT (Cambridge, USA), in 1992 he began his independent career at Yale University (New Haven, USA). In 2006 he moved to the University of Illinois (Urbana-Champaign, USA) and returned to UC Berkeley as the Henry Rapoport Chair in 2011. His research focuses on the discovery and understanding of new chemical reactions catalyzed by transition metal complexes and artificial metalloenzymes. He was awarded the Wolf Prize in Chemistry in 2019 and the A. C. Cope Award in 2021.

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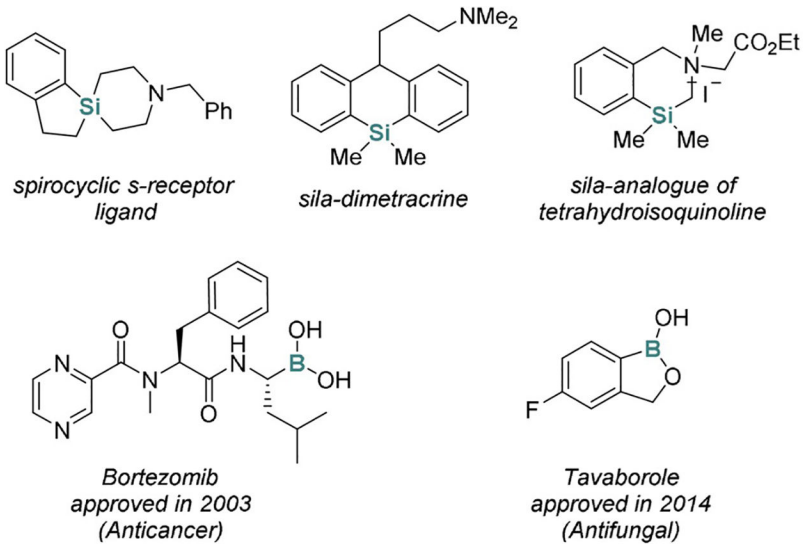

Figure 1.
Representative compounds containing silicon or boron.

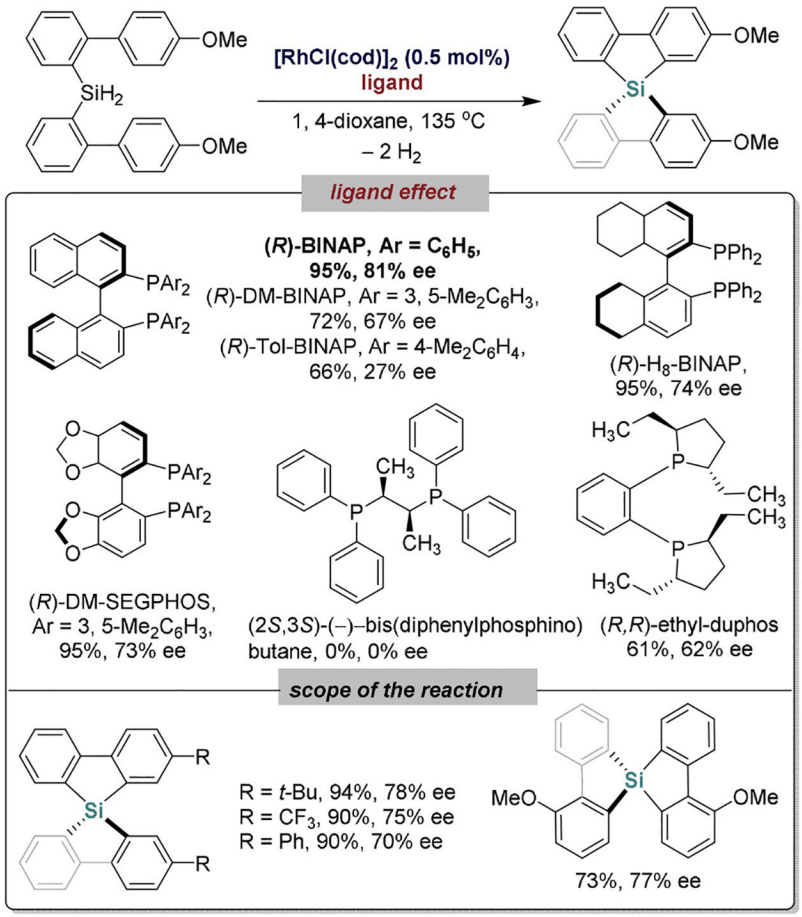

Figure 2.

Rhodium-catalyzed enantioselective silylation of aryl C–H bonds for the synthesis of spirosilabifluorene derivatives.

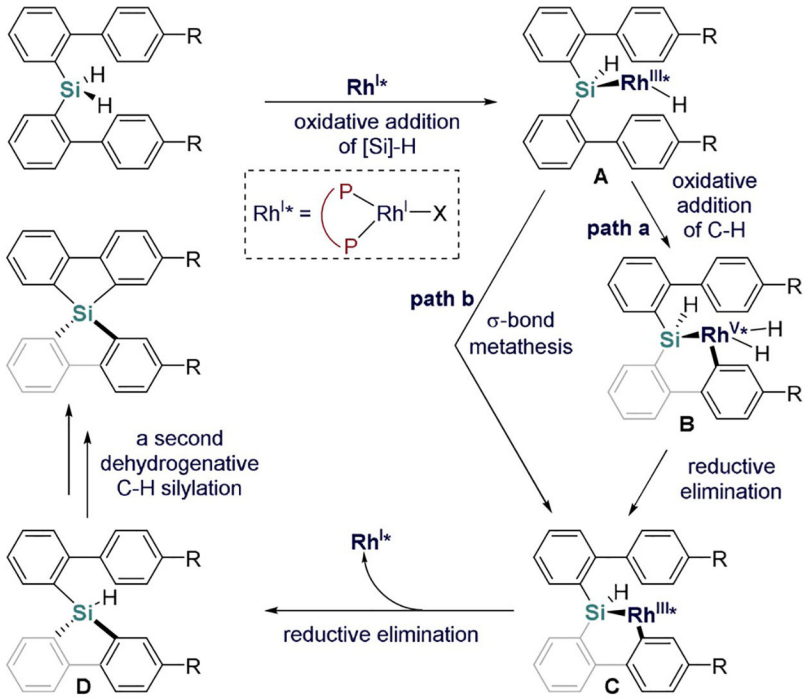

Figure 3.
Proposed catalytic cycle for the rhodium-catalyzed synthesis of spirosilabifluorenes.

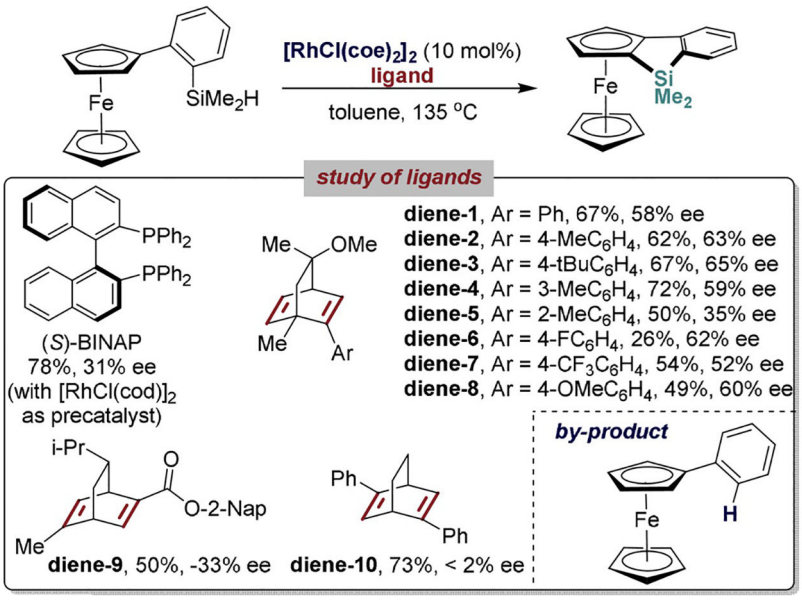

Figure 4.

