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Review

Forging C–heteroatom bonds by transition-metal-catalyzed enantioselective C–H functionalization

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SUMMARY

Direct C–H functionalization has recently emerged as one of the most efficient strategies to access structurally complex molecules from readily accessible feedstocks in an atom- and step-economic manner. In particular, enantioselective C–H activation has garnered increasing attention by enabling chemists to efficiently assemble valuable chiral compounds by asymmetrically manipulating C–H bonds into useful functionalities. Apart from the extensively studied C–C bond formation, very few endeavors have been focused on the C–X formation analogs. Motivated by the utility of the latter approach in constructing academically and industrially important heteroatom-containing chiral compounds, we provide herein an overview on C–X forming asymmetric C–H activation reactions proceeding through C–H metalation. The advancements are organized according to the employed catalytic systems, which include Pd(II) catalysis, group-9 $Cp^{x}M(III)$ catalysis, monovalent group-9 metal catalysis, and multi-boryl/silyl Ir(III) catalysis, with emphasis on the design philosophy, mechanism, and mode of enantiocontrol.

INTRODUCTION

One of the central goals of modern organic chemistry is to construct complex molecules from readily accessible and abundant feedstocks. Transition metal-catalyzed C–H activation reactions hold great potential by making use of ubiquitous but otherwise inert C–H bonds as synthetic handles. During the past two decades, numerous novel methods have been developed in this vibrant research area, enabling the highly efficient and selective transformation of abundant and simple hydrocarbons into higher-value products in an atom and step-economic fashion.[1–5] These methods have also enabled the late-stage functionalization of structurally complex molecules and provided a range of unprecedented disconnections for retro-synthetic analysis, which has had a great impact on organic synthesis.[6–8] In particular, the development of asymmetric C–H functionalization reactions has allowed the efficient and diverse construction of valuable chiral molecules. Several approaches have been developed, including radical involved hydrogen atom abstraction,[9,10] metallocarbene or metallonitrene insertion,[11] and C–H metalation that generates a well-defined metal-carbon bond.[12–18]

Despite the robustness of the latter approach, most efforts have been focused on the construction of C–C bonds, leaving the C–heteroatom (C–X) bond formation far less studied.[12–18] This is striking when considering the ubiquity of heteroatom-containing chiral compounds in natural products, pharmaceuticals, agrochemicals, and materials, as well as versatile chiral building blocks. One of the major challenges in C–X forming asymmetric C–H activation reactions is that the enantiocontrol in asymmetric

The bigger picture

Transition-metal-catalyzed enantioselective C–H activation provides an efficient and atom-economic access to valuable chiral molecules from readily available feedstocks. The generation of minimized waste and the availability of unprecedented disconnection have significantly impacted organic synthesis. Considering the academic and industrial importance of heteroatom-containing chiral molecules, it is surprising that enantioselective C–H activation/C–heteroatom (C–X) bond-forming reactions are far less investigated than the C–C formation counterparts. In this review, we summarize the advances in C–X bond-forming asymmetric C–H activation proceedings through C–H metalation, organized based on the utilized catalytic systems.

C–H activation might be dramatically influenced by the large number of competitive coordination anions. These anions could be *in situ* generated by oxidants/electrophilic functionalization reagents (e.g., $PhI(OAc)_2$, Ac_2O/I_2, *N*-fluorobenzenesulfonimide (NFSI) etc.), which are typically required in large amount for C–X formations. As a result, previously established catalytic systems are limited to the construction of only a few types of C–X bonds from specific C–H bonds. Nevertheless, recent research endeavors on this topic have led to the assembly of optically active products bearing various types of chirality (such as central, axial, and planar chirality) by manipulating otherwise inert C–H bonds into a range of C–X bonds (such as C–B, C–N, C–O, C–F, C–Si, C–Ge, and C–I bonds) in an enantioselective fashion. In this tutorial review, we try to provide an overview of the advancements in C–X bond-forming catalytic asymmetric C–H activation proceeding through C–H metalation. Asymmetric C–H functionalization reactions via outer-sphere mechanism[9–11] and Pd-catalyzed asymmetric allylic C–H functionalizations proceeding through [(π-allyl)Pd] intermediates[19] will not be included. The achievements are organized according to the catalytic systems characterized by transition metals and chiral ligands. These include Pd(II) catalysis, group-9 $Cp^xM(III)$ catalysis, monovalent group-9 metal catalysis and multi-boryl/silyl Ir(III) catalysis (Figure 1). Emphasis would be placed on the mechanisms and modes of chiral induction. We believe that such a classification would be beneficial for a better understanding of the design philosophy, application, and limitations of each catalytic system.

Pd(II) CATALYSIS

Pd(II)-catalyzed C–H functionalization is arguably the most well-investigated reaction in the field of C–H activation.[2–4] However, enantioselective C–H functionalization based on this strategy is predominantly focused on C–C bond formation. A formidable challenge lies in that Pd(II)-catalyzed C–H activation/C–X bond formation generally requires the use of excess strong oxidants (e.g., $PhI(OAc)_2$, $BzO\text{-}NR_2$) and/or inorganic bases. These components could generate large amount of coordinating counter anions that compete with chiral ligands during the enantio-determining step, resulting in racemic background reaction and eroded chiral induction. To date, only a handful of examples of Pd(II)-catalyzed asymmetric C–H activation/C–X formation reactions have been developed.

Mono-N-protected amino acid (MPAA)

In 2008, Yu and co-workers reported the first Pd(II)-catalyzed enantioselective C–H alkylation of both $C(sp^2)$–H and $C(sp^3)$–H in pyridine-containing compounds using mono-*N*-protected amino acid (MPAA) as chiral ligands.[20] This has triggered the prosperity of MPAA enabled Pd(II)-catalyzed asymmetric C–H activation reactions, including several C–X formation variants.[21]

In 2013, Wang, Yu, and co-workers reported a Pd(II)-catalyzed enantioselective intramolecular $C(sp^2)$–H activation/C–O forming reaction enabled by *N*-Boc-Ile-OH ligand (**MPAA-1**) based on desymmetrization strategy (Figure 2A).[22] The reaction was carried out in the presence of excess $PhI(OAc)_2$ oxidant, representing the first example of enantioselective C–H functionalization through Pd(II)/Pd(IV) catalysis. The remarkably high reactivities and enantioselectivities could be predominantly ascribed to two facts: (1) the competitive coordination of acetate anion that hampers the enantioselectivity was minimized because the coordinating ability of such monodentate component is relatively lower than the bidentate MPAA-type chiral ligands; (2) **MPAA-1** was used in relatively high loading (40 mol % of ligand for 5 mol % of $Pd(OAc)_2$ catalyst) in most examples to compete over excess acetate. Various

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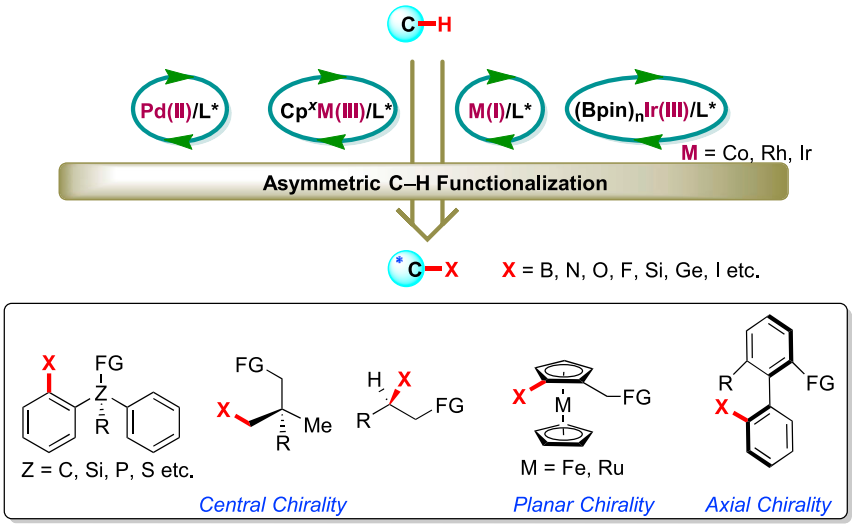

Figure 1. Formation of C–X bonds by transition metal-catalyzed asymmetric C–H functionalization

α-quaternary carbon-containing biarylacetic acids were compatible, furnishing chiral γ-lactones in moderate to good yields with high enantioselectivities (89% to 96% ee).

MPAA ligands have also enabled the enantioselective C–H iodination based on both desymmetrization and kinetic resolution strategies (Figure 2B). In 2013, the Yu group pioneered an enantioselective C–H iodination through desymmetrization of trifluoromethanesulfonyl-protected diarylmethylamines.[23] In this mild iodination protocol (30°C), iodine was used as both the iodination reagent and the sole oxidant (Figure 2B; Equation 1). The high degree of chiral induction was ascribed to the judicious choice of *N*-Bz-Leu-OH (**MPAA-2**) as ligand and the combination of CsOAc and Na_2CO_3. The influence of competing coordination anions in inorganic bases was minimized by the increased ligand loading (40 mol %) and the addition of DMSO co-solvent (15 equiv). DMSO was proposed to suppress the racemic background reaction by sequestering the small portion of chiral ligand free Pd species. The protocol has further enabled the kinetic resolution of racemic benzylamines, affording highly enantioenriched iodinated products and substrates in up to 244 selectivity factors (*s* factor, Figure 2B; Equation 2).[24] Meanwhile, You and co-workers developed the kinetic resolution of quinoline-*N*-oxides through Pd(II)-catalyzed asymmetric C–H iodination, using **MPAA-3** as chiral ligand (Figure 2B; Equation 3, *s* factors, 4.1 to 27).[25] This method features a rare example of constructing axial chirality through C–H activation/C–X formation.

Mechanistic studies in related work indicate that MPAA acts as a bidentate dianionic ligand.[21,26,27] The amidate moiety in MPAA participates in the concerted-metalation deprotonation (CMD) process, while the side chain of the amino acid provides the source of chirality and affects the bite angle. The enantioselective C–H cleavage was proposed to proceed through a transition state with minimized repulsion between the substrate and amino acid side chain (Figure 2C, **TS-2A**).

Acetyl-protected aminomethyl oxazoline (APAO)

Based on the structure of MPAA, Yu and colleagues developed a class of bidentate acetyl-protected aminomethyl oxazoline (APAO) ligands for Pd(II)-catalyzed asymmetric C(sp^3)–H arylation, alkenylation, and alkynylation.[28] Beyond these Pd(II)/

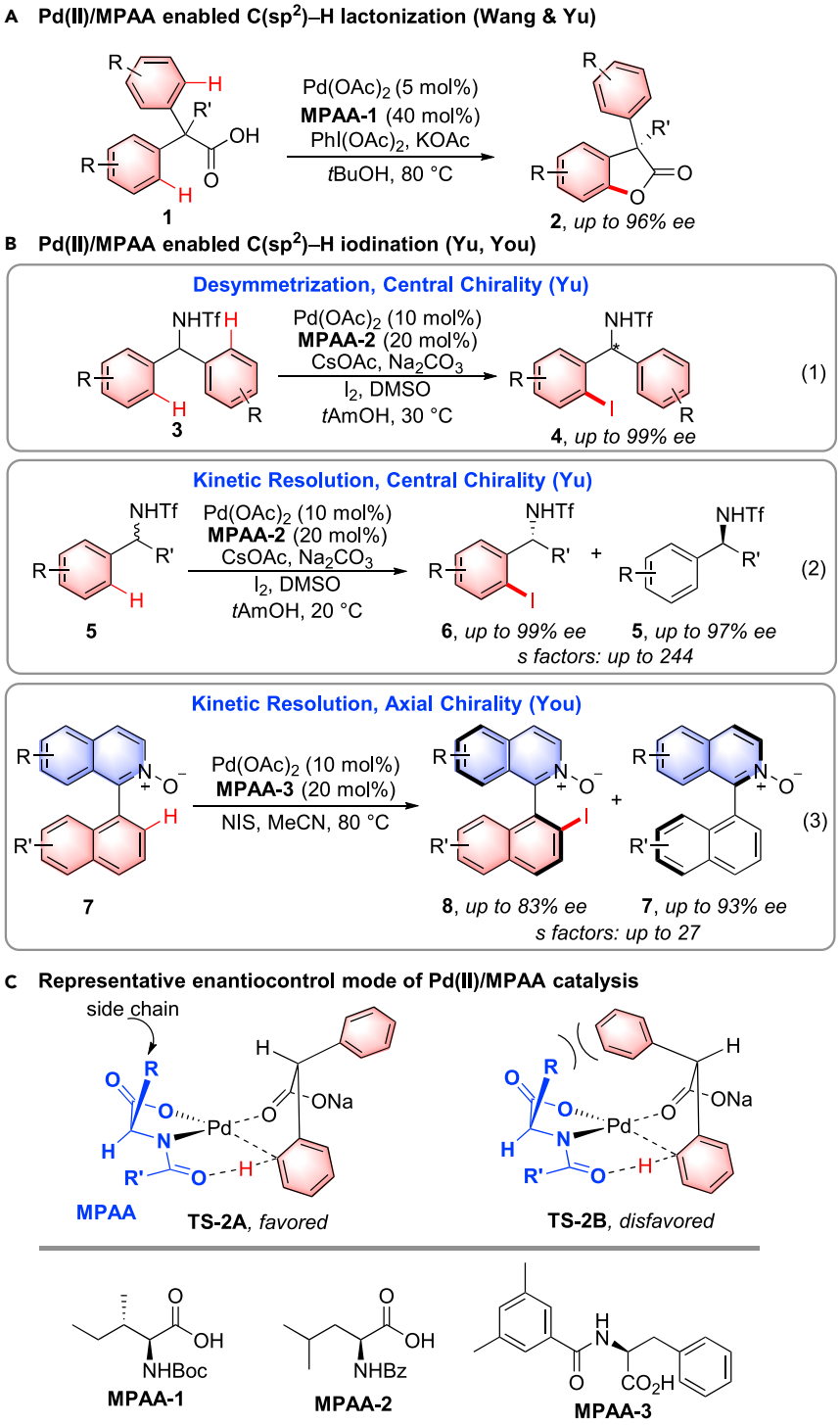

Figure 2. Pd(II)-catalyzed asymmetric C–H functionalization with MPAA ligands

(A) Pd(II)/MPAA enabled C(sp^2)–H lactonization.

