The Catalytic Formation of Atropisomers and Stereocenters via Asymmetric Suzuki-Miyaura Couplings

Gaspard Hedouin,[†] Susanta Hazra,[†] Fabrice Gallou,[‡] Sachin Handa*[†]

[†]Department of Chemistry, University of Louisville, 2320 S. Brook Street, Louisville, Kentucky 40292, United States

[‡]Chemical & Analytical Development, Novartis Pharma AG, Basel 4056, Switzerland

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ABSTRACT: Although Suzuki-Miyaura cross-coupling is one of the most convenient and well-developed cross-coupling reactions, its applications to the asymmetric version to deliver highly functionalized atropisomers or non-racemic coupling products have been less explored. Besides some excellent work reported intermittently, the asymmetric Suzuki-Miyaura reaction remains a significant challenge, particularly for preparing highly functionalized heterocyclic atropisomers. A concise but critical knowledge on this topic may further inspire researchers across various subdisciplines to develop innovative and practical solutions to tackle this problem. Therefore, this concise review aims to summarize the pioneering work on asymmetric Suzuki-Miyaura cross-couplings and cover the implementations via homogeneous or heterogeneous catalysis reported during recent years. Most notably, the use of transition-metals other than palladium is also described.

Introduction

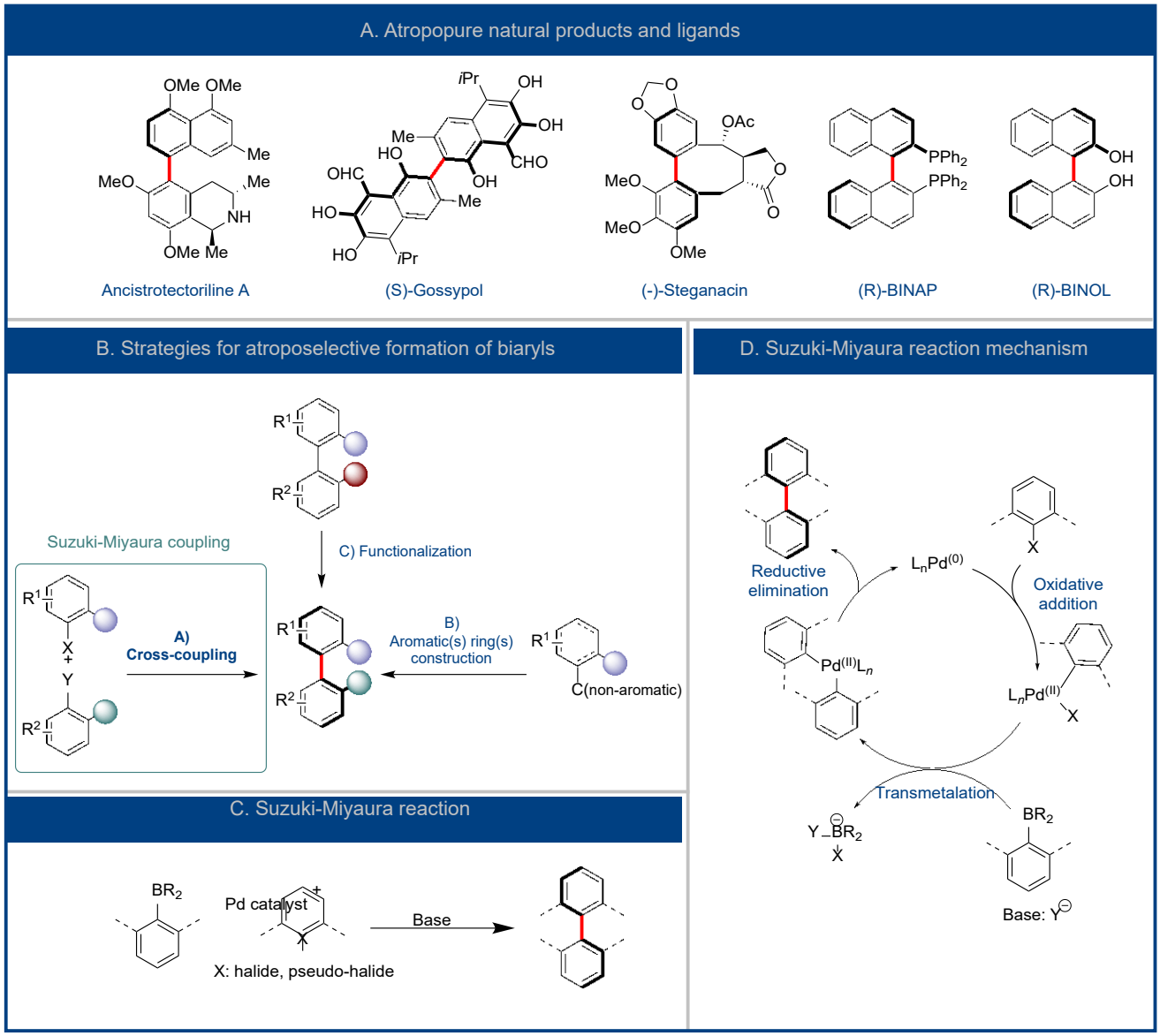
Palladium-catalyzed Suzuki-Miyaura (SM) cross-coupling is one of the most useful C–C bond-forming reactions to construct biaryl compounds. Since its seminal discovery by Miyaura and Suzuki in 1979, this transformation has gone through many advancements that led to numerous robust and environmentally friendly modern catalytic methods.[1–3] The use of stable and highly- to mildly-reactive aryl (pseudo)halides and organoboron coupling partners made this reaction more appealing. Most of the time, air and water do not affect the reactions outcome, and therefore, reaction handling is not an issue at any scale. Although the SM cross-coupling has been well-practiced, its asymmetric version is yet not fully established. The palladium (Pd)-catalyzed asymmetric SM reaction is mostly useful for constructing $C(sp^2)$-$C(sp^2)$ bond to form atropisomers.

Atropisomers are the form of axially chiral compounds that are formed due to hindered rotation between a single bond. In atropisomers, the steric strain or other contributors, such as ortho substituents, create a high rotational barrier, allowing the isolation of individual conformers. Notably, axial chirality is a critical element in many natural products, biologically-active compounds (Ancistrotectoriline A,[4] Gossypol[5] or Steganacin[6]), privileged chiral ligands (BINAP and BINOL derivatives), and many compounds for the area of material science (Scheme 1A).[7–11] To prepare atropisomers, several strategies have been documented in the literature, including the construction of aromatic rings by cycloaddition or chirality transfer, cross-coupling between two aryl units to build a stereogenic axis, and functionalization of prochiral or racemic biaryls (Scheme 1B).[12–14] Enzymatic, organo-, or transition-metal catalysts have been employed to accomplish this goal.[15–21] Among these methods, transition-metal catalyzed cross-couplings of two aryl units, particularly the asymmetric SM coupling, represents a straightforward synthetic strategy (Scheme 1C).