Ligand effect in the rhodium-catalyzed enantioselective synthesis of planar chiral benzosiloloferrocenes by silylation of C(sp^2)–H bonds. coe = cyclooctene.

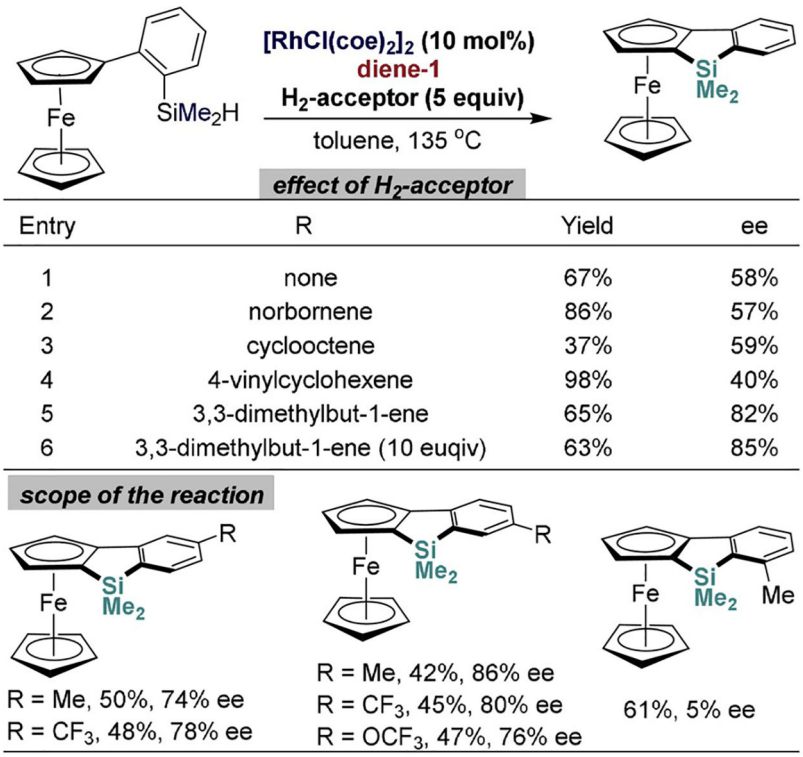

Figure 5.

Ligand effect and scope of the rhodium-catalyzed enantioselective synthesis of planar chiral benzosiloloferrocenes by silylation of C(sp^2)–H bond.

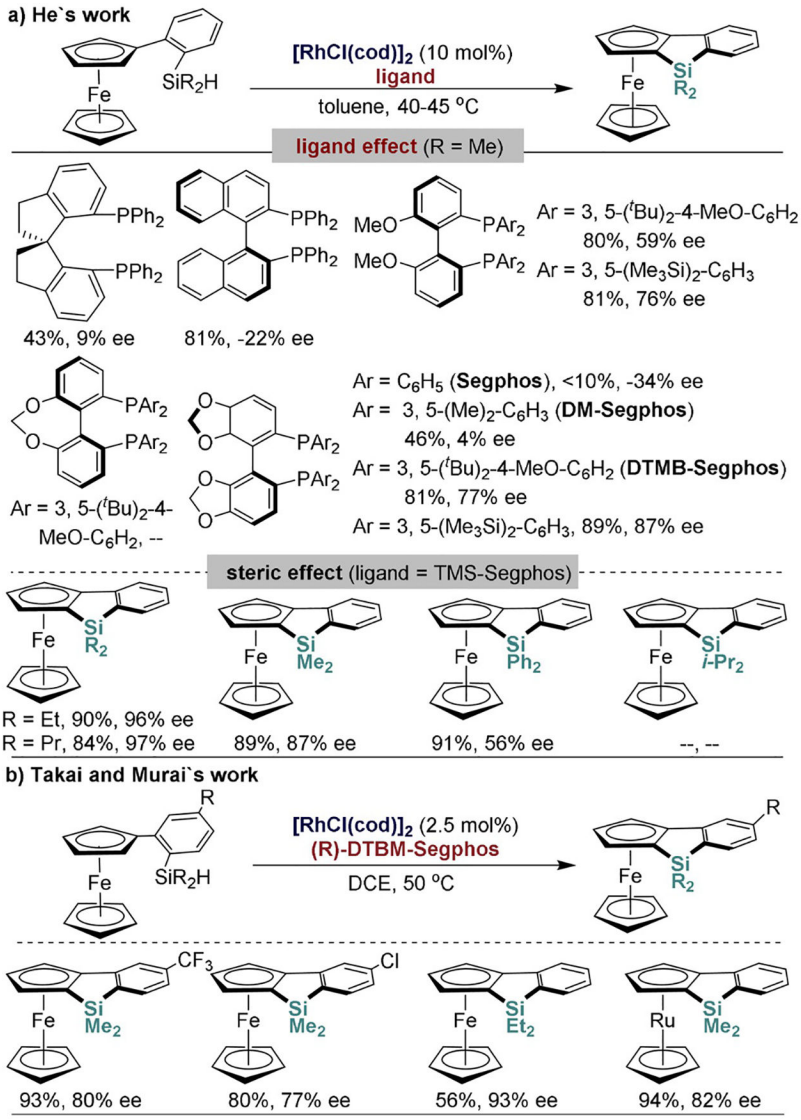

Figure 6.

Rhodium-catalyzed enantioselective synthesis of planar chiral benzosiloloferrocenes by silylation of C(sp^2)–H bonds.

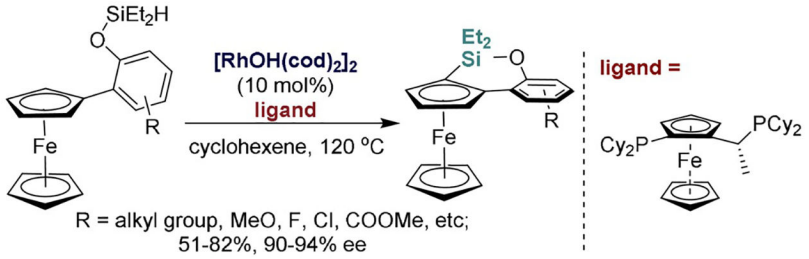

Figure 7.

Rhodium-catalyzed enantioselective synthesis of planar chiral six-membered-ring fused ferrocene derivatives by silylation of C(sp^2)–H bond.