(B) Pd(II)/MPAA enabled C(sp^2)–H iodination.

(C) Representative enantiocontrol mode of Pd(II)/MPAA catalysis.

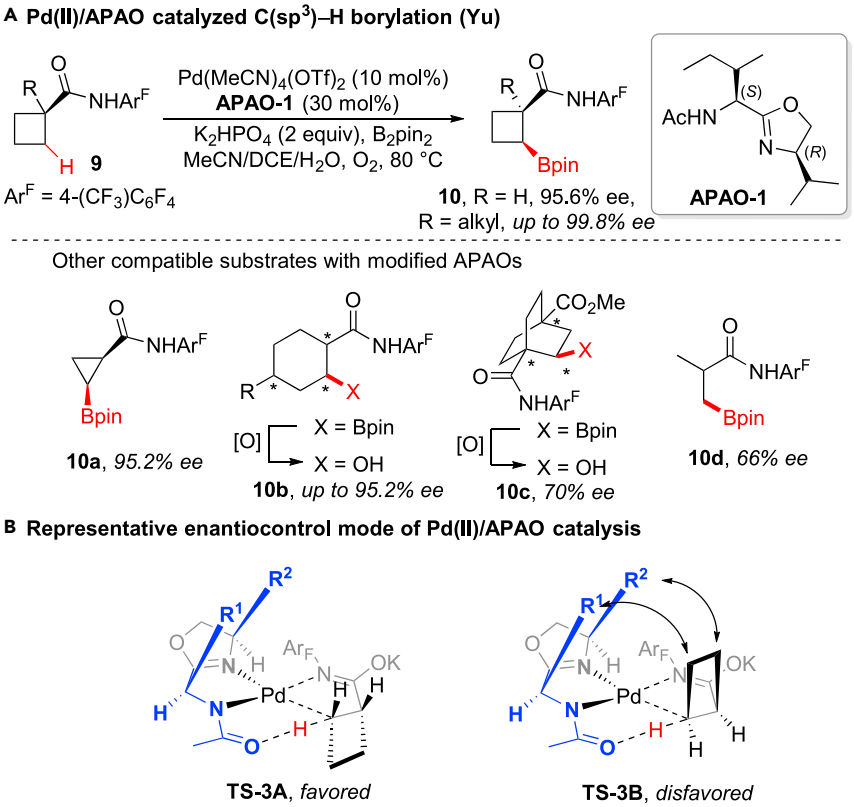

Figure 3. Pd(II)-catalyzed asymmetric C(sp^3)–H borylation with APAO ligands

(A) Pd(II)/APAO catalyzed C(sp^3)–H borylation.

(B) Representative enantiocontrol mode of Pd(II)/APAO catalysis.

Pd(IV) process, they further applied APAOs to the asymmetric C(sp^3)–H borylation that underwent Pd(II)/Pd(0) catalytic cycle (Figure 3).[29] A range of borylated cyclobutanecarboxylic amides were obtained in good yields with excellent enantioselectivities (up to 99.8% ee). Interestingly, α-alkyl substitution at the amide could slightly enhance the enantioselectivity. Utilization of ligands lacking a stereogenic center on either the oxazoline motif or the side chain only led to decreased reactivity and enantioselectivity. The crucial role of both chiral centers on the APAO ligand backbone was explained by an enantiocontrol mode shown in Figure 3B. This protocol was also expanded to include the desymmetrization of other cyclic systems (e.g., cyclopropane and cyclohexane), as well as *gem*-methyl groups of acyclic aliphatic amides. Crucial to this success is the adjustment of the steric hindrance and relative configuration of the two chiral carbons within the ligands. The enantioenriched borylation products could be readily transformed into fluoro-, hydroxyl-, and aryl-containing compounds without erosion of chirality.

1,1′-Bi-2-naphthol (BINOL)

Enantioselective functionalization of unbiased methylene C(sp^3)–H bonds has been a longstanding challenge in asymmetric synthesis.[30,31] In 2018, Shi and co-workers reported the first strongly coordinating bidentate directing group (DG) enabled Pd(II)-catalyzed enantioselective arylation of unbiased methylene C–H bonds.[32] The key to the success was the combination of their previously established 2-pyridinylisopropyl (PIP) DG with non-C_2 symmetric chiral phosphoric acid ligands.[32] They further identified 3,3′-disubstituted BINOLs as a type of more readily accessible and efficient chiral

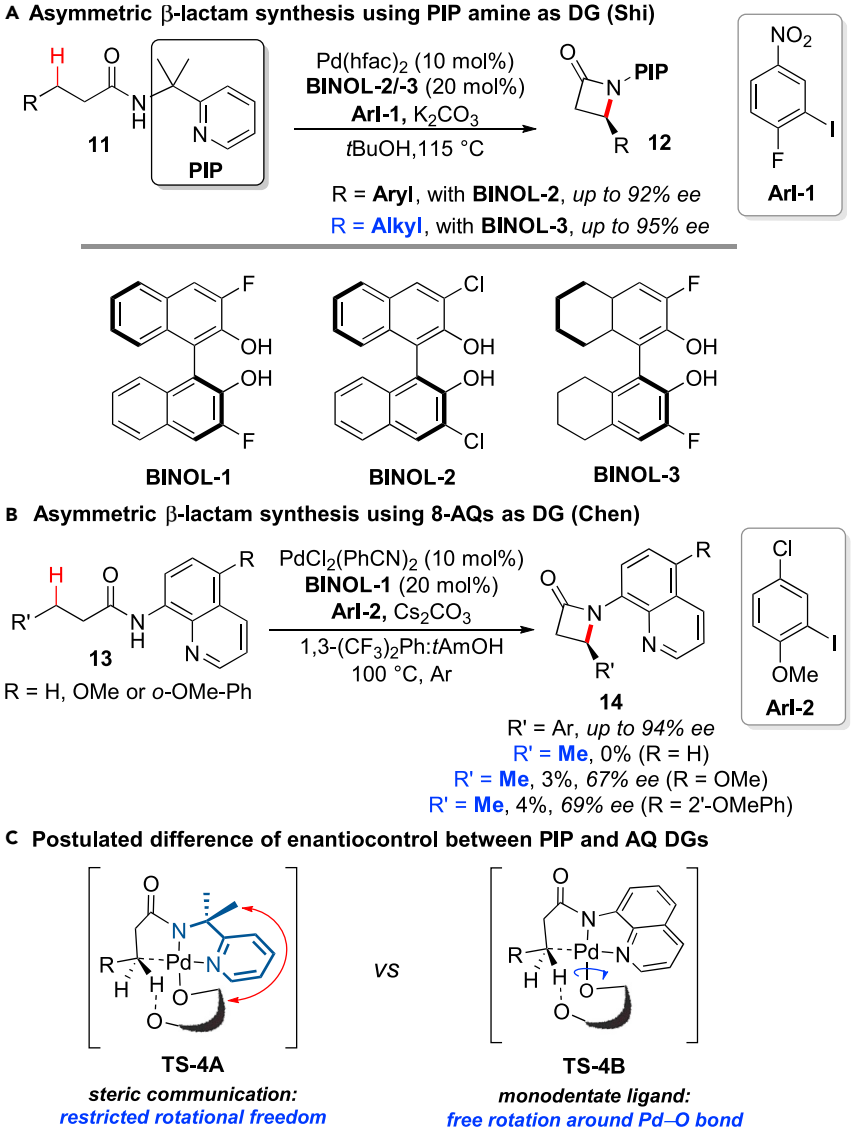

Figure 4. Pd(II)-catalyzed intramolecular asymmetric C(sp^3)–H amidation with BINOL-derived ligands

(A) Asymmetric β-lactam synthesis using PIP amine as DG.

(B) Asymmetric β-lactam synthesis using 8-AQs as DG.

(C) Postulated difference of enantiocontrol between PIP and AQ DGs.

ligands, which found its broad application in highly enantioselective alkynylation, alkenylation/aza-Wacker cyclization, and inter-/intramolecular arylation of unbiased methylene C(sp^3)–H bonds.[33,34] Very recently, the groups of Shi[35] and Chen[36] independently developed Pd(II)-catalyzed intramolecular enantioselective C(sp^3)–H amidation using 3,3′-disubstituted BINOL ligands enabled by bidentate DGs, streamlining the synthesis of a series of chiral β-lactams (Figure 4). Judicious choice of Pd(II) catalyst, iodoarene oxidants and bidentate DGs was crucial for the remarkable reaction performance. Although Chen's choice of 8-aminoquinoline-derived DGs delivered good yields and high enantioselectivities exclusively for benzylic methylene C(sp^3)–H bonds, both benzylic and unbiased methylene C(sp^3)–H bonds are compatible with Shi's system using PIP DG. The improved enantioselectivity for aliphatic

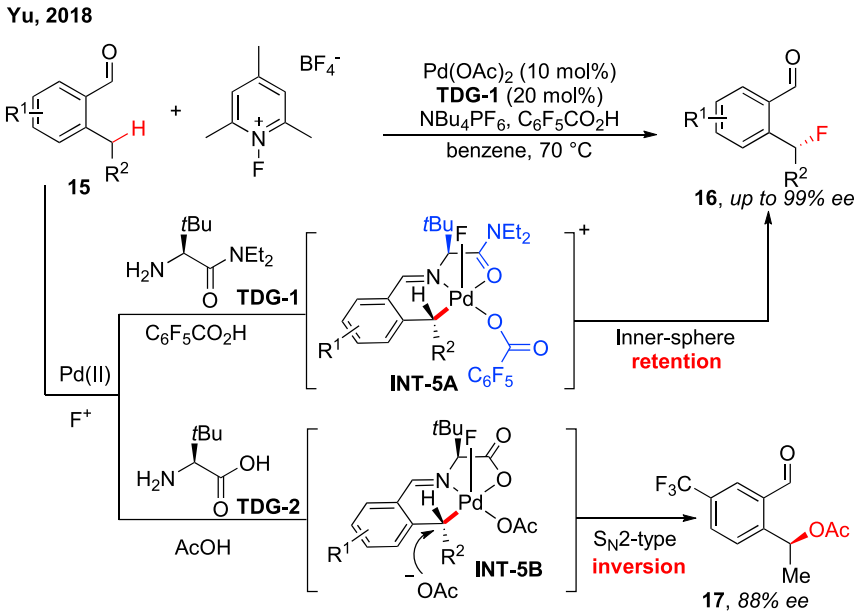

Figure 5. Pd(II)-catalyzed asymmetric C(sp^3)–H fluorination enabled by chiral TDG strategy

substrates in the latter case might be a result of steric communication between the *gem*-dimethyl moiety of PIP DG and the backbone of the chiral ligands (Figure 4C).[34]

Transient directing group (TDG)

Transient directing group (TDG) has recently emerged as an appealing strategy to improve the overall atom- and step-economy of transition-metal-catalyzed C–H activation. The reversible installation and removal of TDG allows the use of native substrates without the tedious installation and removal of external DGs. Additionally, the utilization of chiral TDG has brought new opportunities to catalytic asymmetric C–H activation,[37,38] as exemplified by the pioneering work of Yu and co-workers on enantioselective C–H arylation of 2-alkyl-benzaldehydes with *L-tert*-leucine as TDG.[39] Based on the same strategy, they further established the enantioselective fluorination of benzylic C(sp^3)–H bonds (Figure 5).[40] This was particularly challenging due to the sluggish C(sp^3)–F reductive elimination (RE) from Pd(IV) intermediates. The chemoselectivity and enantioselectivity were improved by increasing the side-chain bulkiness of TDG and utilizing $C_6F_5CO_2H$ in the place of acetic acid. More importantly, the replacement of chiral amino acid TDGs with the corresponding diethylamides generated a cationic Pd(IV) species, which strongly favors C(sp^3)–F RE over undesired C–O formation pathway. The opposite absolute configuration of the enantioenriched C–O formation by-product with the fluorinated product was explained by two distinct mechanisms. The former was supposed to be generated via S_N2-type RE, whereas the latter was a result of inner-sphere RE. A series of *ortho*- or *meta*-occupied *o*-alkyl benzaldehydes bearing electron-deficient substituents were fluorinated in moderate to good yields and high enantioselectivities (up to 99% ee). Importantly, the resulting *ortho*-fluorinated product could be transformed into diverse C–N, C–O, and C–S bonds, which greatly enriched the synthetic diversity of this protocol.