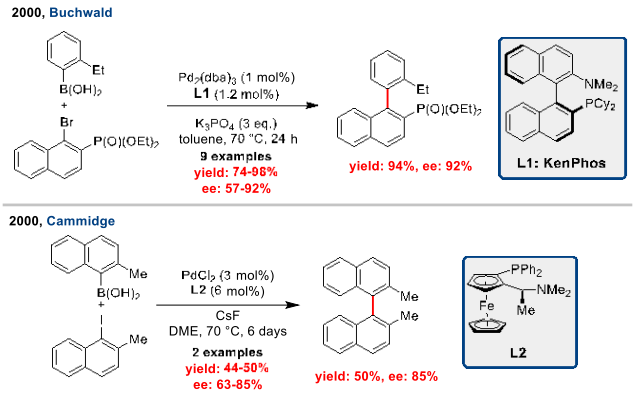
The general mechanism involves the oxidative addition of aryl (pseudo)halides to the ligated Pd(0), forming the aryl-Pd(II) intermediate, that further undergoes transmetalation by boron nucleophile leading to the desired coupling product after the reductive elimination step. Under the influence of non-racemic ligand, the preferential formation of one of the two atropisomers can be afforded after the reductive elimination (Scheme 1D). The Buchwald and Cammidge groups have independently reported the first two examples of Pd-catalyzed asymmetric SM cross-couplings. Both groups described the preparation of biarylic scaffolds under different conditions using the phosphine-amine ligands **L1** and **L2** (Scheme 2).[22,23] Since then, numerous catalytic systems, substrates design, and specific conditions have been specifically elaborated. The main strategies include designing spatially well-defined ligands and temporary or permanent installation of directing groups (DG) in substrates.

Notably, a few reviews appeared in the literature covering the advancements until 2016,[24–26] as well as a book chapter in 2019.[27] Therefore, this review only includes critical analysis, general update, summary of the previous and the newly designed catalysts for homogeneous and heterogeneous catalysis, and non Pd-based metal catalysts until January 2022.

Scheme 1. Asymmetric SM cross-couplings. (A) Examples of axially chiral natural products and ligands. (B) Strategies for atroposelective formation of biaryls. (C) Reaction outline. (D) General mechanism



Scheme 2. First examples of asymmetric SM coupling



Homogeneous Pd-catalyzed asymmetric SM cross-couplings

Diastereoselective SM cross-coupling

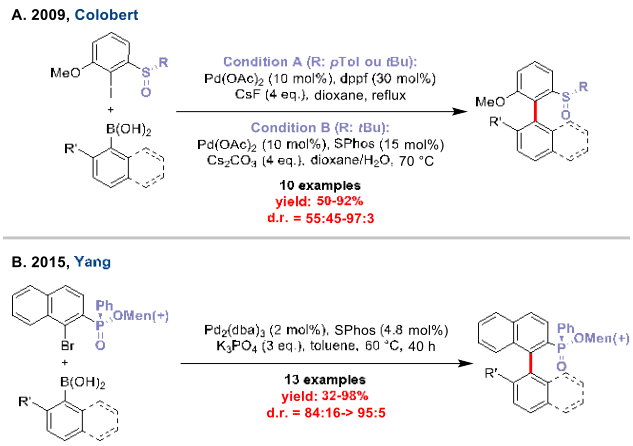
Since the pioneering reports of Cammidge and Buchwald, significant efforts have been made to improve asymmetric SM couplings, especially with a focus on either the catalyst or substrates design. Although most of the reported work is related to enantioselective SM couplings, a few groups have described the diastereoselective couplings using a chiral directing group on the aryl halide coupling partner. Uemura[28,29] and Nelson[30] have described the diastereoselective SM coupling using planar chromium complexes. Afterward, Nicolaou,[31] Lipshutz,[32] and Baudoin[6,33] applied the same approach for the total synthesis of the Vancomycin, Korupensamine A, and Steganacin derivatives.

Researchers have also developed several specific chiral directing groups to achieve this diastereoselective couplings. Colobert's group demonstrated the use of sulfoxide moiety as the

chiral directing unit using an achiral Pd-catalyst to deliver biaryls with moderate-to-excellent diastereoselectivity.[34] Instead of *para*-tolylsulfinyl group, the utilization of *tert*-butylsulfinyl directing group facilitates the formation of the desired products with better diastereomeric ratio, whereas the catalyst loading remains high for both conditions. In addition, the substrate scope is limited in terms of aryl halides—the conditions were only effective for aryl iodides (Scheme 3A).

A few years later, Yang's group reported the use of chiral phosphinate auxiliary to achieve the formation of axially chiral biaryls with excellent diastereoselectivities and good yields.[35,36] Likewise, the scope is also limited to bromoarylphosphinate electrophile with the demonstration on only two examples (Scheme 3B). Recently, Cheon and co-workers reported the use of a chiral amine directing group to achieve the formation of several alkaloids, including Ancistrotanzanine B, Ancistrotectoriline A, and various of their derivatives.[4] These diastereoselective SM reactions allow the delivery of biarylic compounds with good diastereoselectivities. However, this methodology requires the addition of the auxiliary and then its removal. For those reasons, the enantioselective catalytic approach represents a more straightforward and exciting way to prepare atropisomeric scaffolds.

Scheme 3. Diastereoselective SM coupling with chiral directing groups



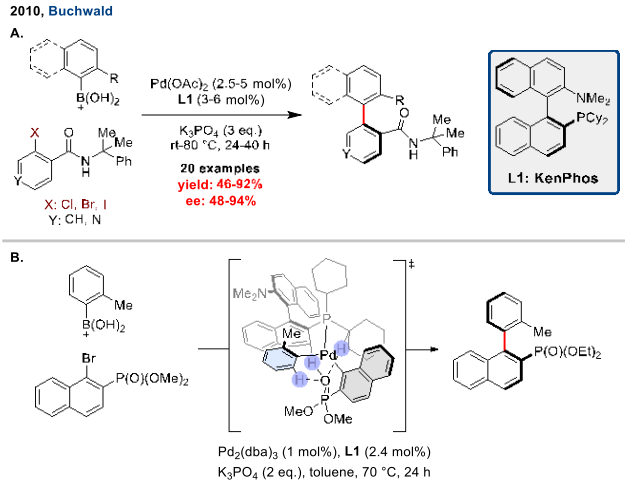
Enantioselective SM cross-couplings

The use of non-racemic phosphine ligands and their derivatives

Phosphine ligands have predominantly contributed to the field of general asymmetric catalysis as well as asymmetric SM reactions, as shown by the pioneering work of Cammidge and Buchwald in their early reports. Various fine-tuned ligands have been explored for this transformation.