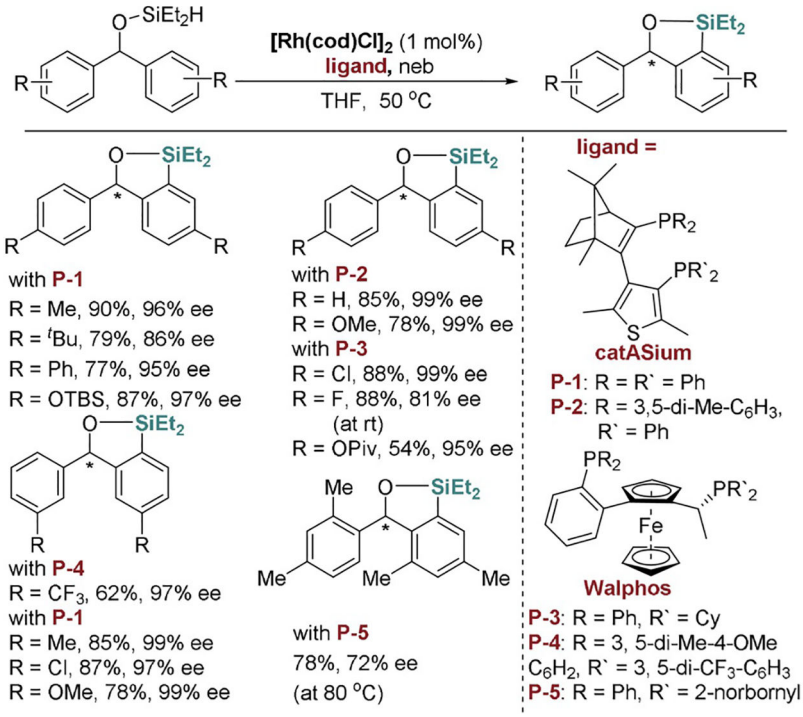

Figure 8.

Rhodium-catalyzed desymmetrization of diarylmethoxysilanes by silylation of aryl C–H bonds.

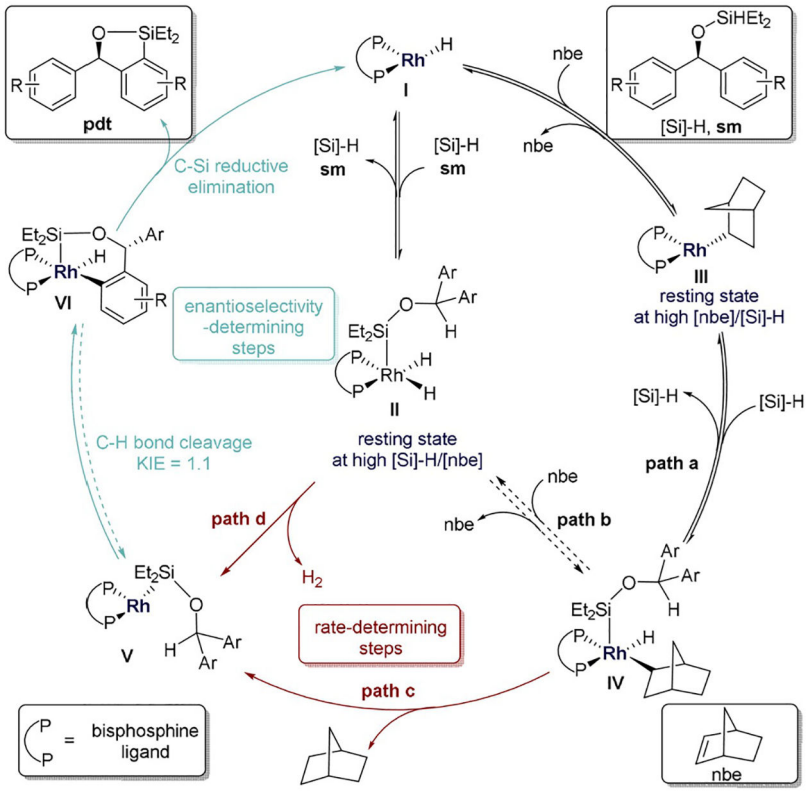

Figure 9.

Proposed catalytic cycle for the rhodium-catalyzed desymmetrization of diarylmethoxysilanes by silylation of aryl C–H bonds.

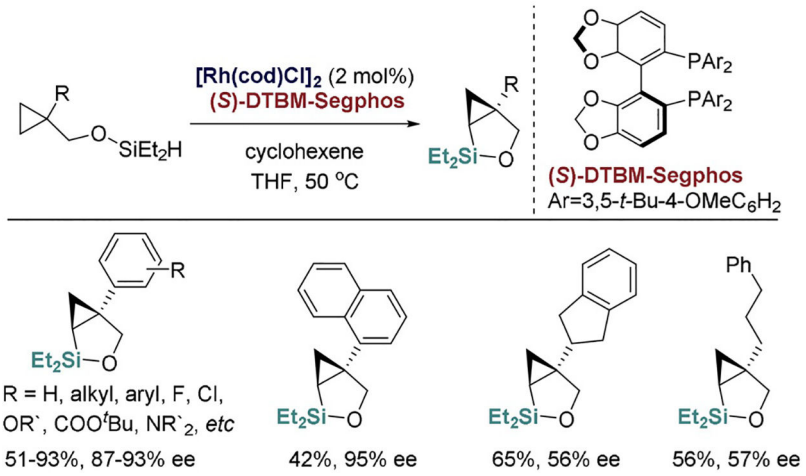

Figure 10.

Rhodium-catalyzed enantioselective intramolecular silylation of cyclopropylmethanol derivatives.

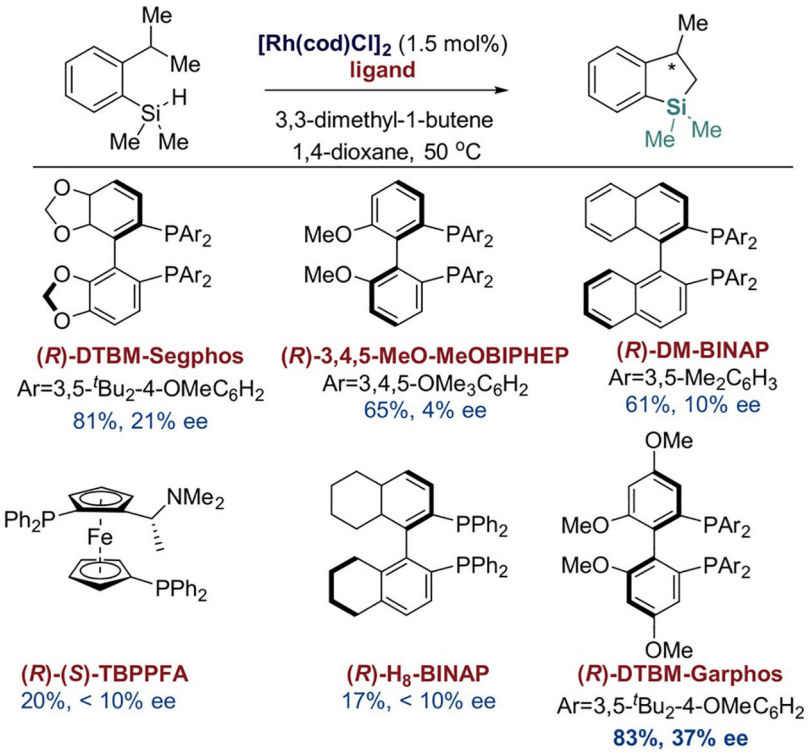

Figure 11.
Rhodium-catalyzed enantioselective silylation of alkyl C(sp^3)–H bonds.