GROUP 9 $Cp^xM(III)$ CATALYSIS

Ever since the independent elegant work by the Cramer[41] and Rovis[42] groups in 2012, enantioselective C–H functionalization based on $Cp^xM(III)$ catalysis have

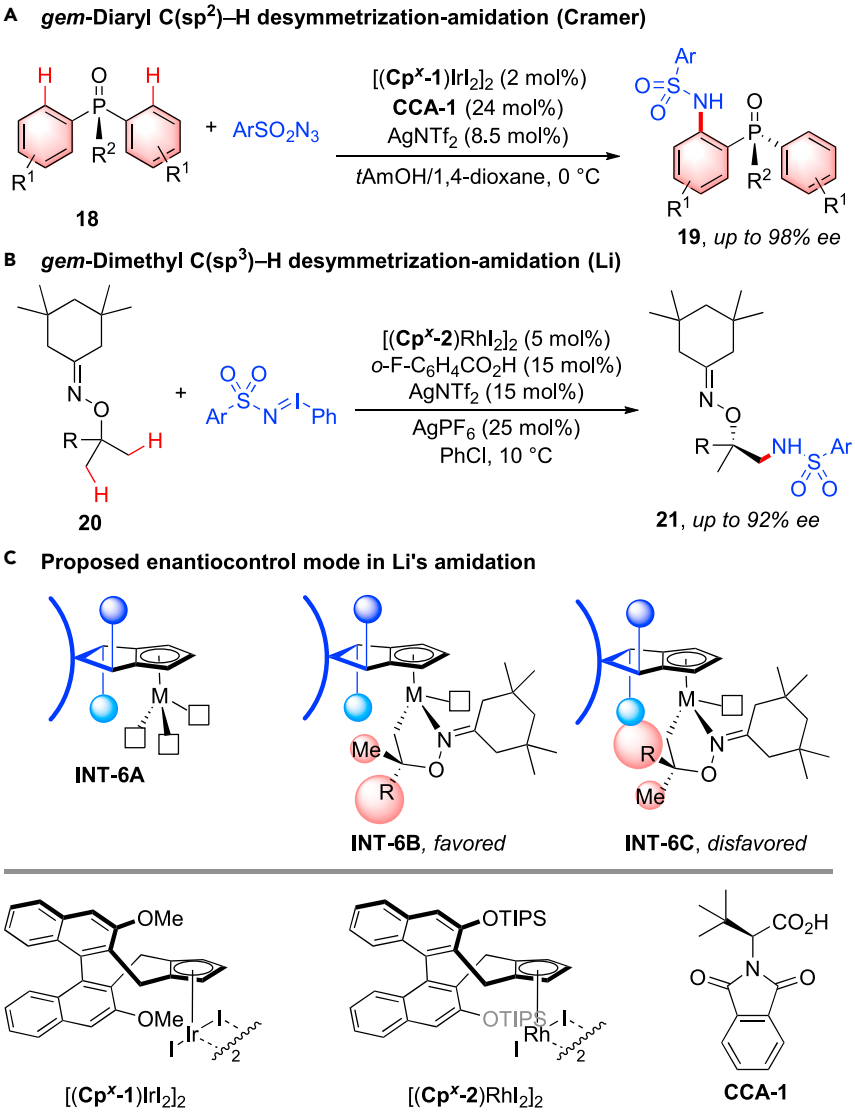

Figure 6. Chiral Cp^{x}M(III)-catalyzed asymmetric C–H amidation

(A) gem-Diaryl C(sp^2)–H desymmetrization-amidation.

(B) gem-Dimethyl C(sp^3)–H desymmetrization-amidation.

(C) Proposed enantiocontrol mode in Li's amidation.

been extensively studied.[17,43–46] Thus far, two types of chiral catalytic systems have enabled the asymmetric C–H activation/C–X formation, namely, the use of chiral Cp^x ligands[43,46] and the combination of achiral Cp^{x}M(III)/chiral carboxylic acid (CCA) ligands.[17] To note, these advancements are limited to C–N bond formation using nitrene precursors (such as azides, oxazolones, and iodonium imides) as the amidation reagent.

Chiral Cp^{x}M(III) catalysis

Although the history of chiral Cp^x could be dated back to 1978, asymmetric transformations enabled by such chiral scaffolds have experienced a long-term lethargy due to the low level of enantiocontrol. This situation was changed in 2012, when the Cramer[41] and Rovis[42] groups independently developed Rh(III) catalyzed asymmetric

C–H functionalization by designing a novel chiral Cp^x ligand and artificial metalloenzymes, respectively. To date, various chiral Cp^x ligands based on different skeletons have been developed, leading to transition metal catalysts with three labile coordination sites (Figure 6C, **INT-6A**) and a persistent chiral environment throughout the catalytic cycle.[43–46] Numerous C–C formation reactions involving stereochemistry determining migratory insertion processes have been developed with these ligands. On the contrary, asymmetric C–X formation that calls for stereo-determining C–H cleavage is much less developed.

In 2017, Cramer and co-workers developed the asymmetric C–H amidation of diarylphosphine oxides with sulfonyl azides using synergistic catalysis (Figure 6A).[47] The enantiotopic carbons in the substrates were differentiated in the presence of chiral **Cp^x-1** and *N*-Phth-Tle-OH (**CCA-1**), affording phosphine-stereogenic products with high efficiency and enantiopurity (up to 99:1 er). Replacement of **CCA-1** with its (*R*)-enantiomers resulted in diminished reactivities and enantioselectivities, indicating a strong matched-mismatched effect between chiral Cp^x and the CCA ligand. Moreover, the products could be stereo-retentively reduced to the corresponding chiral phosphines.

Besides combining with CCA, Li and co-workers recently demonstrated that proper achiral acids could also enhance the chiral induction of chiral Cp^xM(III) catalysis.[48] In their work on chiral Cp^xRh(III)-catalyzed C(sp^3)–H amidation through desymmetrization of *gem*-dimethyl group, the employment of *o*-fluoro-benzoic acid rather than CCA was crucial for the chiral induction (Figure 6B).[48] Other key factors were the utilization of bulky oximine DG, the introduction of a bulky substituent on the prochiral carbon center, and the employment of highly reactive iodonium imides as the *N*-source. This method provides an efficient access to chiral α-methyl β-amino alcohols. Mechanistic studies revealed that C–H activation is the rate-determining step and is irreversible. An enantiocontrol mode that well explains the absolute configuration of the products was proposed, in which the unreacted methyl group was disposed closer to the blocking group of chiral **Cp^x-2** (Figure 6C, **INT-6B**).

Achiral Cp^xM(III) with CCA ligands

The introduction of CCAs into achiral Cp^xM(III)-catalyzed asymmetric C–H functionalization was first demonstrated by Chang in 2015.[49] Based on their mechanistic studies on the C–H amidation of diarylphosphine oxides, a plausible mechanism involving a cationic Cp*Ir(III) monocarboxylate species as the active catalyst for C–H cleavage was proposed (Figure 7B). This has motivated them to pursue an asymmetric version by employing a chiral *O*,*O*-dipivaloyl-*L*-tartaric acid (Figure 7A, **CCA-2**). Although only a maximum of 32% ee was obtained, this seminal work has paved the way for synthetically meaningful achiral Cp^xM(III)/CCA-catalyzed asymmetric C–H activation, with pioneering contributions from the Yoshino and Matsunaga group,[17,45,50–55] the Ackermann group,[56] and our group.[57,58]

In 2019, the Matsunaga group reported the first cobalt-catalyzed enantioselective C(sp^3)–H amidation.[52] A range of thioamides were readily amidated with dioxazolones in good yields and enantioselectivities in the presence of a bulky *t*-butyl cyclopentadienyl (Cp^{*tBu}) ligated Co(III) catalyst and an (*S*)-H_2-BHTL (**CCA-3**) ligand (Figure 7C, up to 96:4 er). Compared with the commonly encountered Cp*Co(III) catalyst, the sterically more hindered Cp^{*tBu}Co(III) catalyst delivered improved enantioselectivity, probably through enhanced steric communication. They further reported an alternative approach using a chiral 2-aryl ferrocene carboxylic acid ligand (**CCA-4**) with less pronounced enantioselectivity (up to 85:15 er).[54]

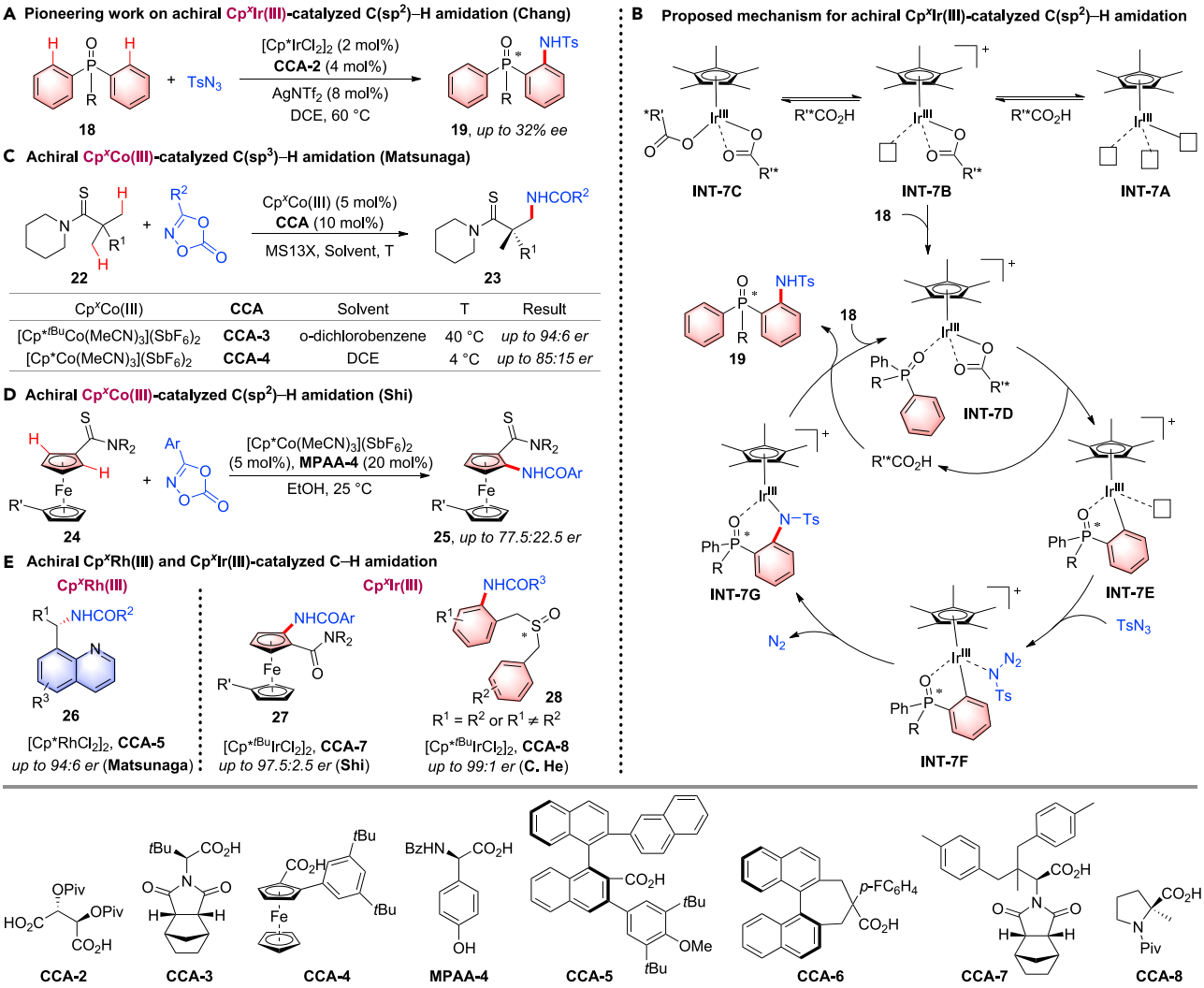

Figure 7. Achiral Cp^{x}M(III)/CCA-catalyzed asymmetric C–H amidation

(A) Pioneering work on achiral Cp^{x}Ir(III)-catalyzed C(sp^2)–H amidation.

(B) Proposed mechanism for achiral Cp^{x}Ir(III)-catalyzed C(sp^2)–H amidation.

(C) Achiral Cp^{x}Co(III)-catalyzed C(sp^3)–H amidation.

(D) Achiral Cp^{x}Co(III)-catalyzed C(sp^2)–H amidation.

(E) Achiral Cp^{x}Rh(III) and Cp^{x}Ir(III)-catalyzed C–H amidation.

In the same year, the Shi group established the construction of planar chirality by the achiral Cp*Co(III)/MPAA-catalyzed enantioselective C–H amidation of ferrocene-derived thioamides with dioxazolones (Figure 7D).[57] MPAA ligands were proven inferior to *N*-phthaloyl-protected amino acids in promoting enantiocontrol, among which *N*-benzyol-protected *D*-*p*-hydroxylphenylglycine (**MPAA-4**) was optimal. Although only moderate enantioselectivities were obtained, subsequent recrystallization of a representative product afforded the (S_p)-product in >99% ee and an overall yield of 40%.