One of the major drawbacks of the catalytic asymmetric SM reaction is generally the limited substrate diversity. Indeed, to ensure high enantioselectivities, an achiral bulky directing group on aryl halide is mainly required to generate secondary interactions in the transition state, favoring one atropisomer. The phosphonates ester or phosphine oxide groups have been usually the most common directing groups that serve this purpose. After the seminal work, Buchwald's group has extensively worked to broaden the scope of this reaction.[37] High enantioselectivities have been achieved using chloro-, bromo- or iodo- aryls bearing an amide moiety. The authors have also performed the reaction on diverse scaffolds, including pyridine and sterically hindered electrophiles. However, the enantioselectivity was moderate (Scheme 4A).

Scheme 4. Non-racemic monophosphines ligand for asymmetric SM reaction. (A) The use of coupling partners containing amide directing group. (B) Stabilization of transition state by hydrogen bonding



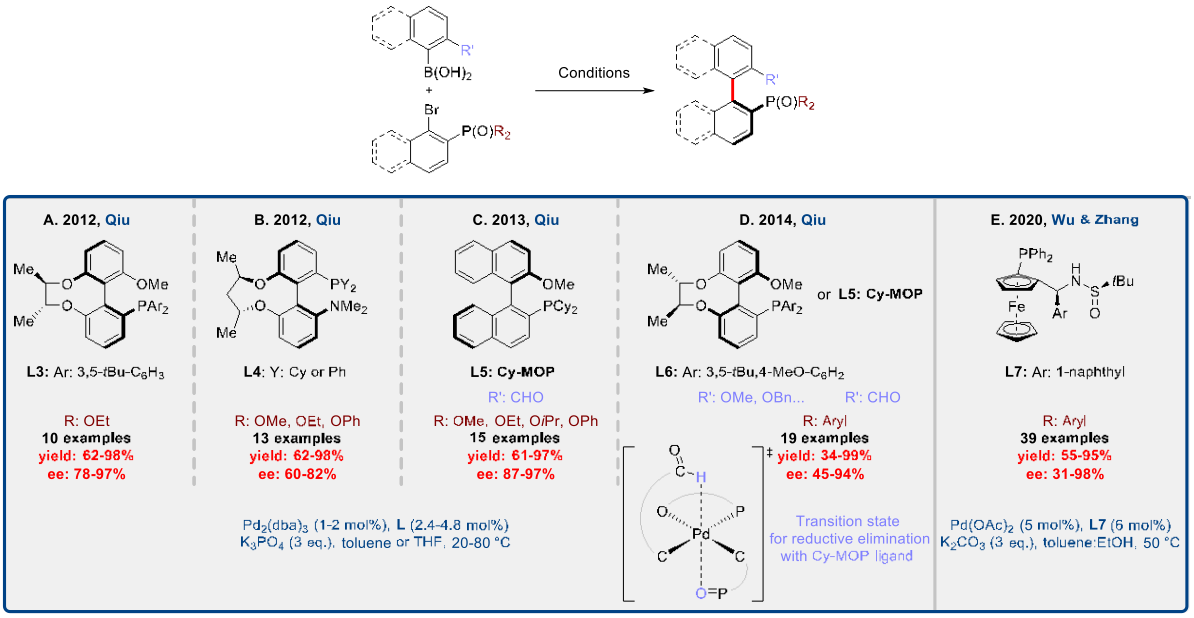
Furthermore, the authors conducted mechanistic investigations to understand the origin of enantioselectivity during the reaction with phosphonates as directing group and KenPhos (**L1**) as a ligand on the Pd. The DFT calculations were performed to determine the more stable transition state for the reductive elimination, that showed the importance of the secondary interactions (i.e., H-bonding between the oxygen from the phosphonate with hydrogens from the ligand and the aryl boronic unit) to favor one atropisomer over another (Scheme 4B). In addition to an optimized ligand, these secondary interactions are often primordial to achieve a high level of selectivity.

Later, Qiu and coworkers also developed several axially chiral ligands to achieve the cross-couplings of aryl bromides bearing phosphonate esters (Scheme 5).[38,39] In this work reported in 2012 and 2013, the authors explored axially chiral bridged biphenyl monophosphines to afford the desired products in good-to-excellent enantioselectivities. Notably, the ligand **L3** affords better enantioselectivities compared to **L4** (Scheme 5A, B). Nevertheless, in this second report, authors also demonstrated that the phosphonate directing group in the substrate can be modified without affecting the enantioselectivity. One year later, the same group described the asymmetric SM reaction with Cy-MOP ligand (**L5**) to afford biarylic scaffolds with excellent enantioselectivities. The o*rtho*-substituted formyl boronic acid has been used to obtain desired products with high levels of enantioselectivity. To further expand the substrate scope, authors have explored the triflate electrophile, i.e., naphthyl triflate containing an *ortho*-nitro substituent yielding difunctionalized biaryls in high enantioselectivities (Scheme 5C).[40]

The same authors also described the formation of axially chiral scaffolds in high optical purities using phosphine oxide as directing group on the aryl halide coupling partners. Moreover, authors performed the computational investigations to determine the more stable transition state for the reductive

elimination in the reaction intermediate containing Pd-Cy-MOP complex. The high enantioselectivity arises from the octahedron configuration with the interaction between the Pd and the hydrogen of the formyl group as well as the oxygen atom of the phosphonate. Nonetheless, when the boronic acid was *ortho*-substituted with an ether residue, the ligand had to be optimized. The fine-tuned bridged biaryl ligand **L6** allows the formation of the desired biaryls in good-to-excellent atroposelectivity (Scheme 5D).[41]

Scheme 5. Asymmetric SM coupling with phosphonate or phosphine oxide aryl bromide and phosphine ligand



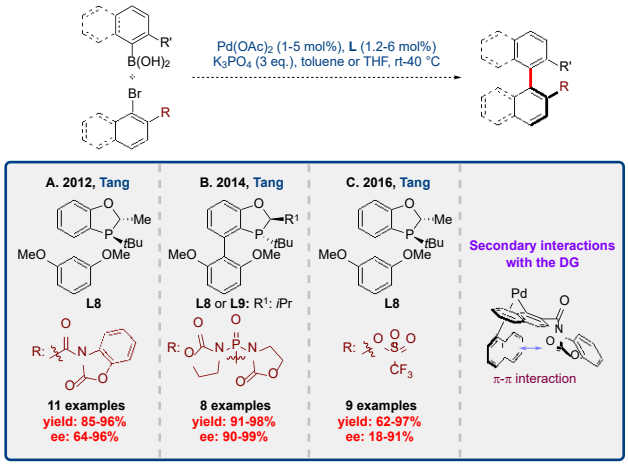
The asymmetric SM cross-coupling of more hindered biaryls with similar ligands have been also documented.[42]

Recently, the SM coupling of aryl bromides with phosphine oxide substituent could be accomplished by Wu and Zhang yielding atropisomeric biaryls phosphines oxides. The authors were able to obtain the expected products in high-to-excellent enantioselectivities. The methodology was also utilized for a large scale (350 mmol) reaction using a phosphine-sulfinamide ligand **L7**. These phosphine oxides can be easily reduced to obtain chiral phosphines ligands which have been mostly applied for the hydrosilylation of olefins.[43] The major drawback of this methodology was related to the ligand **L7** synthesis, i.e., moderate yield and low diastereoselectivity (Scheme 5E).