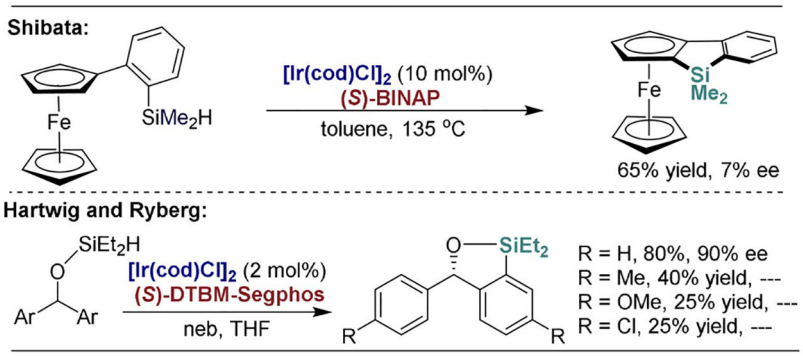

Figure 12.
Iridium-catalyzed enantioselective silylation of C(sp^2)–H bonds.

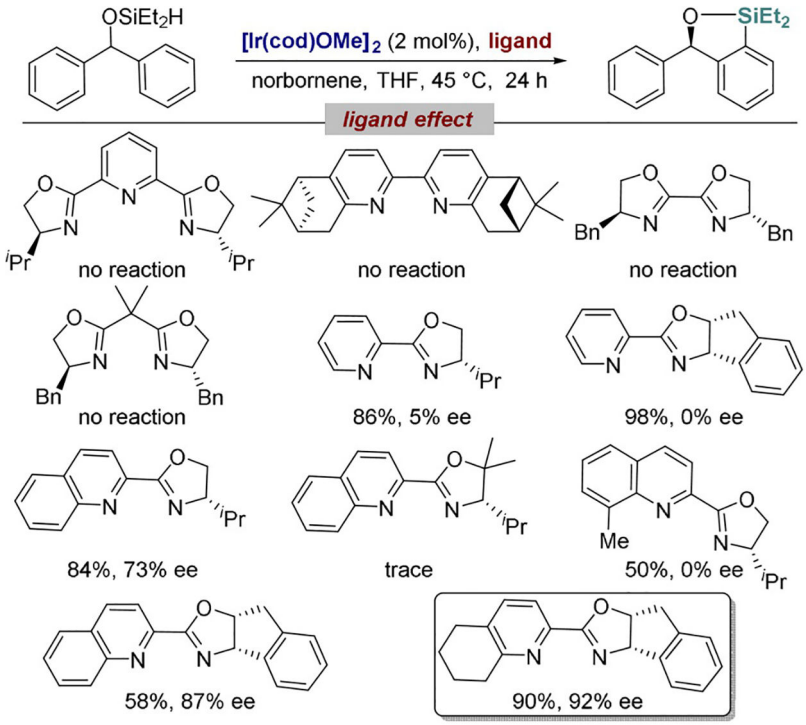

Figure 13.

Development of a chiral dinitrogen ligand for the iridium-catalyzed enantioselective silylation of an aryl C–H bond in diarylmethanol derivatives.

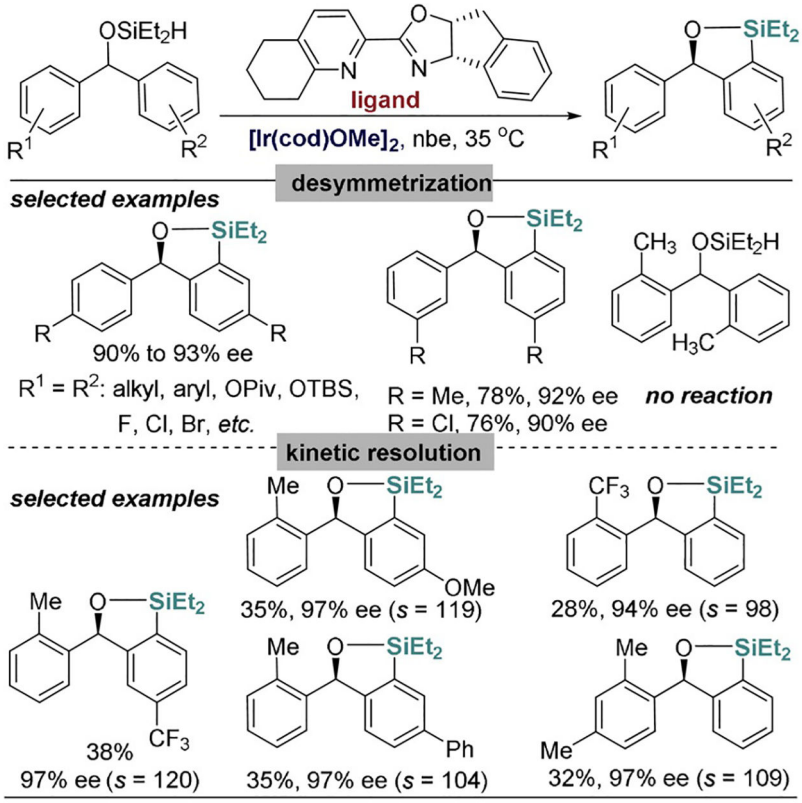

Figure 14.

Scope of the iridium-catalyzed enantioselective silylation of an aryl C–H bond in diarylmethanol derivatives.

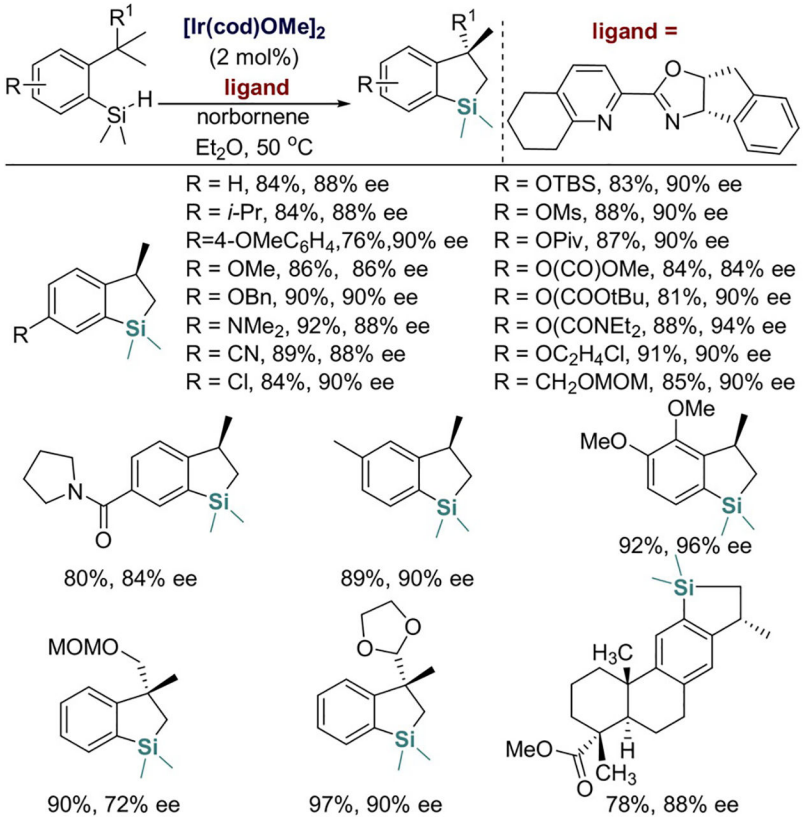

Figure 15.