Matsunaga and co-workers elegantly demonstrated that the combination of the achiral Cp^{x}Rh(III) catalyst with a novel type of binapthyl-based CCA could enable the asymmetric C–H amidation of 8-alkylquinolines (Figure 7E).[53] The optimized ligand **CCA-5**, modularly synthesized in 5 steps, was efficient for the challenging

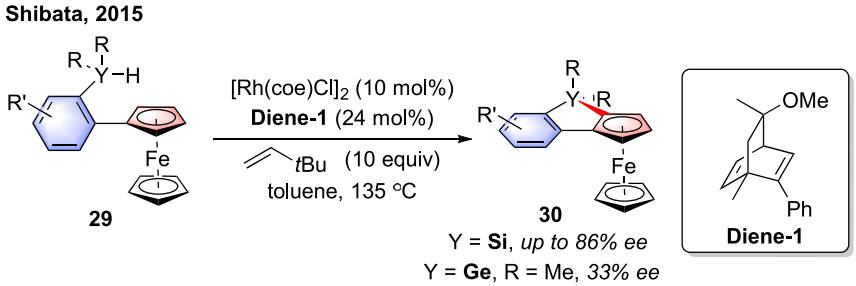

Figure 8. Rh(I)-catalyzed asymmetric C(sp^2)–H silylation and germination with chiral diene ligands

differentiation of enantiotopic benzylic methylene C(sp^3)–H bonds. Various functional groups with respect to both 8-alkylquinolines and dioxazolones are amenable with this method, affording the target amination products in good yields and enantioselectivities (up to 98% yield and 94:6 er) at low temperatures (4°C). Recently, they also developed a new type of pseudo-C_2-symmetric tunable ligand with a binaphthyl backbone (**CCA-6**), which is efficient for Cp*^{tBu}Rh(III)-catalyzed enantioselective C(sp^3)–H amidation of 2-alkylpyridines via desymmetrization of *gem*-dimethyl group.[55]

Compared with the Co(III) and Rh(III) catalysis, the development of achiral Cp^{x}Ir(III)/CCA catalysis was left far behind, despite the promising results in Chang's pioneering work.[49] Recently, Shi and co-workers reported the first achiral Cp*^{tBu}Ir(III)/CCA-catalyzed C–H amidation of ferrocene carboxamides, a type of inferior substrates in their previous Co(III) catalysis (Figure 7D).[58] Steric hindrance of both the *N*-protecting group and side chain of the amino acid-derived CCAs is crucial for the high enantioselectivity. To note, the optimal ligand **CCA-7** bearing increased side-chain bulkiness could be prepared via a single-step manipulation of (*S*)-H_2-BHTL (**CCA-3**) using their previously established Pd(II)-catalyzed γ-C(sp^3)-H arylation.[59] In the meantime, the C. He group independently developed a Cp*^{tBu}Ir(III)-catalyzed enantioselective C–H amidation of dibenzyl sulfoxides.[60] A range of sulfur-stereogenic sulfoxides were obtained in high enantioselectivities through either desymmetrization (Figure 7E, **28**, $R^1 = R^2$) or parallel kinetic resolution ($R^1 \neq R^2$). The key to their success was the employment of a bulky pivaloyl-protected methyl proline ligand (**CCA-8**).

MONOVALENT GROUP-9 METAL CATALYSIS

Monovalent group-9 metals, including Co(I), Rh(I), and Ir(I), are amenable to insert into C–H bonds through oxidative addition in the presence of proper neutral ligands.[61] To date, two classes of bidentate neutral chiral ligands, including chiral dienes and bisphosphine ligands, have been discovered to promote asymmetric C–H functionalization through such a process.

Chiral diene ligand

Olefins have the ability to form metal–alkene complexes by donating their π-electrons to an empty orbital of the metal, while accepting the back donation of the metal electrons to their antibonding π* orbitals at the same time. This has led to the development of chiral diene ligands for asymmetric catalysis. Although multiple substituents are generally presented to stabilize these ligands, their relatively active nature has hampered their broad application in asymmetric C–H activation.[62,63] In 2015, the group of Shibata established the first synthesis of planar chiral benzosiloloferrocenes through Rh(I)-catalyzed asymmetric intramolecular C(sp^2)–H silylation

(Figure 8).[64] The employment of Carreira's chiral **diene-1** ligand and a bulky H_2 acceptor (3,3-dimethylbut-1-ene) are vital for the high chemo- and enantioselectivity. To note, the H_2 acceptor is required in large excess to guarantee high enantioselectivities, probably by inhibiting undesired hydrogenation of the chiral diene ligand. The reaction is sensitive to the steric hindrance of the directing atom, as reflected by the significantly decreased ee in cases of sterically more demanding silyl groups and larger germyl counterparts.

Chiral bisphosphine ligand

Chiral bisphosphine ligands are both good σ-donors and π-acceptors. They represent one of the most privileged types of chiral ligands for transition-metal-promoted asymmetric catalysis. These well-documented and easily accessible chiral scaffolds are tunable in terms of chirality types, basicity, and steric hindrance. The combination of these ligands with monovalent group-9 metals results in chiral catalysts with high electron density that enable both hydrosilyl-directed intramolecular C–H silylation[65,66] and aldehyde C–H activation/ketone hydroacylation.[67]

Intramolecular C–H silylation of hydrosilanes

In 2013, Takai and colleagues reported an enantioselective C–H silylation that gave rise to axially chiral spiro-9-silabifluorenes (Figure 9A).[68] In the presence of Rh(I)-catalyst and (*R*)-1.1′-binaphthyl-2.2′-diphenyl phosphine (*R*-BINAP) ligand (**PP-1**), the dihydro bis(biphenyl)silanes underwent double-dehydrogenative cyclization to afford chiral spiro scaffolds in high yield and moderate level of enantiocontrol. In their proposed mechanism, the chirality of products is determined during the first dehydrogenative cyclization.[68,69] This has inspired a recent boost in SiH_2-steered enantioselective intramolecular C–H silylation of dihydrosilanes toward the construction of silicon-stereogenic silanes.

In 2020, C. He and co-workers established an enantioselective C(sp^2)–H silylation/olefin hydrosilylation sequence for the construction of quaternary silicon-stereogenic chiral silanes (Figure 9B).[70] The reaction of biaryl dihydrosilanes with bulky olefins (such as 3,3-dimethylbut-1-ene) occurred smoothly in the presence of (*R*,*Sp*)-Josiphos (**PP-6**). Further expansion of this protocol to the metallocene system relied on the utilization of (*R*)-Segphos (**PP-3**). In contrast to the case of biaryl dihydrosilanes, sterically less demanding olefins (including linear aliphatic alkenes and vinyl ethers) are well applicable, indicating the enhanced priority of SiH_2-steered C–H activation/silylation over the alkene hydrosilylation process for metallocene substrates. Based on their mechanistic experiments and preliminary calculations, a mechanism involving an enantio-determining dehydrogenative cyclization process and a subsequent stereospecific hydrosilation was suggested (Figure 9C). This strategy was further applied to methyl C(sp^3)–H activation, giving rise to a range of silicon-stereogenic dihydrobenzosiloles. (**37**)[71]

The enantioselective preparation of monohydrosilanes via C–H silylation appears to be more challenging due to the remaining highly reactive Si–H bonds, as indicated by the poor yields obtained in Takai's and C. He's mechanistic studies.[69,70] Recently, the group of W. He accomplished this goal by replacing the aryl spectator attached on the silicon atom with alkyl groups longer than methyl groups (**38** and **39**, R = alkyl).[72] The scope of this protocol is remarkably broad with respect to both the two aryl rings and the alkyl chain, affording various enantioenriched silicon-stereogenic monohydrosilanes with good enantioselectivities. The products could readily react with various compounds (e.g., alkynes, alkenes, ketones, and alcohols) under Rh(I) catalysis to generate quaternary organosilanes without compromising the

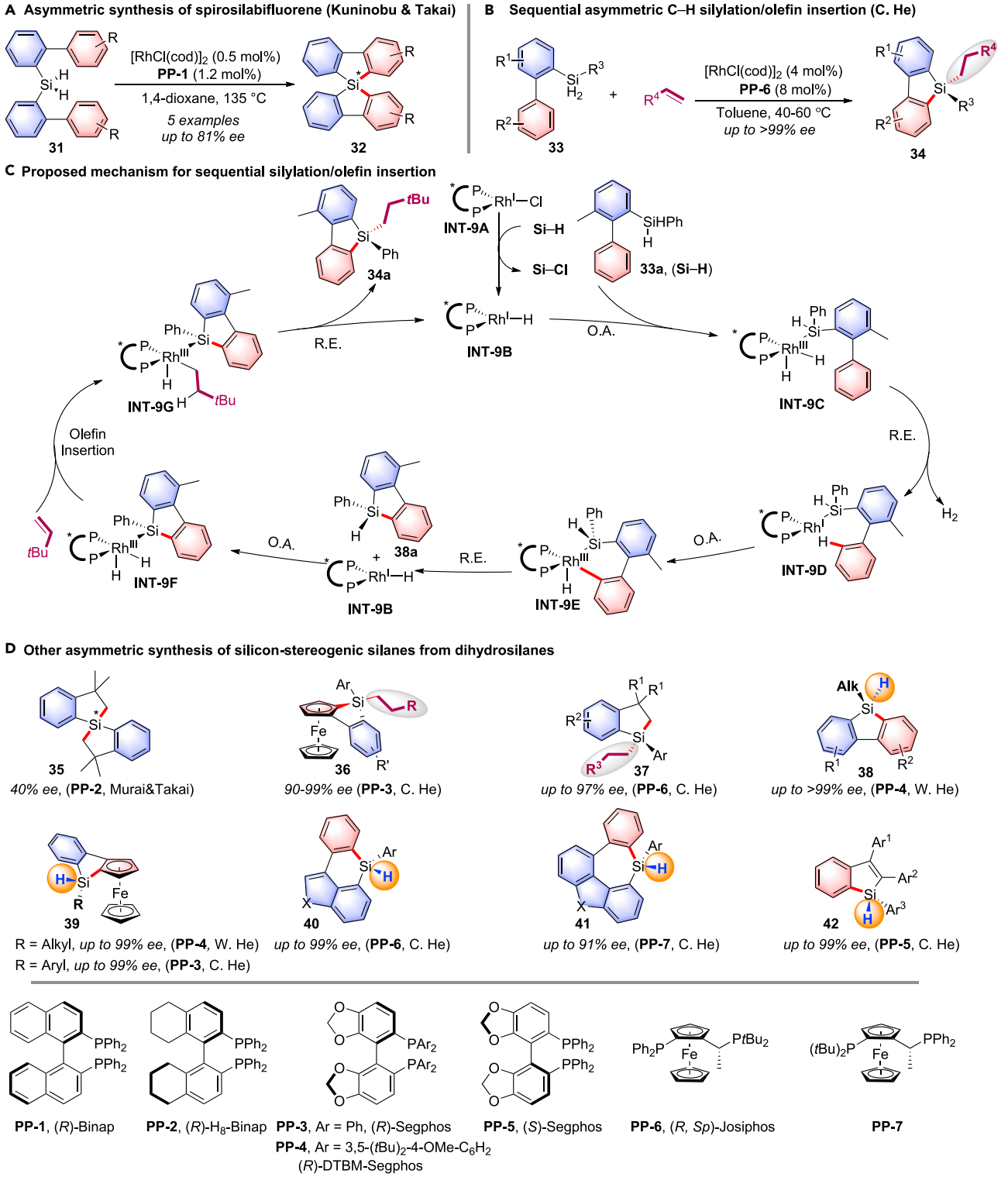

Figure 9. Rh(I)-catalyzed asymmetric C–H silylation with chiral bisphosphines for the preparation of silicon-stereogenic silanes from dihydrosilanes

(A) Asymmetric synthesis of spirosilabifluorene.

(B) Sequential asymmetric C–H silylation/olefin insertion.

(C) Proposed mechanism for sequential silylation/olefin insertion.

(D) Other asymmetric synthesis of silicon-stereogenic silanes from dihydrosilanes.