Although the atroposelective SM reaction can proceed without directing group on aryl halides, the enantioselectivity is generally low or only excellent for limited substrates.[44] In 2018, Patel and co-workers computationally investigated each steps of the SM coupling to predict the stereoselectivity using fine-tuned ligands.[45] Interestingly, authors revealed that the selectivity is affected during every step of the reaction (i.e. oxidative addition, transmetalation and reductive elimination). Their computationally optimized complex bearing a *P*-stereogenic ligand could allow the formation of extremely hindered *tetra*-substituted binaphthyls in high enantioselectivity. However, the substrate scope was limited.

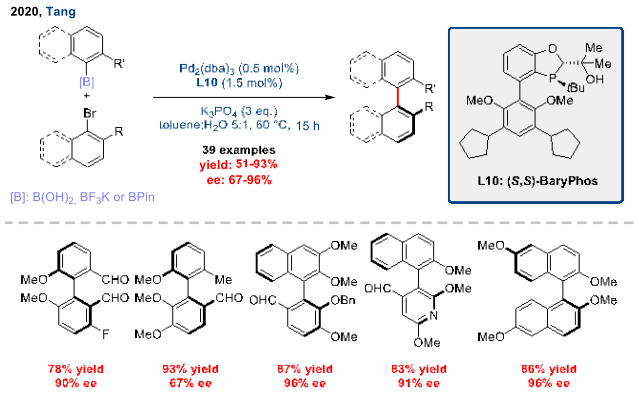
As demonstrated by the groups of Qiu and Buchwald, the secondary interactions between the directing group and the catalyst allow an enhancement of the enantiomeric excess. Likewise, Tang's group has significantly contributed to the field of asymmetric SM reaction during the past years using the BI-DIME-type *P*-stereogenic ligands and derivatives. In 2012, this team of researchers first reported the usage of carbonyl-benzooxazolidinone, which can be further derivatized as directing group to form various biaryl scaffolds in very good atroposelectivities.[46] By DFT calculations, authors also demonstrated that the π-π interaction between the oxygen of the directing group and the naphthyl unit of the boronic acid are involved in the stabilization of the transition state during reductive elimination, likely enhancing the stereoselectivity (Scheme 6A).

Scheme 6. Enantioselective SM coupling using *P*-stereogenic ligands and varied directing group on aryl halide coupling partners



Two years later, the same group also reported the enantioselective SM coupling using the BOP (bis(2-oxo-3-oxazolidinyl)phosphinyl) directing group and BI-DIME-type ligand **L8**.[47] Even if the scope was not extensive, the products were obtained mostly in excellent enantioselectivities. In the same report, the authors have demonstrated the total synthesis of michellamine B and korupensamines A and B using the same cross-coupling chemistry. Once again, polar π-π interactions between the oxygen of the directing group and the naphthyl group of the boronic acid are reported to be responsible for the more stable transition state (Scheme 6B). Based on the same principle, the authors also used the triflates as directing group to deliver biarylic atropisomers with moderate-to-good enantioselectivities, which mainly depend on the structure of boronic acid nucleophile (Scheme 6C).[48]

Scheme 7. Palladium-catalyzed asymmetric SM reaction with (*S*,*S*)-BaryPhos ligand



One of the main challenges in asymmetric SM reactions is to find an efficient ligand, enabling the reaction in excellent enantioselectivity, simultaneously allowing the formation of diverse heterobiarylic compounds. Very recently, Tang and coworkers achieved this goal with a tailored ligand BaryPhos (**L10**), yielding a diverse array of biaryl products bearing electron-rich or electron-deficient substituents in excellent enantioselectivities and with a low catalyst loading (Scheme 7).[5] The authors have also evaluated their methodology on the total synthesis of (-)-gossypol. Likewise, some other groups have developed interesting phosphorus ligands for asymmetric SM reactions. However, those ligands are not as effective as Tang's ligands.[49,50]

Non-phosphorus-based ligands for the enantioselective SM reaction

Although most of the Pd complexes utilized in asymmetric SM couplings contain phosphorus-based ligands, researchers have also developed other types of ligands for this reaction. One of the earliest examples was the successful application of C_2-symmetric *bis*-hydrazones ligand **L11** that was used to prepare unfunctionalized biaryls (Scheme 8).[51] Using this chiral Pd complex, the products were obtained in excellent optical purities. However, in many cases, one week reaction was required to achieve high yields at room temperature (Scheme 8A). Later, the authors have also explored this reaction using a phosphinohydrazone ligand to accomplish the transformations in slightly lower enantiomeric ratios.[52]

Among other ligand families, Lin's group described the first asymmetric Pd-catalyzed SM couplings using a chiral diene ligand.[53] Remarkably, the addition of free diene ligand **L12** to the pre-prepared Pd complex allows the enhancement of enantiomeric excess and reaction yields to achieve the desired biaryls (Scheme 8B).