Enantioselective silylation of alkyl C–H bonds catalyzed by an iridium catalyst containing a chiral N,N-ligand.

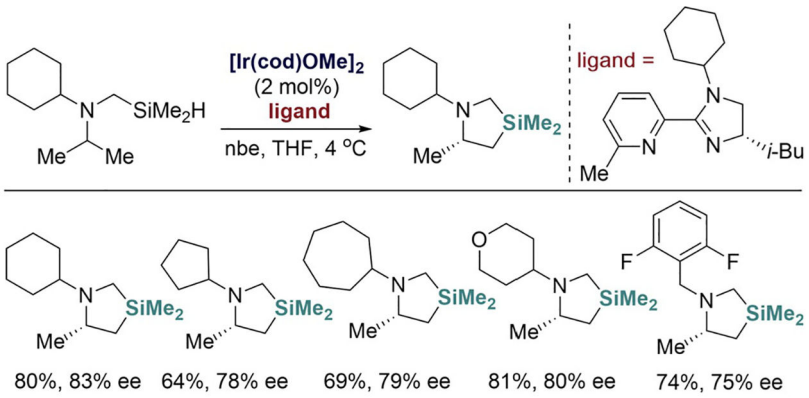

Figure 16.

Enantioselective silylation of C–H bonds of alkyl amines catalyzed by an iridium catalyst bearing an imidazoline ligand.

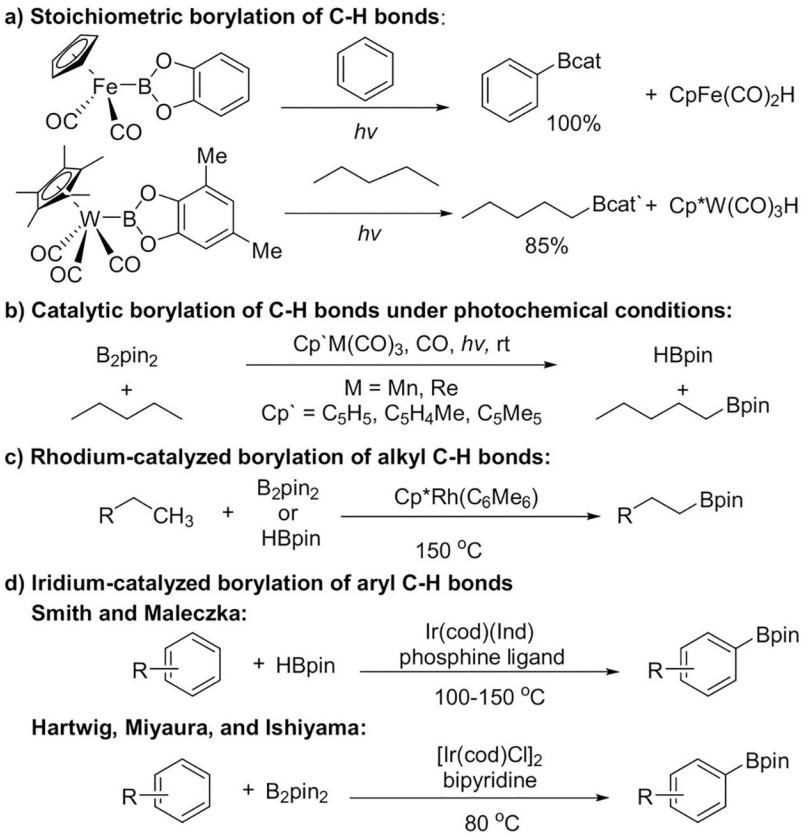

Figure 17.

Development of stoichiometric and catalytic borylation of C–H bonds.

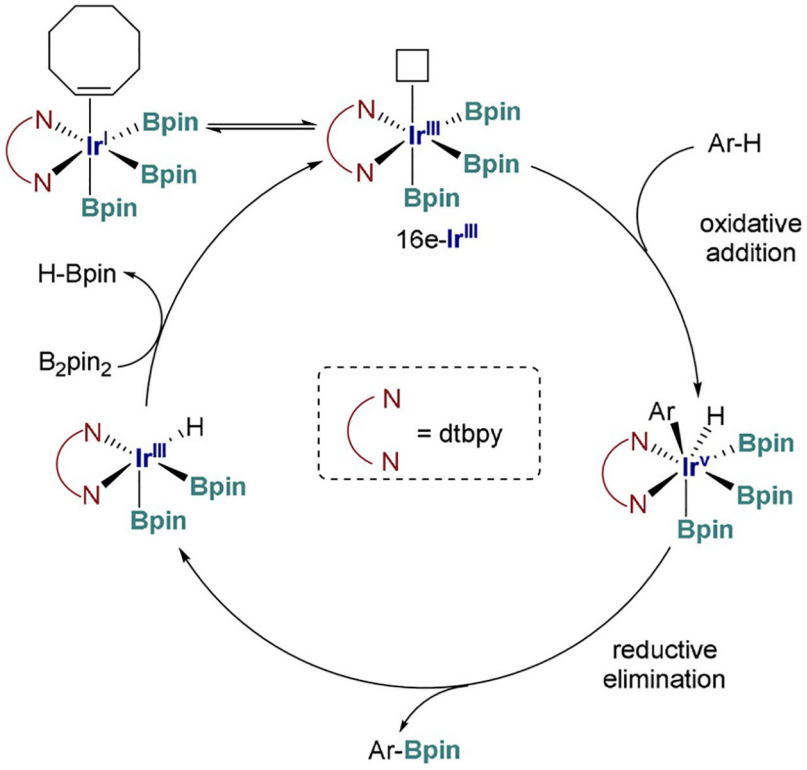

Figure 18.
A general catalytic cycle for the borylation of aryl C–H bonds catalyzed by an iridium catalyst containing a bipyridine ligand.

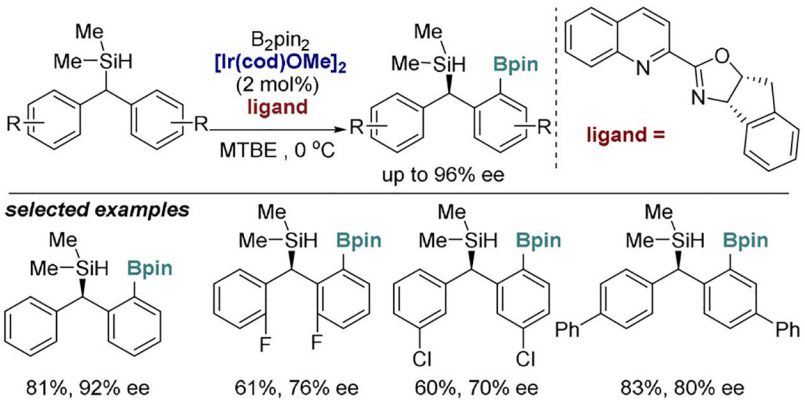

Figure 19.
Iridium-catalyzed silyl-directed enantioselective borylation of aryl C–H bonds.