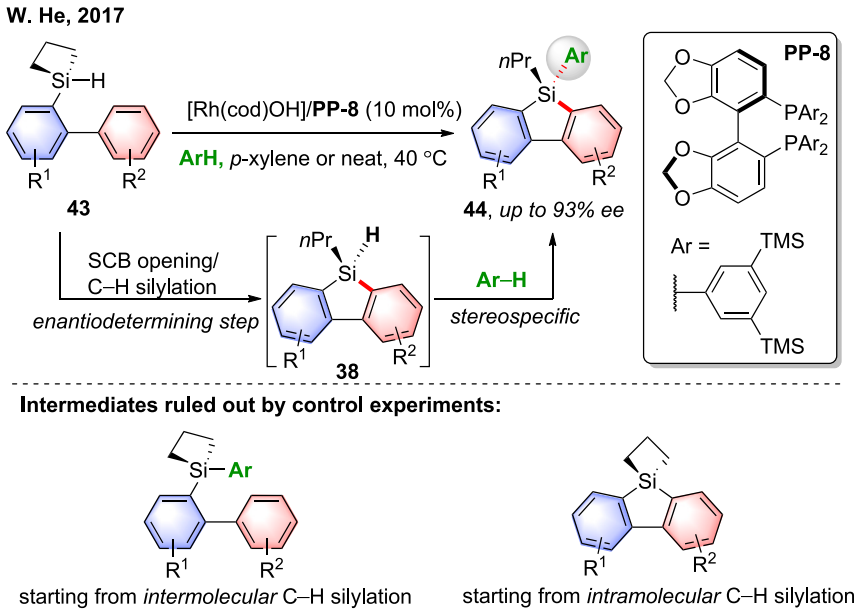

Figure 10. Preparation of silicon-stereogenic silanes through Rh(I)-catalyzed 2-biaryl silacyclobutanes opening/C–H silylation

enantiopurity. Meanwhile, C. He and co-workers achieved the construction of 6- and 7-membered chiral monohydrosilanes (**40** and **41**) by adopting fused aryl-ring-containing dihydrosilanes and Josiphos-type ligands.[73] The resulting rigid and enantioenriched triorgano-substituted silicon-stereogenic heterocycles exhibit bright blue fluorescence and circular polarized luminescence signals, implying the potential application in optoelectronic material science. With the aid of chiral Segphos ligand, enantioselective preparation of silicon-stereogenic ferrocenyl-hydrosilanes (**39**, R = Aryl) and 1H-benzosiloles (**42**) based on similar strategy was also achieved.[74]

In the C–H silylation mentioned earlier, the directing ability of the silyl group was realized upon Si–H oxidative addition. In 2017, the group of W. He established a Si–C cleavage alternative proceeding through 2-biaryl silacyclobutanes (SCB) opening, silyl directed intramolecular C–H silylation and a subsequent intermolecular dehydrogenative silylation with arenes (Figure 10).[75] Various enantioenriched quaternary silicon-stereogenic silanes were obtained in the presence of Rh(I) catalyst and a bulky Segphos-type ligand (**PP-8**). The possible pathways starting from intermolecular/intramolecular C–H silylation has been ruled out, because the corresponding intermediates were not detected in a low conversion reaction mixture, and efforts to transform them into the product **44** under standard conditions failed. Although the isolation of intermediate **38** also failed, the transformation of its enantioenriched analog into the target product was proven to be stereospecific and independent of the ligand chirality. These experiments supported the proposed reaction sequence and the stereo-determining role of SCB opening/C–H silylation step.

In addition to the preparation of silicon-stereogenic silanes, Rh(I)/bisphosphine catalysis has also enabled the construction of planar chiral and carbon-stereogenic silanes. In 2015, W. He and co-workers established Rh(I)-catalyzed asymmetric dehydrogenative silylation of Fe and Ru metallocenes, enabling the generation of various planar chiral products (Figure 11A, using **PP-8** ligand).[76] The good to excellent enantioselectivities were attributed to the small dihedral angle and steric hindrance of

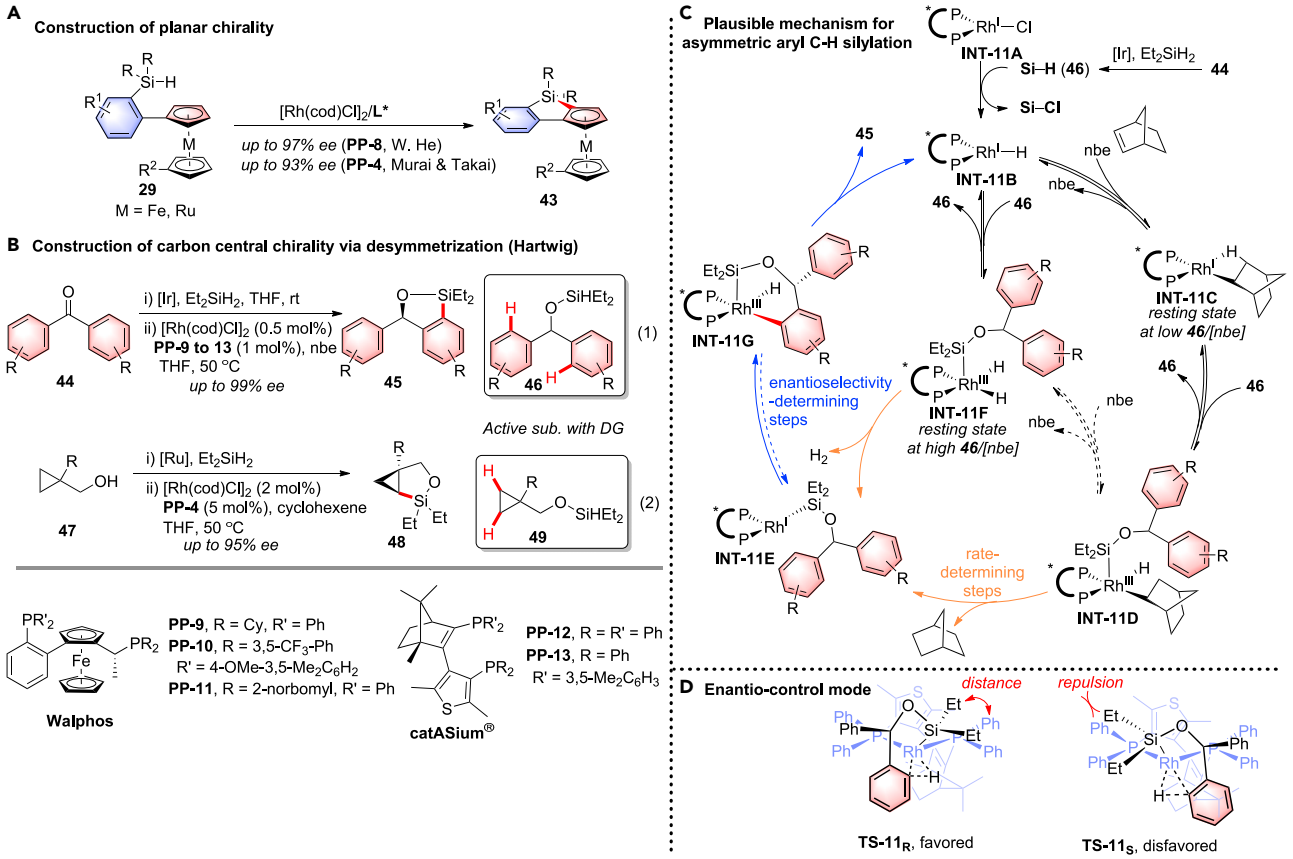

Figure 11. Rh(I)-catalyzed C–H silylation with chiral bisphosphine ligands to construct carbon-stereogenic centers and planar chirality

(A) Construction of planar chirality.

(B) Construction of carbon central chirality via desymmetrization.

(C) Plausible mechanism for asymmetric aryl C–H silylation.

(D) Enantio-control mode.

Segphos-type ligands, as well as the bulkier substituted silicon atoms in the substrates. Shortly after that, the same transformation was independently accomplished by Murai and Takai with less pronounced enantioselectivity (Figure 11A, using **PP-4** ligand).[77] The measured photophysical and electrochemical properties of these products indicate their potential application in material science.

Meanwhile, the group of Hartwig developed a desymmetrization/C–H silylation of biaryl (hydrodo)silyl ethers that *in situ* generated from the corresponding ketones or alcohols (Figure 11B, Equation 1).[78] Key to success of this protocol was the presence of $[Rh(cod)Cl]_2$ catalyst, a Walphos or catASium® family of chiral bisphosphine ligand and stoichiometric amount of norbornene as H_2 acceptor. The protocol provided access to a range of carbon-stereogenic silanes through desymmetrization of (*in situ* generated) symmetric diarylmethanols. Its ability of transforming two enantiomeric diarylmethanols into different silylated products has further enabled the ee upgrade of enantioenriched starting materials. In this process, the high site selectivity was predominantly controlled by the configuration of chiral ligand. C–Si bonds in the products was transformed into diverse C–C and C–X bonds without erosion of chirality. The same group has later proposed a mechanism based on detailed mechanistic studies (Figure 11C).[79] Two distinct pathways with or without the participation of norbornene are viable, depending on the ratio of compound **46** and norbornene. The rate-determining

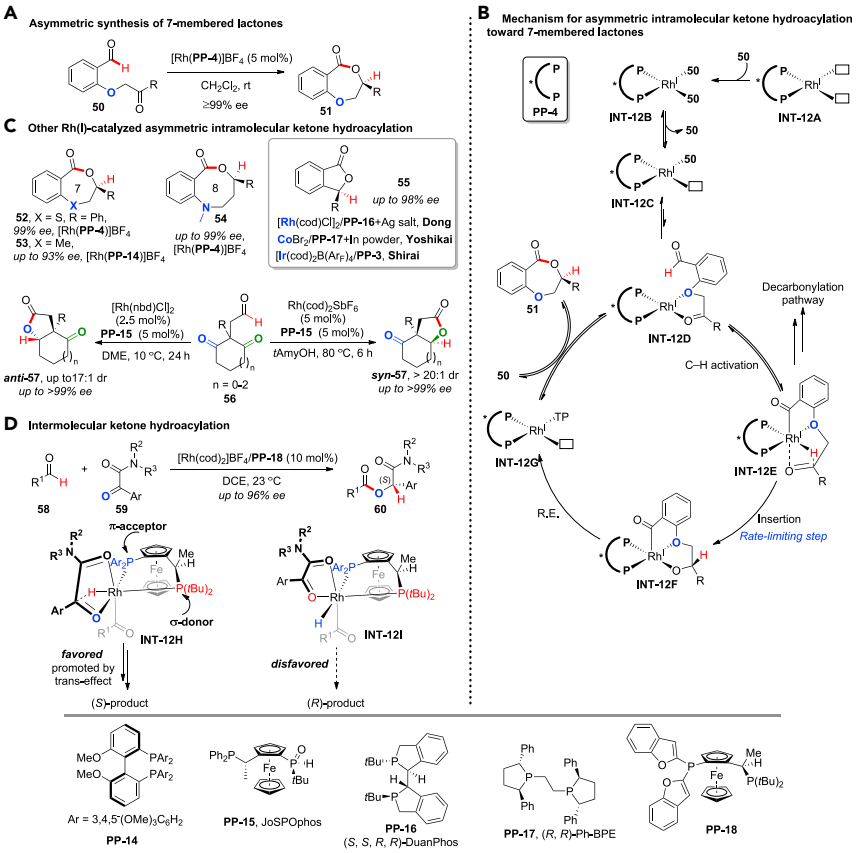

Figure 12. Asymmetric ketone hydroacylation enabled by monovalent group-9 metals and bisphosphine ligands

(A) Asymmetric synthesis of 7-membered lactones.

(B) Mechanism for asymmetric intramolecular ketone hydroacylation toward 7-membered lactones.

(C) Other Rh(I)-catalyzed asymmetric intramolecular ketone hydroacylation.

(D) Intermolecular ketone hydroacylation.

steps were proposed to be the release of dihydrogen or norbornane, and both the cleavage of C–H bond and the formation of C–Si bond were found to influence the enantioselectivity. Density functional theory (DFT) calculations suggested that the enantioselectivity originates from the steric repulsion between the aryl group in the ligand and alkyl group in the substrate in the disfavored transition state (Figure 11D).

To date, Rh(I)-catalyzed enantioselective C(sp^3)–H silylation via desymmetrization was only achieved with limited success, as reported by Murai and Takai (lower than 37% ee).[80] However, Hartwig and colleagues successfully addressed the desymmetrization of strained methylene C(sp^3)–H bonds in cyclopropylmethanol-derived silanes (Figure 11B; Equation 2).[81] A broad set of enantioenriched oxasilolanes were obtained with Rh(I)/(*S*)-DTBM-Segphos (**PP-4**) as catalyst and cyclohexene as H_2 acceptor. Much higher enantioselectivities were observed with substrates bearing aryl substituents rather than alkyl groups, suggesting the importance of aryl-aryl interaction in the stereo-model between the substrate and ligand.

Aldehyde C–H activation/ketone hydroacylation

The increased electron density of group-9 metals with chiral bisphosphine ligands has also allowed the oxidative addition of aldehyde C–H bonds. This has led to

the prosperity of asymmetric aldehyde C–H functionalizations.[67] In this context, asymmetric hydroacylation of ketones that forge C–O bonds has received much attention because it provides an atom-economic alternative for chiral ester preparation.