Monodentate chiral *N*-Heterocyclic Carbenes (NHC) ligands have also been utilized in asymmetric SM cross-couplings. Although in the first reports, moderate enantioselectivities were achieved,[54] the Shi's group very recently described an outstanding catalytic Pd system bearing a chiral monodentate NHC ligand **L13**.[55] Several steps are required to obtain the pure ligand or Pd-complex, however, its efficiency for this reaction allows the formation of the expected products under mild conditions and in excellent enantioselectivities. Furthermore, the reaction tolerates various functional groups on the aryl halides. The reaction also works with aryl chloride, bromide, and triflate electrophiles. Likewise, the catalytic system also enables efficient cross-couplings with different nucleophiles, such as $B(OH)_2$, Bpin, Bneo, and BF_3K. Numerous heteroaryl substrates, including quinoline, pyridine, indole, and thiazole are well tolerated, yielding the heterobiarylic scaffolds in excellent enantioselectivities. Finally, it was also possible to achieve the formation of more hindered, tetra-substituted biaryls, again in excellent atroposelectivities (Scheme 8C). This catalytic system has proven to be one of the most efficient and functional group tolerant for the formation of a wide variety of biaryl compounds via asymmetric SM reaction. Other uncommon catalytic systems, such as Pd-PEPPSI complex bearing a chiral triazolylidene ligand or chiral CNN pincer Pd complex have also been employed for the enantioselective SM cross-coupling with relatively lower chiral induction.[56,57]

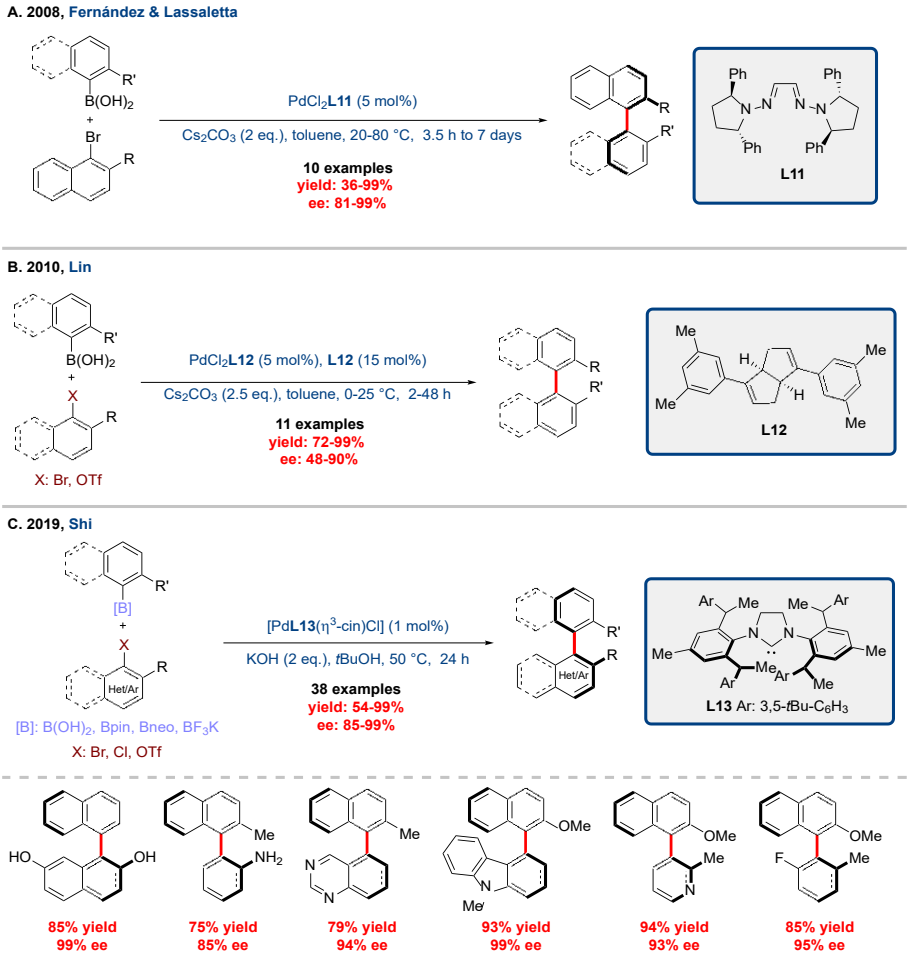
Asymmetric SM cross-couplings for the preparation of heterocyclic and other type of atropisomers

Another challenge in the enantioselective Suzuki-Miyaura coupling is to find an efficient catalytic system capable of diversifying the scope for heterocyclic compounds in excellent enantioselectivities. The heterocyclic scaffolds are ubiquitous in natural products and biologically active compounds. These scaffolds generally bind strongly with Pd and deactivates the catalyst or adversely affect the selectivity. Nonetheless, the methodology has been disclosed by Czarnocki's and co-workers in 2016, accomplishing the asymmetric SM reaction of 3-pyridines to enable catalytic formation of heterobiaryl atropisomers. However moderate enantioselectivities were obtained with a very limited substrate scope (Scheme 9A).[58]

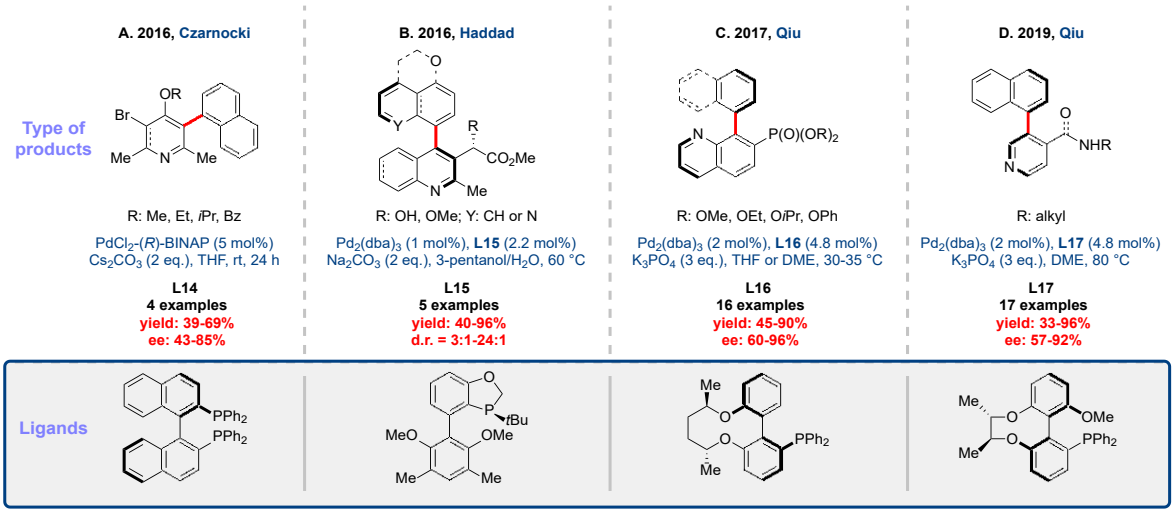
In the same year, Haddad and co-workers also achieved the diastereoselective SM couplings of 4-chloroquinolines under mild conditions using a *P*-stereogenic ligand **L15** derived from BI-DIME.[59] Although the desired scaffolds are obtained in very good diastereomeric ratio, the scope remained limited. Nonetheless, this catalytic methodology was applied to the total synthesis of an HIV integrase inhibitor (Scheme 9B).