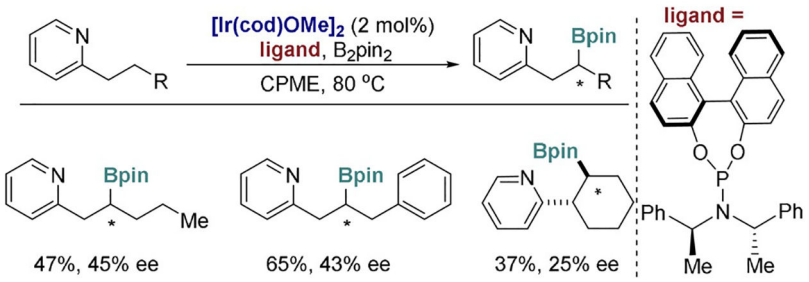

Figure 20.

Enantioselective borylation of β-C(sp^3)–H bonds of 2-alkyl-pyridines catalyzed by an iridium catalyst containing a monophosphoramidite ligand.

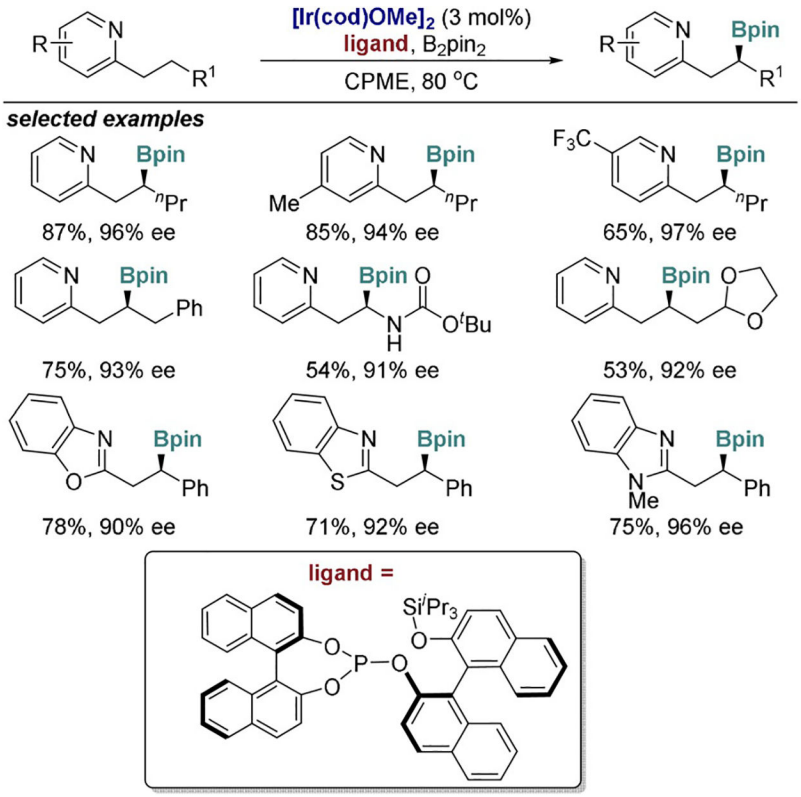

Figure 21.

Enantioselective borylation of β-C(sp^3)–H bonds of 2-alkyl-pyridines catalyzed by an iridium catalyst containing a monophosphite ligand.

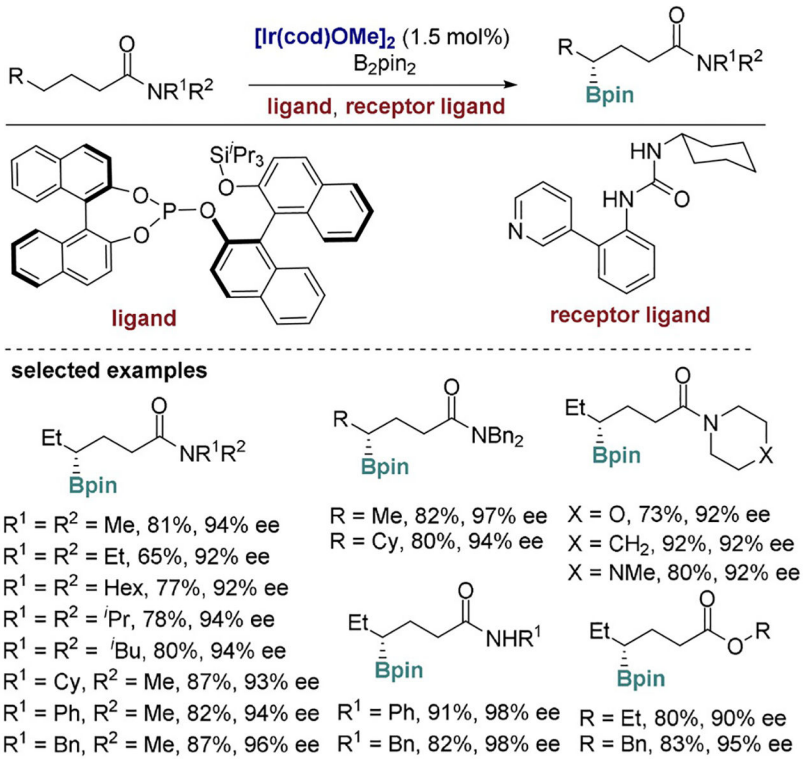

Figure 22.

Iridium-catalyzed enantioselective γ-C(sp^3)–H borylation of amides and esters.

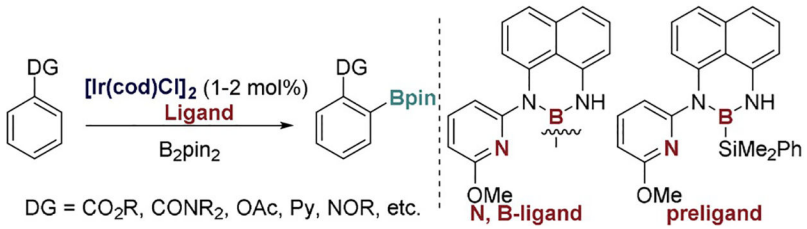

Figure 23.

Development of an N,B-ligand for directed borylation of aryl C–H bonds.

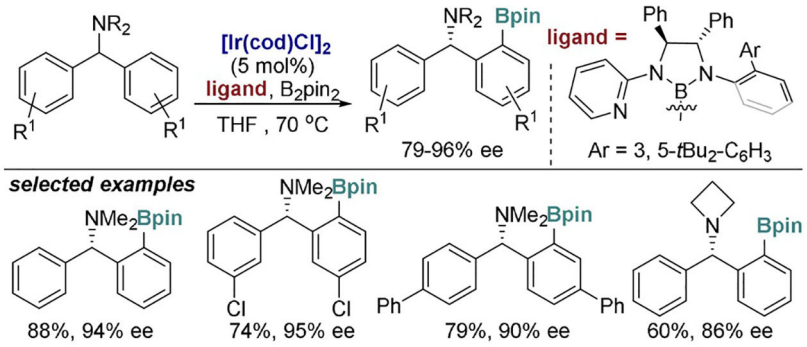

Figure 24.

Iridium-catalyzed desymmetrization of diarylmethyl amine derivatives by borylation of aryl C–H bonds.