The milestone research on this topic was an Rh(I)-catalyzed intramolecular reaction toward 7-membered lactones established by Dong and co-workers (Figure 12A).[82] A correlation between the ligand basicity and reaction performance (reactivity, chemo-, and enantioselectivity) was discovered. The bulky and modest basic (*R*)-DTBM-Segphos (**PP-4**) afforded 7-membered lactones in the optimal yields and enantioselectivities (≥99% ee) with the amount of decarbonylated products minimized. In their subsequent experimental and theoretical studies, both racemic and asymmetric versions were investigated.[83] In the case of dppp ligand, the dissociation of unactivated dimer precatalyst into an active monomeric catalyst is required. Thus, an initiation period was observed for racemic hydroacylation. However, in the asymmetric version, the sterically bulky (*R*)-DTBM-Segphos ligand has hampered the formation of dimer precatalyst, thus omitting initiation. On the basis of their experimental and computational studies, a mechanism involving an aldehyde C–H oxidative addition, an enantio-determining and turnover-limiting ketone insertion, and C–O RE was proposed (Figure 12B). In the structure of the key Rh(III) species **INT-12E** generated upon C–H activation, the hydride is oriented *cis* to both the acyl group and ketone, as indicated by their computational studies. The crucial role of ether oxygen for this reaction was ascribed to coordination. Further investigation on enantioselective intramolecular ketone hydroacylation focused on varying the ring skeletons (**52** and **53**),[84] expanding (**54**)[84] or shrinking (**55**)[85] the ring size, and the desymmetrization of diketones (**57**)[86] using proper chiral bisphosphine ligands.

In 2014, Dong further implemented an intermolecular version of asymmetric hydroacylation. This was achieved based on the consideration that aldehyde C–H bond activation could occur without chelation and that ketones possessing a DG would retard undesired aldehyde dimerization or decarbonylation pathways and enhance enantioselectivity (Figure 12D).[87] The envisaged reaction was eventually developed by utilizing ketoamides as coupling partners and a newly designed Josiphos-type ligand (**PP-18**). Bulky aryl groups and proper tertiary amide motifs on the ketoamides are beneficial for the high reactivities and enantioselectivities. A stereocontrol model based on the trans-effect of phosphine ligands was supported by DFT calculations (Figure 12D). The kinetic isotope effect (KIE) of 2.6 in this reaction is significantly larger than intramolecular ketone hydroacylation (KIE = 1.79 ± 0.06), probably due to the increased energy barrier of aldehyde C–H cleavage in the absence of chelation. The second-order dependence of reaction rate on catalyst concentration and a small positive non-linear effect suggest the reasonability of a homobimetalic C–H activation step.

Beyond Dong's Rh(I) catalysis, the asymmetric synthesis of γ-lactones (Figure 12C, **55**) was also achieved by combining Co(I) or Ir(I) catalysts with chiral bisphosphine ligands. In Yoshikai's Co(I) catalysis,[88] sub-stoichiometric amount of indium powder is required to reduce $CoBr_2$ precatalyst and to prevent potential catalyst deactivation. To the best of our knowledge, this is the only demonstration of forming C–X bonds via Co(I)/chiral bisphosphine catalyzed asymmetric C–H activation. Years later, Shirai reported an Ir(I) catalytic system with a less basic (*R,R*)-Segphos ligand (**PP-3**) in which the employment of $B(Ar^F)_4$ anion containing Ir(I) precursor was crucial.[89] Another demonstration of Ir(I)/chiral bisphosphine catalysis is presented by Hartwig in the enantioselective C–H silylation of diarylmethanols (the same

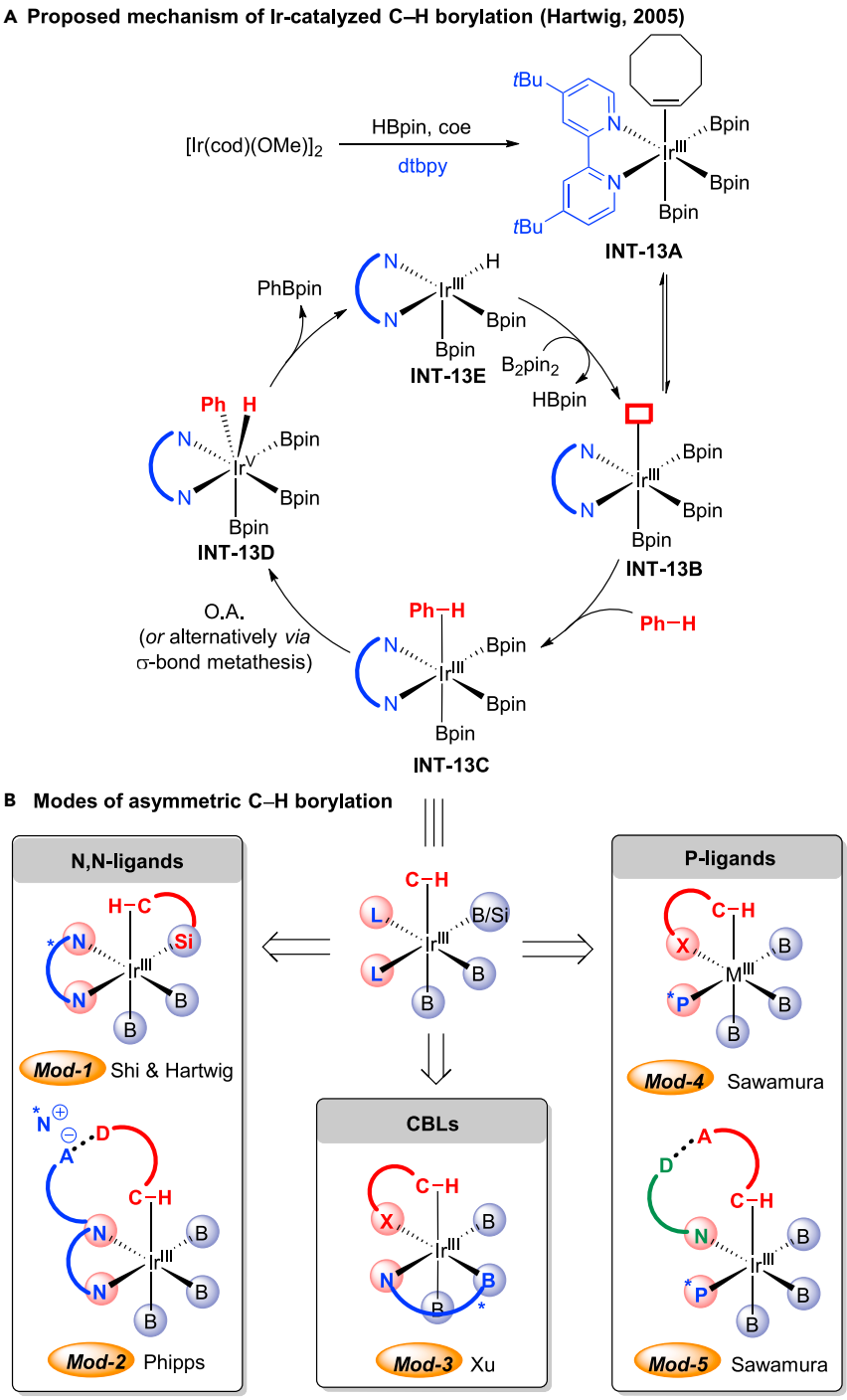

Figure 13. Design philosophy for Ir-catalyzed asymmetric C–H borylation

(A) Proposed mechanism of Ir-catalyzed C–H borylation.

(B) Modes of asymmetric C–H borylation.

transformation with Figure 11B; Equation 1).[78] In this system, diphenylmethanol-derived substrate was silylated in 80% yield and 90% ee with higher temperature and catalyst loading than Rh(I) catalysis (**Ir**: over 80°C, 4 mol % catalyst versus **Rh**:

50°C, 1 mol % catalyst). However, the scope of this Ir(I)-catalysis is so limited that any variation on the aryl ring would result in a dramatically decreased conversion.

These comparisons imply that monovalent group-9 metals exposed to similar ligand sphere resemble in catalytic reactivity. However, to enable the same transformation with a different transition metal, carefully tailoring the electronic and steric property of the ligand is required.

MULTI-BORYL/SILYL Ir(III) CATALYSIS

Multi-boryl/silyl Ir(III) catalysis is a unique catalytic mode that is mainly applied in C–H borylation and silylation. It is mechanistically different from $Cp^xM(III)$ catalysis because the C–H cleavage proceeds through either C–H oxidative addition or σ-bond metathesis rather than CMD process. A majority of these reactions rely on iridium catalysts, with fruitful asymmetric variants recently been established.[90] The most widely accepted mechanism for C–H borylation was proposed in Sakaki's theoretical work[91] and confirmed by the group of Hartwig in their experimental mechanistic investigation for racemic non-directed C(sp^2)–H borylation (Figure 13A).[92] The catalytic process involves the generation of Ir(III) species (**INT-13A**) from the Ir(I)-precatalyst, olefin, borane, and dinitrogen ligand. Subsequent dissociation of the olefin leaves a vacant site for the aryl C–H bond to approach (**INT-13C**). The C–H cleavage might proceed via either oxidative addition that forms Ir(V) species (**INT-13D**) or σ-bond metathesis, as supported by their isotope labeling studies, kinetic studies, and reaction order measurement. Finally, the RE generates the target product and an Ir(III) hydride intermediate (**INT-13E**), which upon reaction with diborane regenerate the active catalyst (**INT-13B**). The design philosophy of all the existing catalytic systems for asymmetric C–H borylation might be inspired by the structure of the 16-electron trisboryl Ir(III) complex **INT-13C** (Figure 13). In nearly all the catalytic asymmetric C–H borylation reactions, the key Ir(III) intermediate to promote C–H cleavage is ligated by two neutral sites and three boryl groups or with a boryl group replaced by silyl (**Mod-1**). To render the C–H cleavage asymmetric, researchers employed extra interactions, such as coordination (**Mod-1**, **Mod-3**, and **Mod-4**) and non-covalent interactions (**Mod-2** and **Mod-5**), in their design, so as to fix the substrates tightly to the chiral environment. Various chiral ligands have been developed for these distinctly attached substrates, leading to ligand spheres resembling **INT-13C**.

There has long been a debate on the mechanism of Ir-catalyzed C–H silylation in the presence of a dinitrogen ligand. Among the extensive computational studies, whereas Sunoj's work suggested a Ir(I)/Ir(III) process,[93] Li's[94] and Huang's[95] investigations suggested that an Ir(III) promoted C–H bond oxidative addition that generates Ir(V) species is energetically favored. The latter approach was supported by Hartwig's recent experimental mechanistic studies for iridium-catalyzed racemic intermolecular C(sp^2)–H silylation.[96] To note, the mechanism is distinct from C–H silylation catalyzed by Rh-bisphosphine complexes in the earlier section, wherein a silyl Rh(I) species is the active catalyst for C–H cleavage. Rh(III) promoted C–H cleavage is less facile, probably due to the change in ligand sphere and the central metal.

Chiral dinitrogen ligand

In 2017, Shi and Hartwig established an iridium-catalyzed asymmetric C–H borylation of diarylmethylsilanes in the presence of a chiral dinitrogen ligand,[97] which represents one of the earliest asymmetric C–H borylation. The choice of **61** as substrates is vital for this transformation. The hydrosilyl group in **61** provides a unique coordination mode by replacing one of the three boryl groups in **INT-13C** and hence facilitates chiral induction (**Mod-1**). Undesired C–Si formation pathway is inhibited by the

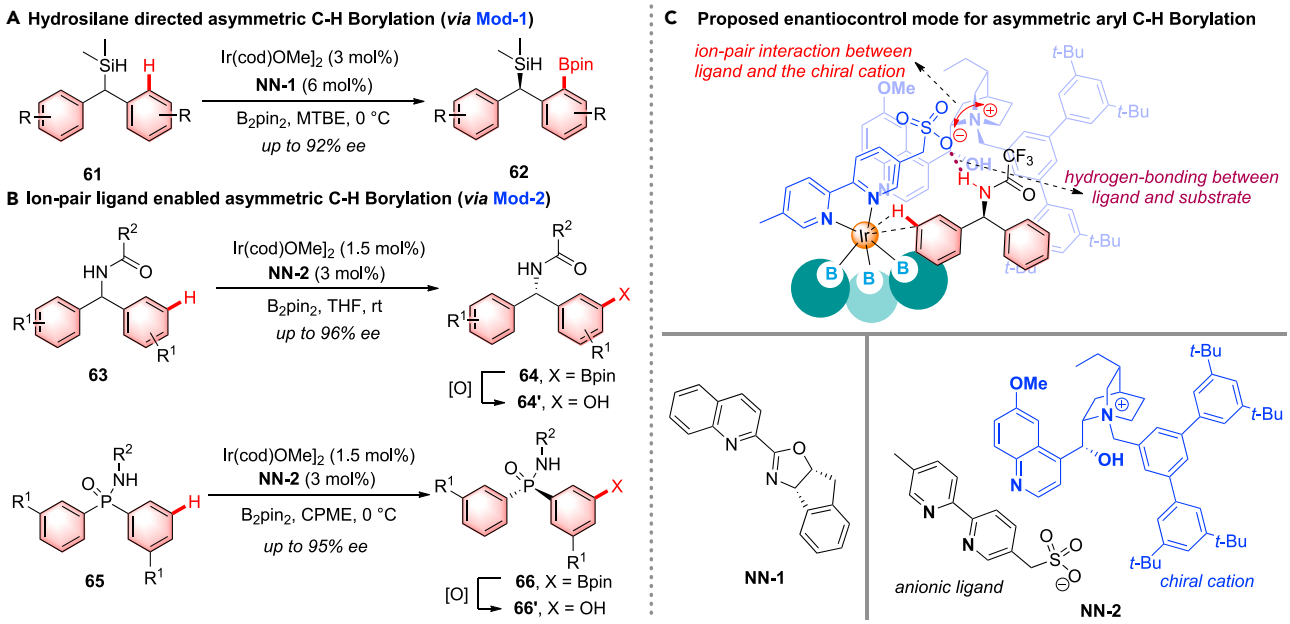

Figure 14. Ir-catalyzed asymmetric C–H borylation with chiral dinitrogen ligands

(A) Hydrosilane directed asymmetric C–H borylation (via Mod-1).