Using a bridged monophosphine ligand **L16** and Pd, the cross-couplings of 8-bromoquinolines bearing a phosphonate directing group has also been disclosed by Qiu's group.[60] The axially chiral heterocycles are afforded in good yields and excellent atroposelectivies (Scheme 9C). Applying a similar procedure and with another bridged biaryl monophosphine ligand **L17**, Qiu and coworkers reported the enantioselective Suzuki-Miyaura couplings of 3-bromopyridines containing an amide as a directing group.[61] The products are formed in moderate-to-very good enantioselectivities. The methodology was showcased on a wide range of substrates (Scheme 9D)

Scheme 8. Enantioselective SM couplings using non-phosphine ligands. (A) C2-symmetric bis-hydrazone ligand. (B) Diene ligand. (C) N-Heterocyclic Carbene ligand

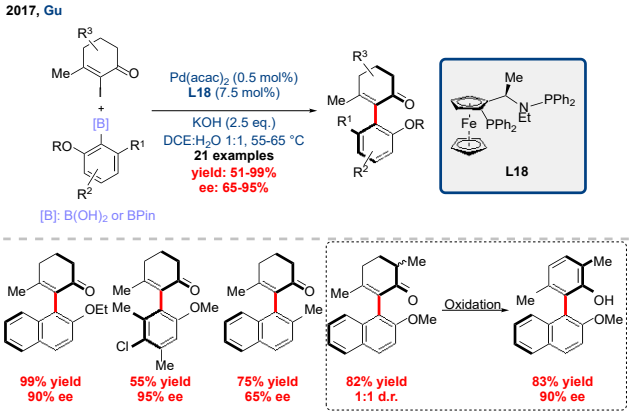


Scheme 9. Preparation of heteroaromatic atropisomers via enantioselective SM cross-couplings



Additionally, the preparation of different atropisomers has been disclosed by Gu and co-workers using iodo-cyclohexenones.[62] Authors have achieved the cross-couplings using a phosphine-aminophosphine ligand **L18** and $Pd(acac)_2$ to afford very unusual atropisomers in moderate-to-high enantioselectivities under mild conditions. However, chlorinated solvent was required to achieve the transformation. Interestingly, these atropisomers can be further functionalized and rearomatized without loss of enantioselectivity to afford chiral biaryls (Scheme 10).

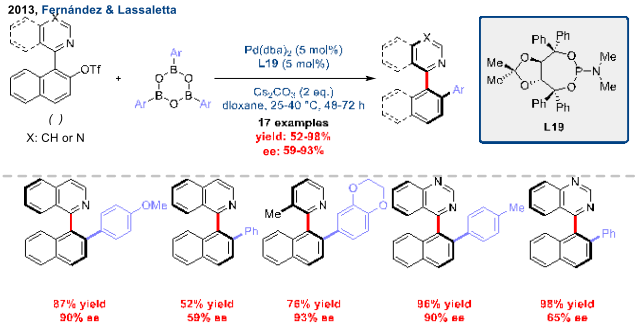
Scheme 10. Enantioselective SM reaction using iodo-cyclohexenones as electrophiles



Miscellaneous applications of Pd-catalyzed asymmetric SM reactions

The kinetic resolution (KR) is a powerful tool to transform a racemic substrate into one enantiomer. Using a Pd-catalyzed SM reaction, Fernandez and Lasaletta reported the dynamic kinetic asymmetric transformation (DYKAT) of racemic heterobiaryls using arylboroxines as coupling partners and a TADDOL-derived phosphoramidite ligand **L19**.[63] The desired atropisomers were obtained in excellent yields and enantioselectivities. According to published report, the reactions occurred via a dynamic kinetic asymmetric transformation (Scheme 11).

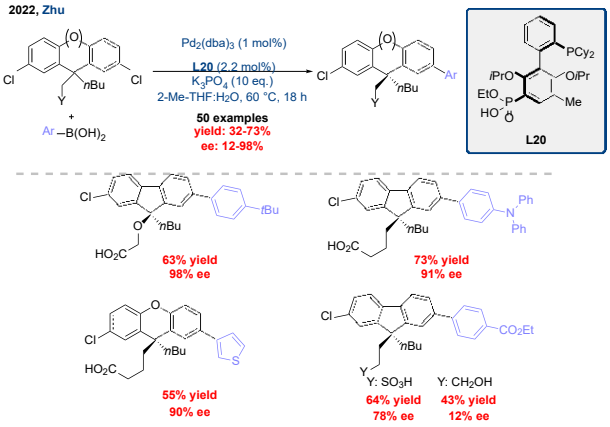
Scheme 11. Dynamic-kinetic Suzuki-Miyaura cross-couplings



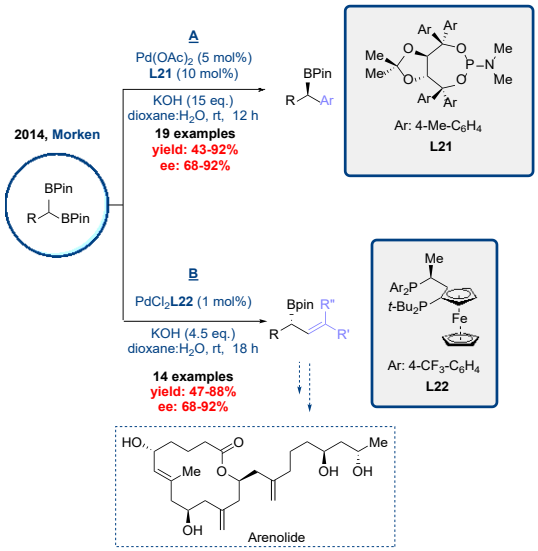
Another straightforward method to get an enantiopure product is the desymmetrization of a prochiral molecule. Very recently, Zhu's group described an original desymmetrization of chlorofluorenes and xanthenes.[64] The design of a specific chiral biaryl ligand **L20** creating ionic interaction with the distal acidic moiety of the aryl chloride, allows the enantioenrichment on a remote quaternary carbon. The products could be delivered in moderate-to-good yields due to the difunctionalized side-products. However, good-to-excellent enantioselectivities are generally obtained (Scheme 12).