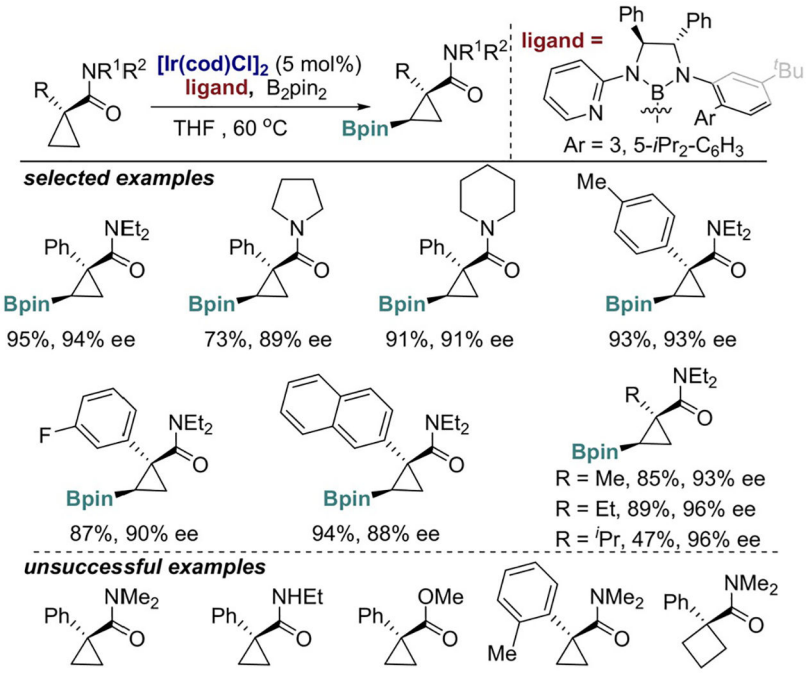

Figure 25.
Iridium-catalyzed enantioselective C(sp^3)–H borylation of cyclopropane derivatives.

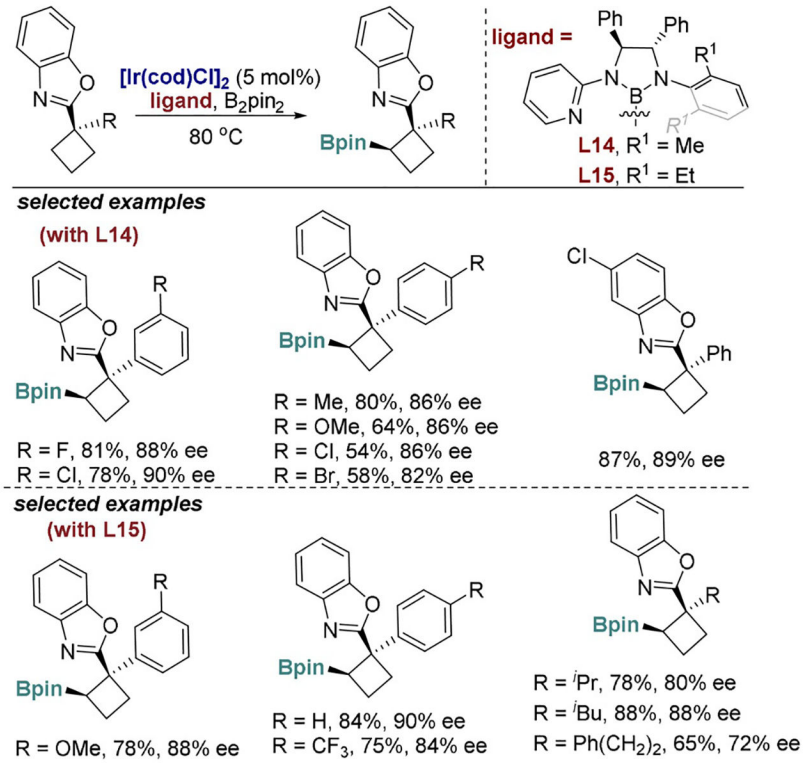

Figure 26.

Iridium-catalyzed enantioselective C(sp^3)–H borylation of cyclobutane derivatives.

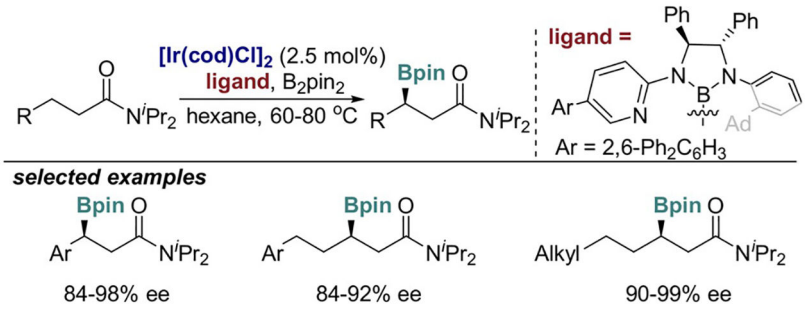

Figure 27.
Iridium-catalyzed enantioselective C(sp^3)–H borylation of amides.

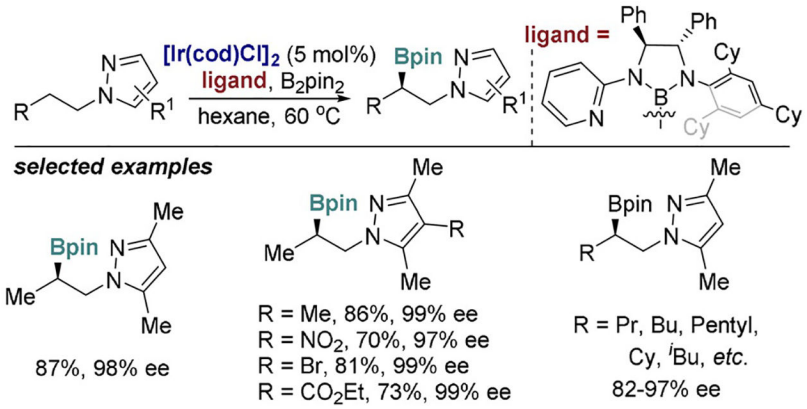

Figure 28.
Iridium-catalyzed enantioselective C(sp^3)–H borylation of pyrazoles.

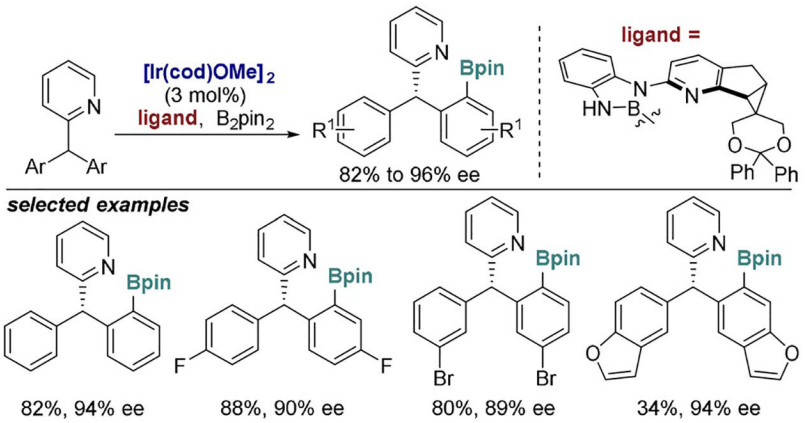

Figure 29.