(B) Ion-pair ligand enabled asymmetric C–H borylation (via Mod-2).

(C) Proposed enantiocontrol mode for asymmetric aryl C–H borylation.

disfavored formation of four-membered silanes from five-membered iridacycles. Extensive ligand optimization reveals that steric hindrance at both the achiral quinolinyl moiety and chiral indane-fused oxazolinyl moiety in the optimized dative nitrogen ligand is crucial for the high enantioselectivity (Figure 14A, **NN-1**). A set of borylated products were obtained in good yields and high enantioselectivities. The boryl group was readily transformed into diverse C–O, C–C, and C–halogen bonds.

A fantastic asymmetric C–H borylation approach was recently developed by the group of Phipps, in which *gem*-diaryl groups located on a carbon or phosphine atom were enantioselectively differentiated by virtue of multiple non-covalent interactions (Figure 14B).[98] The chiral ion-pair ligand (**NN-2**), consisting of a sulfonate-appended bipyridine scaffold and a dihydroquinine-derived chiral cation, allowed the long-range asymmetric induction in the desymmetrizing C–H borylation of various diarylamides (**63**) and diaryl phosphinamides (**65**) at the unconventional remote *meta*-position of the aryl ring. Control experiments suggested that the amide N–H group of the substrate binded with sulfonate through hydrogen bonding, whereas the chiral information of the chiral cation was transferred onto the substrate through ion-pair interactions (Figure 14C). Crucial to the chiral induction were the bulkiness of the chiral cation and the location of the sulfonate moiety (neither too close to affect the reactivity, nor too far to diminish the enantiocontrol). The conversion of the boryl group into substitutions that significantly perturb the electronic properties of aryl ring (such as hydroxyl or nitrile group) also allows the chemoselective follow-up transformations, highlighting the utility of this protocol. This report features a rare example of using chiral cations for asymmetric transition metal catalysis, which was previously mainly confined to organocatalysis.

In addition to enantioselective C–H borylation, chiral dinitrogen ligands have also enabled Ir-catalyzed intramolecular asymmetric C–H silylation reactions. Despite the

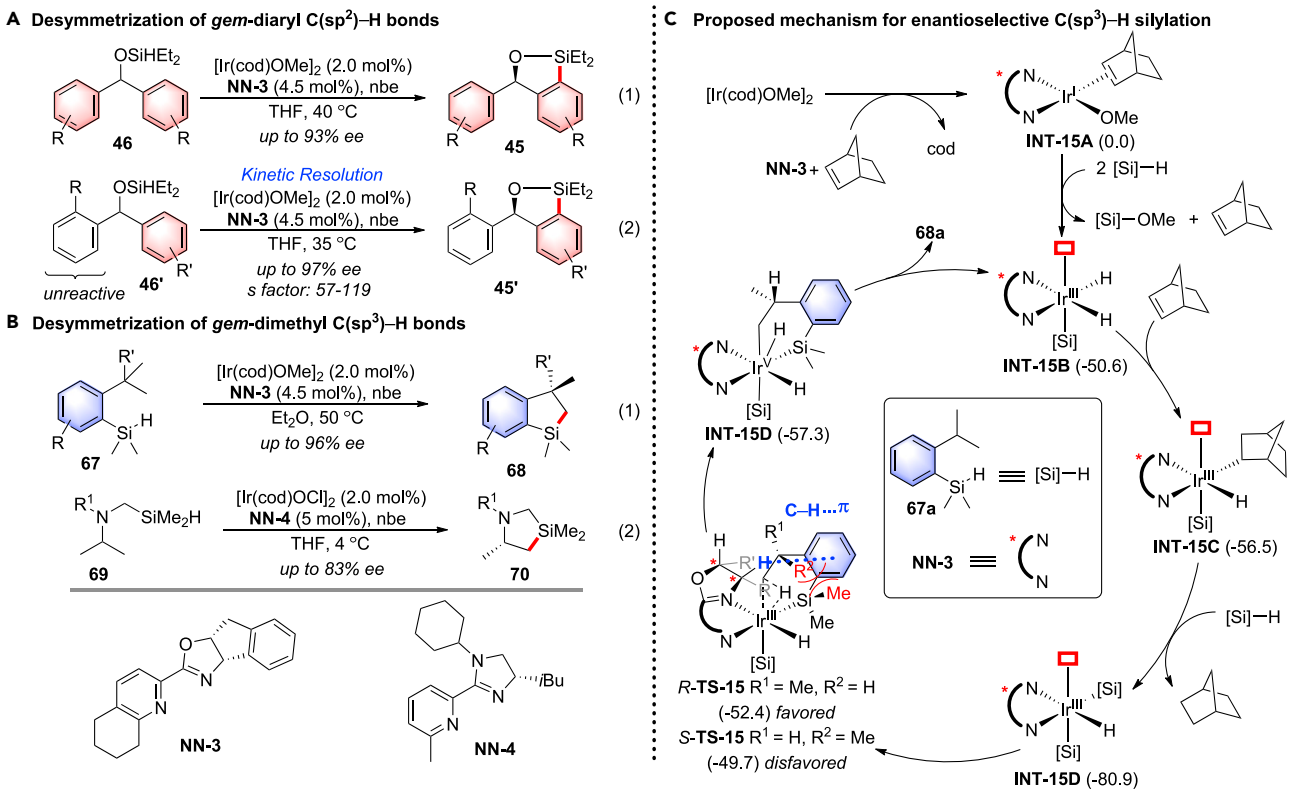

Figure 15. Ir(I)-catalyzed asymmetric C–H silylation with chiral dinitrogen ligands

(A) Desymmetrization of gem-diaryl C(sp^2)–H bonds.

(B) Desymmetrization of gem-dimethyl C(sp^3)–H bonds.

(C) Proposed mechanism for enantioselective C(sp^3)–H silylation.

fact that a plethora of racemic silylation reactions were catalyzed by Ir-bipyridine or Ir-phenanthroline catalysts,[65,66] the majority of asymmetric C–H silylation to date rely predominantly upon Rh(I) catalysis. The challenge of developing chiral iridium catalysts on the basis of planar dative nitrogen ligands was conquered by Hartwig and Shi.[99] Their success was ascribed to the utilization of a novel hydroquinolinyl oxazoline-based ligand (**NN-3**), which enabled the enantioselective C(sp^2)–H silylation of biarylmethanol-derived hydrosilanes (**46**) in good yields and ee's (90%–97% ee, Figure 15A; Equation 1). Inspired by the lack of reactivity for sterically encumbered ortho-substituted aryl rings in this system, they further achieved the kinetic resolution of unsymmetric substrates (**46′**) in high s factors (57–119, Figure 15A; Equation 2).

The same ligand has further promoted the asymmetric synthesis of dihydrobenzosiloles (**68**) through *gem*-dimethyl C(sp^3)–H desymmetrization silylation (Figure 15B; Equation 1).[100] This was previously achieved in only 37% ee with rhodium catalyst and a chiral bisphosphine ligand.[80] The enantioselective *gem*-dimethyl C(sp^3)–H desymmetrization of aliphatic amines (**69**) was also achieved, providing access to enantioenriched 1,2-amino alcohols (Figure 15B; Equation 2).[101] Successful expansion of their (hydrido)silyl docking/silyl directed C–H activation protocol from alcohols to amines was ascribed to the addition of a methylene tether between the silicon atom and the heteroatom, which prevent the formation of unstable silylamine species. The utilization of a more basic picolinyl imidazoline ligand (**NN-4**) was crucial to the high reactivity and enantioselectivity, whereas the earlier mentioned picolinyl oxazoline ligands only provided poor

results. The imidazoline analogs were proposed to increase the electron-richness of the catalysts, thus accelerating C(sp^3)–H oxidative addition.

Based on Hartwig's preliminary mechanistic experiments,[100] Huang and co-workers investigated the mechanism for enantioselective C(sp^3)–H silylation through DFT calculations (Figure 15C).[95] Their study suggested Ir(III)/Ir(V) catalytic cycle, in which the active catalyst for C–H cleavage is an Ir(III) disilyl hydride species. This is in accordance with Hartwig's proposed mechanism for aromatic C–H silylation based on their extensive experimental and computational studies.[96] The oxidative addition of C–H bond is proven to be both the rate-determining and enantioselectivity-determining step. The stereocontrol was ascribed to the steric repulsion between R^2 and a methyl group on the silicon atom, as well as the C–H●●●π interaction between the ligand and the substrate. Calculations suggest that these interactions have led to the favorable formation of ***R*-TS-15** transition state over ***S*-TS-15** by 2.7 kcal/mol.

Chiral bidentate boryl ligand (CBL)

Bidentate ligands that combine a neutral coordinating site with a boryl/silyl group are also operative for Ir-catalyzed borylation. This was independently illustrated by Smith[102] and Li[103] for racemic C–H borylation using phosphine-hydrosilane and pyridyl-borane ligands, respectively. The active Ir(III) complexes generated from these ligands possess two vacant sites, providing opportunities for the coordination of neutral auxiliary, which is beneficial for chiral induction during C–H activation process (**Mod-3**). Based on these considerations, the group of Xu elegantly designed a novel class of chiral bidentate boryl ligand (CBL) consisting of a pyridyl group, a chiral boryl motif, and a sterically congested aryl ring. CBLs could be readily prepared from (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine in three steps. The sterical and electronical tuning at the pyridyl and/or aryl motifs allows Ir-CBL complexes to promote enantioselective borylation of various types of C–H bonds (Figure 16A).

The enantioselective C(sp^2)–H borylation of diarylmethylamines was addressed by employing **CBL-1** ligand bearing a 3,5-dimethylphenyl substituent on the aryl skeleton.[104] Various *N*,*N*-dimethylated symmetric amines were borylated in good yield and high enantioselectivities. (**71**) Kinetic resolution with substrates bearing a 3,5-disubstituted aryl rings afforded enantioenriched chiral amines in moderate to good enantioselectivities, with *s* factors ranging from 9 to 68 (**71′**). DFT calculations supported a C–H oxidative addition involved Ir(III)/Ir(V) mechanism. Modification of the steric hindrance at the CBL aryl ring was further proven crucial for asymmetric methylene C(sp^3)–H borylation of strained 1,1-disubstituted cyclopropanes (**72**),[105] cyclobutanes (**73**),[106] and *N*-β-position of *N*-alkylpyrazoles. (**76**)[107] To note, the protocols applicable for 1,1-disubstituted cyclopropanes[105] and cyclobutanes[106] was not operable for simple cycloalkyl substrates.

Additional tuning at the pyridyl group of CBLs has further enabled the differentiation of the enantiotopic methylene C(sp^3)–H bonds at *N*-α and β-carbonyl positions. In 2020, the Xu group executed enantioselective C(sp^3)–H borylation at *N*-α-position of azacycles bearing proper dialkylcarbamyl DGs (**74** and **75**).[108] For C1-borylation of tetrahydroquinolines (**74**), tremendous challenges arising from competitive directed C(sp^3)–H activation at C3 and *N*′-alkyl chain, non-directed C(sp^2)–H activation at less hindered sites, as well as the difficulties for differentiating enantiotopic methylene C–H bonds (marked in blue). Key to their success was largely ascribed to tuning the sterics at both the arene 2,6-position and pyridine C5-position of the ligand (**CBL-7**). Their proposed models explained that the 2,6-PhC_6H_3 motif on the pyridine ring cooperated with the phenyl group at the diamine backbone to