Instead of racemic starting material, alternative approaches have been established employing prochiral compounds. A seminal work has been disclosed by Willis and coworkers with the desymmetrization of ditriflates compounds to achieve the SM coupling to deliver the new stereogenic C(sp^3)-center in good enantioselectivities.[65] Later, Morken and coworkers contributed to these advancements by achieving the desymmetrization of enantiotopic (*bis*)boronates.[66] Non-racemic boronate esters could be obtained by asymmetric SM arylation of (*bis*)boronates starting material using 5 mol% catalyst possessing a TADDOL-derived phosphoramidite ligand **L21**. The products were obtained in 68-92% enantioselectivities under mild conditions (Scheme 13A). In same year, authors have also reported allylic SM couplings to build new chiral allylic boronates in good enantioselectivities using a diphosphine ferrocenyl ligand **L22/Pd** with a low catalyst loading, i.e., 1 mol% (Scheme 13B).[67] Notably, toxic 1,4-dioxane solvent was utilized for this transformation. A sequential cross-coupling approach allowed the obtention of quaternary stereocenters via the formation of the allylic boronates.[68] This strategy has been utilized in the total synthesis of arenolide.[69] This reaction has also been studied in depth by Hall's group using a similar phosphoramidite ligand to gain insights on the reaction pathway leading to selectivity.[70]

Scheme 12. Desymmetrizing Pd-catalyzed SM reaction



Scheme 13. Desymmetrization of geminal (*bis*)boronates by Pd-catalyzed asymmetric SM couplings



Furthermore, the asymmetric SM reaction has also been exploited for three components reactions as asymmetric Catellani-type reactions. This has been used to demonstrate cooperative catalysis by Pd and norbornene. The first example of asymmetric SM reaction in Catellani-type reaction for the construction of atropisomers has been reported by Gu's group. The reaction was achieved by mixing aryl iodide, boronic acid, and chloromethylbenzoate.[71] This domino reaction, first involving the norbornene catalysis and then the SM cross-coupling, allows the

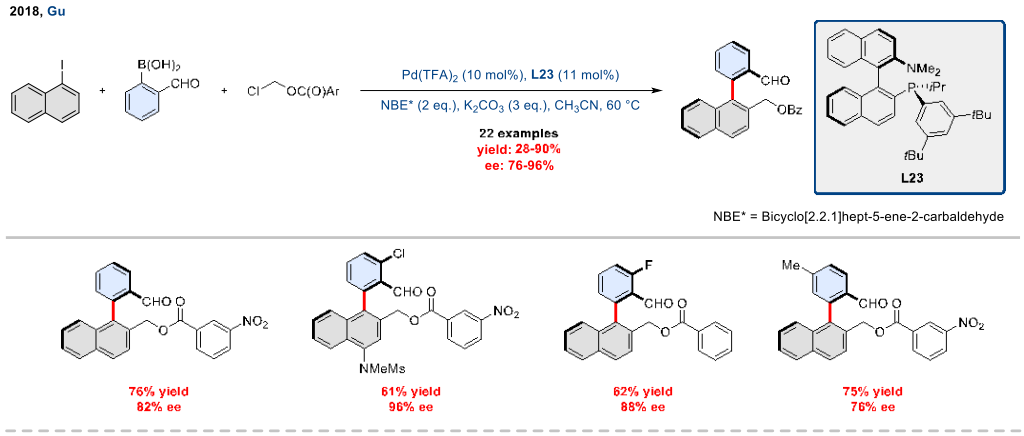
formation of biaryls in good-to-excellent optical purities using a *P*-stereogenic-amine binaphthyl ligand **L23**. It is worth noting that the formyl group on the arylboronic acid was essential to promote the formation of the desired compounds. (Scheme 14).

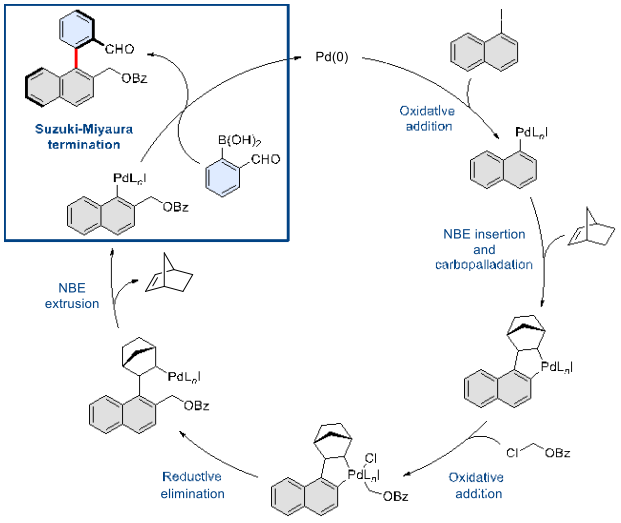
Recently, Zhou and co-workers have also described the preparation of atropoenriched biaryls through asymmetric Catellani and SM reaction.[72,73] The authors have cleverly used a chiral norbornene in catalytic amount and avoided the employment of another external ligand, yielding the biarylic scaffolds in excellent enantioselectivities.

Biocatalytic approach in stereoselective SM reactions

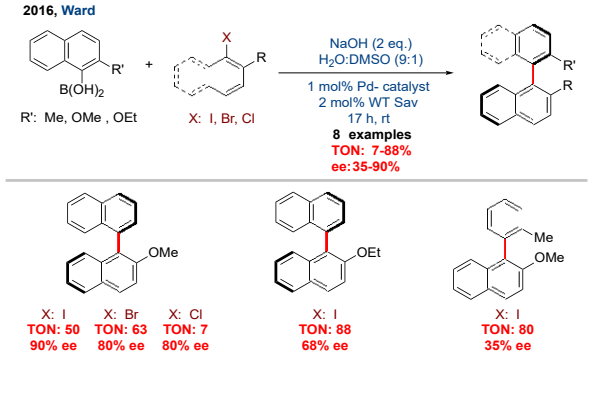
Process chemists often recognize the impact of both environmental and economic metrics when developing new methodologies for chemical manufacturing.[74] Beyond stoichiometric use of coupling partners or reagents, catalysis offers significant benefits, and today, increasing emphasis is being placed on biocatalyst-mediated chemical reactions, more generally termed as biocatalysis. Although the enormous advances that have been made in biocatalysis in the past decade, the utilization of biocatalysts for the synthesis of atropisomers is still limited.[75] In 2008, Ueno and coworkers first attempted to anchor a Pd on a ferritin container to yield an artificial Suzukiase. Although this artificial Suzukiase has high reactivity (TOF = 3500 h^{-1}), the authors did not observe the enantioselectivity for the reaction.[76] In 2016, Ward and coworkers developed an enantioselective artificial Suzukiase based on the biotin–streptavidin technology.[77] Their hypothesis is based on the presence of well-defined second coordination sphere of artificial metalloenzymes (ArMs), which offer a favorable environment to engineer an asymmetric Suzukiase. Authors have incorporated an electron-rich phosphino-Pd moiety within streptavidin, affording an artificial Suzukiase to obtain enantioenriched binaphthyls via SM cross-coupling (up to 90% ee and 50 TONs for 2-methoxy-binaphthyl) under mild reactions conditions (Scheme 15). Although this artificial asymmetric Suzukiase worked under very mild reaction conditions, the substrate scope was limited along with moderate enantioselectivity.