Iridium-catalyzed desymmetrization of 2-pyridyl diarylmethane derivative by borylation of aryl C–H bonds.

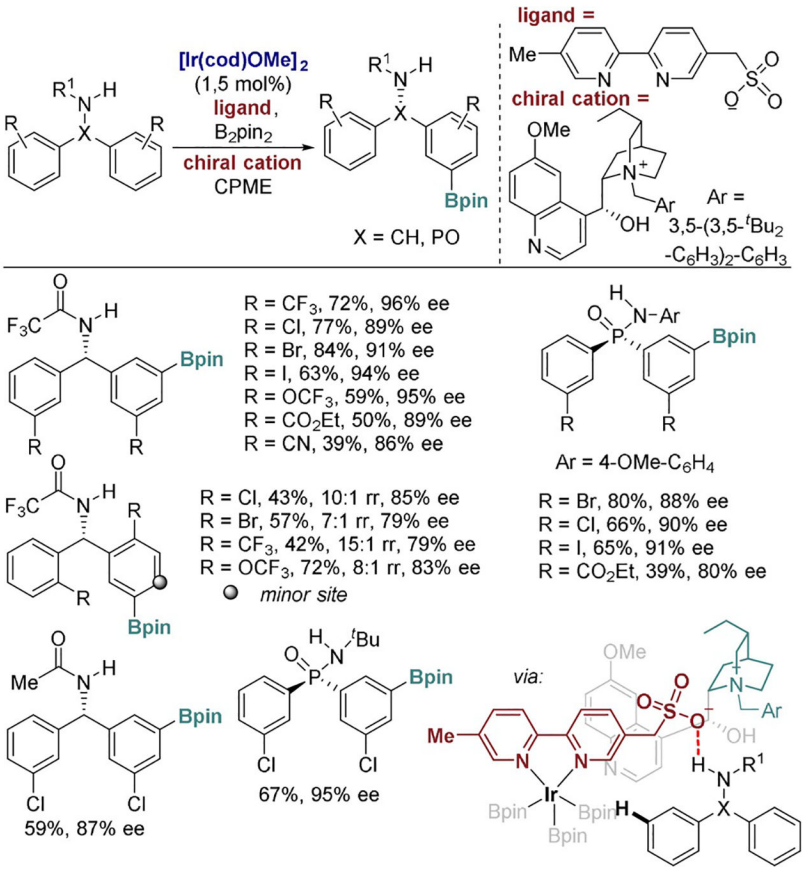

Figure 30.
Iridium-catalyzed enantioselective borylation of remote aryl C–H bonds.

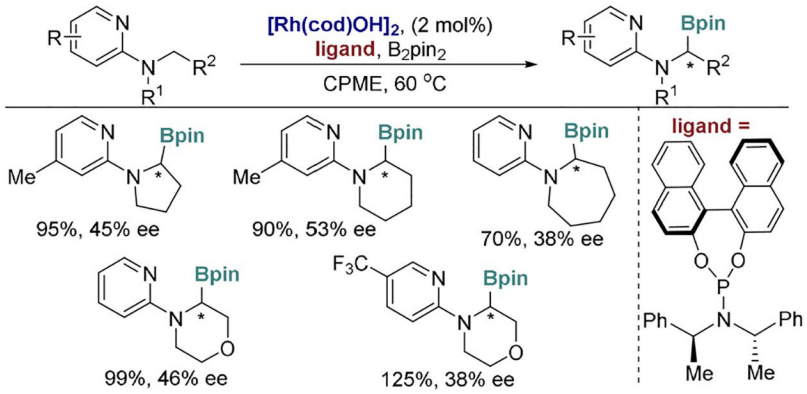

Figure 31.
Rhodium-catalyzed borylation of C(sp^3)–H bonds.

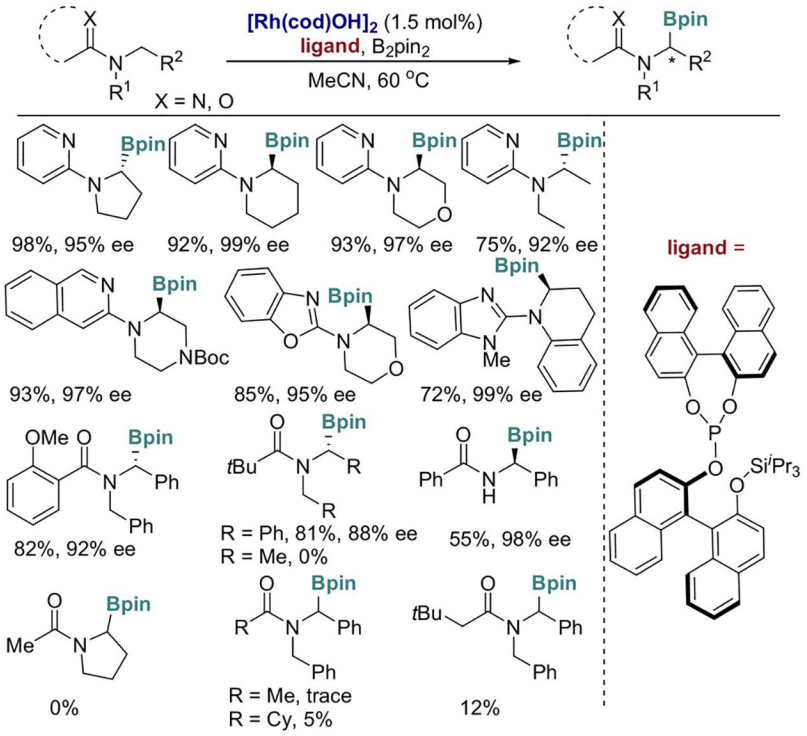

Figure 32.

Enantioselective borylation of C(sp^3)–H bonds at the position α to a nitrogen atom catalyzed by a rhodium monophosphate complex.

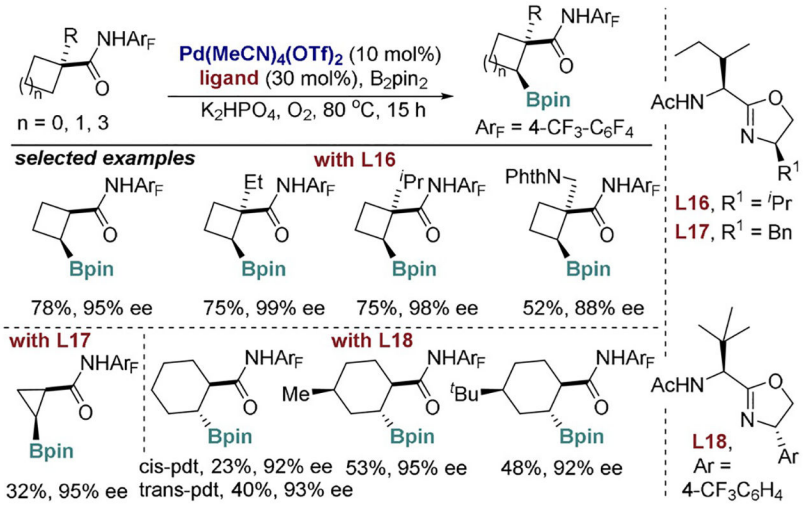

Figure 33.
Palladium-catalyzed borylation of C(sp^3)–H bonds.