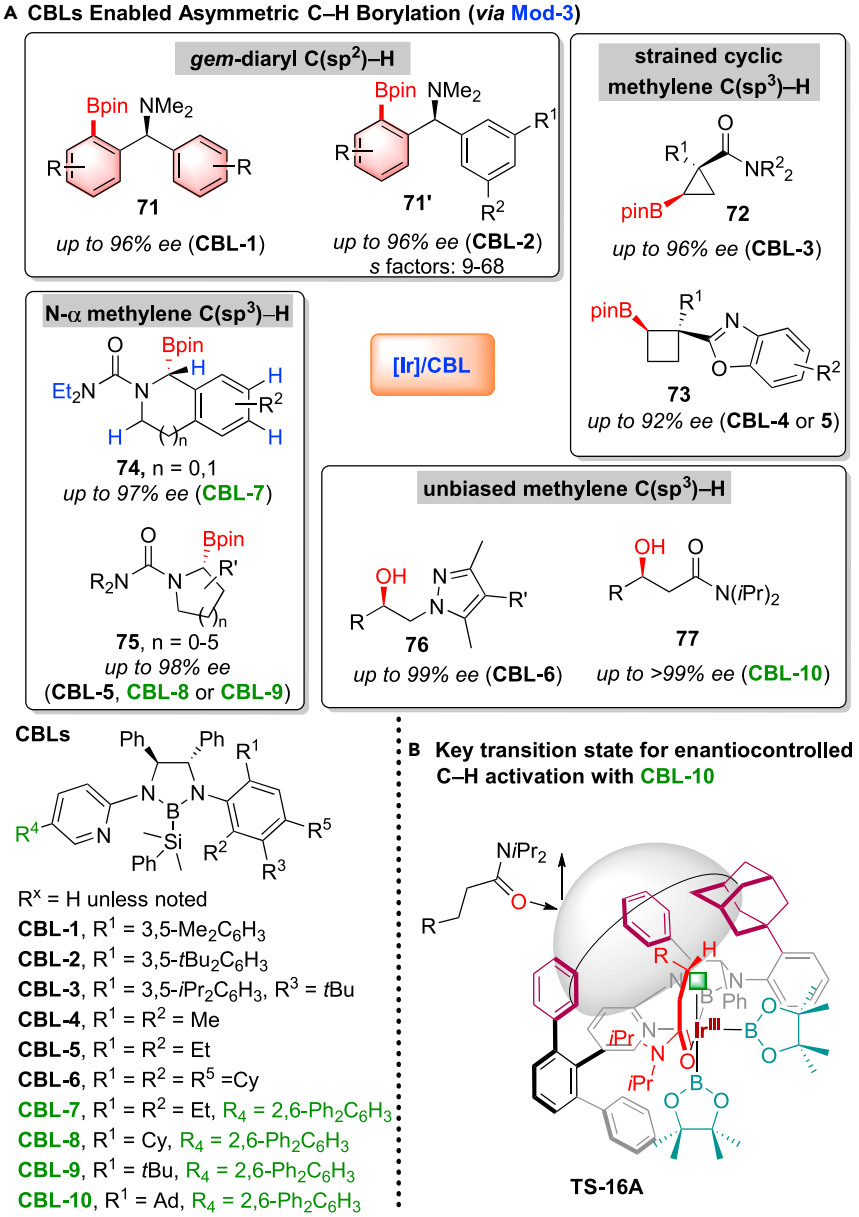

Figure 16. Ir-catalyzed asymmetric C–H borylation with CBL ligands (via Mod-3)

(A) CBLs enabled asymmetric C–H borylation (via Mod-3).

(B) Key transition state for enantiocontrolled C–H activation with CBL-10.

form a shielded apical reaction site at the iridium center (similar to **TS-16A**). The increased steric repulsion was responsible for blocking the approaching of C(sp^2)–H bonds and minimizing the formation of minor enantiomer. Further modification on the aryl ring of the ligand allowed the asymmetric C–H borylation of four- to nine-membered saturated azacycles in moderate to excellent enantioselectivities. (**75**) Unprecedented enantioselective C–H borylation of both unbiased and benzylic methylene C(sp^3)–H at the β-position of aliphatic tertiary amides was also achieved using a similar ligand (**77**, with **CBL-10**).[109] The highly shielded reaction site was proposed to suppress the undesired coordination of a second substrate that leads to an unreactive iridium complex (Figure 16B).

Chiral monophosphite ligand

In 2017, Sawamura and co-workers reported an innovative example of the Ir- or Rh-catalyzed asymmetric methylene C(sp^3)–H borylation of 2-aminopyridines and 2-alkylpyridines. A readily available chiral phosphoramidite was used as chiral ligand, giving the borylation products in moderate ees (25% to 53% ee).[110] After 2 years, the same group demonstrated that monodentate chiral phosphite ligands were even more efficient for Ir-catalyzed asymmetric C–H borylation.[111] Their success relies on a monophosphite derived from two axially chiral BINOL scaffolds, with the remaining hydroxyl group protected by a bulky triisopropylsilyl (TIPS) group (**P-1**). Ligation of this ligand at the less hindered side (the side without silyl group), together with three boryl ligands, results in a catalyst containing a deeply embedded metal center and a narrow chiral reaction pocket with two vacant sites.

This ligand was first applied to neutral auxiliary directed C–H borylation (Figure 17A). In this case, 2-alkylheteroarenes bearing inert enantiotopic methylene C(sp^3)–H bonds was subjected to an Ir-catalyzed asymmetric C–H borylation. A subsequent oxidation afforded the corresponding alcohols in moderate to good yields and high enantioselectivities.[111] Various heteroarenes, such as pyridines (**79A**), *N*-methyl benzoimidazoles, benzothiazoles, and benzoxazoles (**79B**), are adequate neutral auxiliaries to direct the C–H activation. Based on the measured KIE of 3.6, they conducted theoretic calculations focusing on C–H bond cleavage by the catalyst. Careful analysis on the reasonable transition states revealed the crucial role of multiple non-covalent interactions between the substrate and the catalyst in enantiocontrol. The asymmetric borylation of *N*-α-methylene C(sp^3)–H bonds were achieved by further expanding this system to rhodium catalysis.[112] Various heteroarenes and weakly coordinating amides are amenable as DG, affording a remarkably broad substrate scope (**81A**, **B**, and **C**). The protocol was further applied to the facile and highly stereoselective synthesis of bortezomib, an anti-cancer drug that contains an *L*-boroleucine motif (Figure 17A; Equation 3). The presence of competing C(sp^2)–H and tertiary C(sp^3)–H bonds in this dipeptidic substrate further highlights the exclusive site selectivity of this methodology. Mechanism of this rhodium catalysis remains to be investigated.

Inspired by the strong impact of non-covalent interactions on the enantioselectivity of 2-alkylheteroarenes C(sp^3)–H borylation (Figure 17A; Equation 1), they further achieved asymmetric C(sp^3)–H borylation at the unconventionally remote γ-position of simple amides and esters.[113] In this innovative work, an enzyme-like chiral cavity was modularly assembled by the iridium center, the chiral monophosphite ligand, a urea-pyridine-based receptor ligand (**RL**) and three pinacolatoboryl groups. The pyridyl group of **RL** was designed to dock onto the iridium center upon coordination, whereas its urea moiety was designed to bind with the carbonyl group in the substrate through hydrogen bonding. To note, the location of both the binding nitrogen atom and urea motif at the **RL** is crucial for the reactivity as well as the site selectivity. Such an enantio-control mode (**Mod-5**) as depicted in Figure 13B has led to a high-fidelity chiral induction from the monophosphate ligand to various amides and esters, leading to successful differentiation of the enantiotopic γ-methylene C(sp^3)–H bonds. Remarkably, the methodology is compatible with alkenoic acid derivatives bearing terminal (**83a**) or internal double bonds (**83b**, linoleic acid derivative), indicating its potential application in the functionalization of biologically active compounds with extensive hydrocarbon chains. Their quantum chemical calculations indicated that hydrogen bonding, C–H●●●O interactions between several C(sp^3)–H bonds at the substrate backbone and oxygen atoms located on the chiral ligand and Bpin groups, as well as London dispersion interactions are keys to fixing the

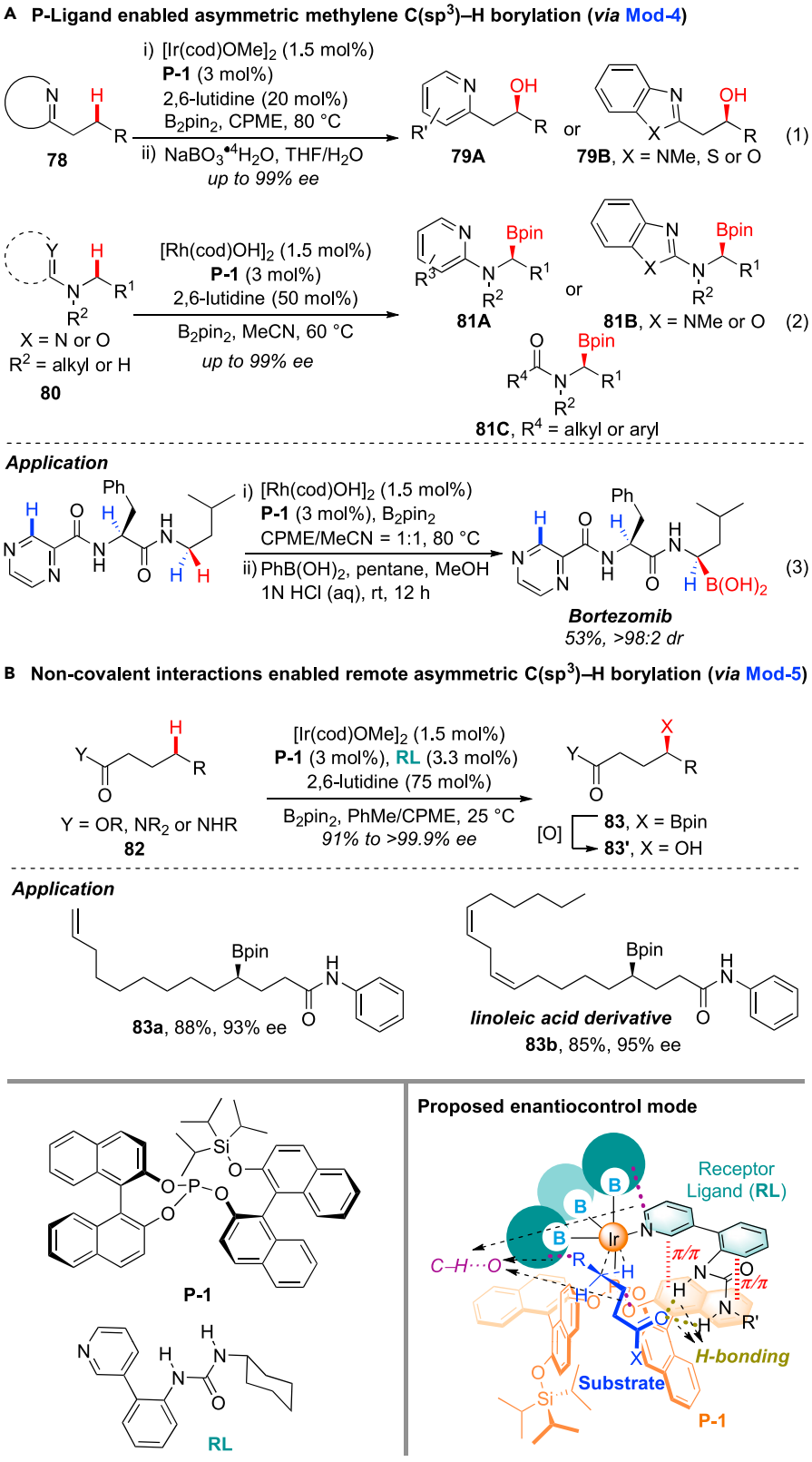

Figure 17. Ir-catalyzed asymmetric C–H borylation with chiral monophosphite ligands

(A) P-Ligand enabled asymmetric methylene C(sp^3)–H borylation (via Mod-4).

(B) Non-covalent interactions enabled remote asymmetric C(sp^3)–H borylation (via Mod-5).

substrate conformation and harnessing asymmetric C(sp^3)–H cleavage. The unprecedented high regio- and enantioselectivity for remote methylene C(sp^3)–H activation with this protocol highlighted the bright prospect of such enzyme-like catalytic modes in addressing remote asymmetric C–H activation.

CONCLUSION AND OUTLOOK

In summary, we provide herein an overview of constructing C–X bonds by means of transition metal-catalyzed asymmetric C–H functionalization, an emerging research field toward the facile preparation of valuable heteroatom-containing chiral scaffolds. By organizing the achievements according to catalytic systems, we were able to discuss the design philosophy, mechanism, application, and limitations of each catalytic system in detail. For example, Pd(II) catalysis that enables the formation of various C–X bonds from diverse types of C–H bonds is underdeveloped due to the sensitivity to competing counter anions. Many other catalytic systems are limited to certain types of functionalizations. For instance, group-9 metal-derived $Cp^xM(III)$ catalysis is limited to amidation with nitrene precursors; monovalent group-9 metal catalysis in the presence of bidentate chiral neutral ligands is confined to intramolecular silylation and ketone hydroacylation; multi-boryl/silyl Ir(III) catalysis is restricted to borylation and silylation. Nevertheless, these methodologies have enabled the construction of diverse chiral scaffolds bearing central, planar, and axial chirality. Besides representative mechanistic studies, we also briefly discussed the design philosophy of several catalytic systems, as exemplified by importance of ligand sphere in designing multi-boryl/silyl Ir(III) catalyzed asymmetric C–H borylation.

Overall, the construction of C–X bonds by transition metal-catalyzed asymmetric C–H functionalization is still in its infancy. For example, the synthesis of axial chirality via this strategy remains to be exploited. Moreover, the state-of-art is limited to Pd, Co, Rh, and Ir catalysts, which highly calls for the employment of other transition metal catalysts, especially earth-abundant 3d metals. Extra attention should be paid to the recently emerged TDG and non-covalent interactions (e.g., hydrogen bonding and ion-pair interactions). Such strategies might not only omit the tedious installation and removal of external DGs but also provide enantiocontrol at unconventional remote positions in an enzyme-like fashion. We believe an eruption of C–X bond formation via asymmetric C–H functionalization reactions will be witnessed in the near future.

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AUTHOR CONTRIBUTIONS

L.-S.W. proposed the topic and gathered the majority of references. Q.Z. further completed the literature survey, briefly set up the overall structure, and wrote the manuscript. B.-F.S. supervised the writing and revised the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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