Scheme 14. Catellani-type reaction including SM reaction for the formation of atropisomeric biaryls





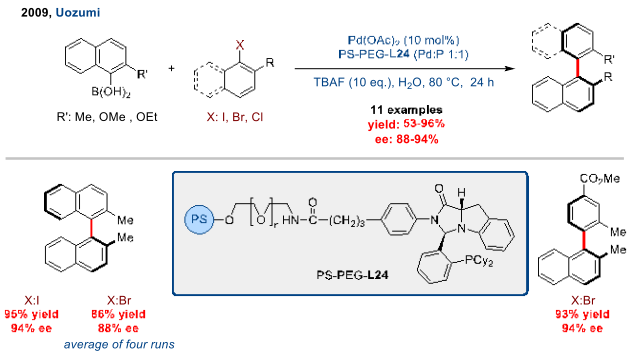
Scheme 15. Asymmetric SM cross-coupling reaction catalyzed by an artificial Suzukiase



Heterogeneous Pd-catalyzed asymmetric SM cross-couplings

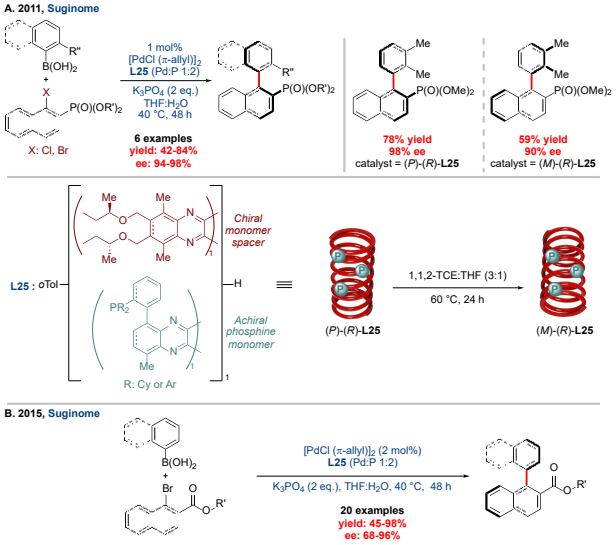
Since asymmetric SM cross-coupling is one of the most employed methodologies for the non-racemic biaryls preparations, different approaches other than ligand design have been implemented to improve this reaction and to make it environmentally friendly. One of the ecological challenges is to accomplish the reaction only in water, thereby avoiding organic solvents. This goal has been accomplished by Uozumi's group using a recyclable catalyst supported on an amphiphilic polystyrene–poly(ethyleneglycol) copolymer (PS–PEG) resin.[78] Initially, the authors demonstrated that their chiral phosphine ligand bearing a tetrahydro-1*H*-imidazo[1,5-*a*]indol-1-one backbone is efficient for the asymmetric SM in organic solvent, and later, they prepared the corresponding supported-ligand to enable chemistry in water. Using this chiral supported-ligand with 10 mol% of Pd loading in water, the authors have showcased the catalytic synthesis of biarylic scaffolds with excellent enantioselectivities starting from aryl chlorides, bromide, and iodides. The catalyst was recycled for four times without observing any erosion of the chiral induction. Nevertheless, five equivalents of boronic acid were necessary to achieve the reactions in higher yields (Scheme 16). Later, the same group described in details the preparation of the non-immobilized and immobilized chiral phosphine ligands and showcased the reaction efficiency.[79]

Scheme 16. Atroposelective SM reaction using a chiral Pd catalyst supported on resin



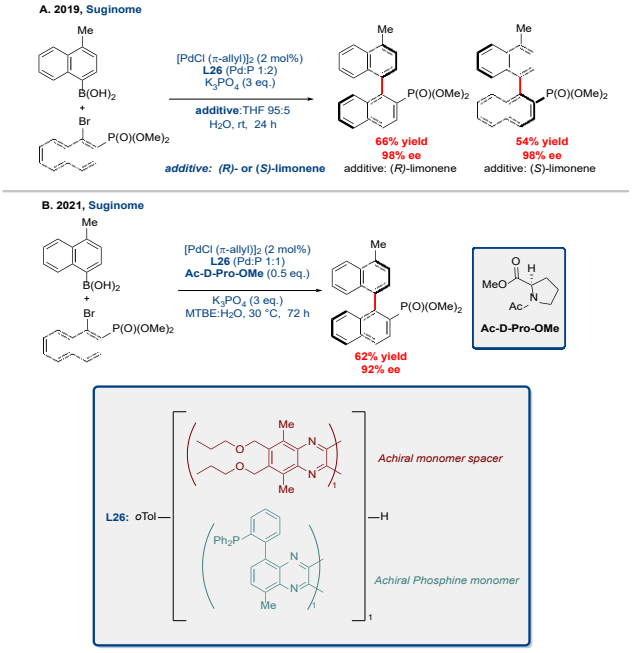
In terms of heterogeneous catalysis, Pd nanoparticles ligated with nonracemic BINAP ligand have also been synthesized, characterized, and employed on asymmetric SM couplings to construct biaryls in moderate enantioselectivities.[80,81]

Scheme 17. Asymmetric SM reaction with chiral PQXphos polymer ligand



A pioneering work on the helically chiral phosphine-based polymeric ligand by Suginome and co-workers has been documented for asymmetric SM couplings. After showing the potential of high-molecular-weight polymeric ligands for the hydrosilylation of styrenes and its reusability, the authors have further applied these copolymers for asymmetric SM cross-couplings. By mixing an achiral biaryl phosphine and the chiral spacer monomer, authors were able to form pure right-handed (*P*) helical structure of PQXphos **L25**.[82] The combination of the chiral polymer and Pd allows the asymmetric SM couplings between aryl bromide substituted with phosphonates and boronic acids in good-to-excellent atroposelectivities. The direction of helix in the polymer, which induced the chirality in the biaryl phosphine axis, could also be switched to obtain the pure left-handed (*M*) structure by heating the polymer in a 1,1,2-trichloroethane:THF solution. The catalytic asymmetric cross-coupling reaction could also be performed with the pure left-handed PQXphos to deliver the opposite enantiomer with excellent atroposelectivities (Scheme 17A).[83,84] Using a PQXphos ligand, the same group also developed the atroposelective SM coupling of 1-bromo-2-naphtoates to provide biaryls in high enantioselectivities (Scheme 17B).[85] Further investigations revealed the impact of ether solvents on the handedness of the chirality of the polymer.[86] In MTBE, the polymer is purely right-handed (*P*). In contrast, it is left-handed (*M*) in 1,2-DME solvent. Both binaphthyl enantiomers scaffolds could then be furnished with high enantiopurities by asymmetric SM reaction with this chiral helical polymer just by switching the solvent.

Scheme 18. Asymmetric SM coupling with achiral polymer phosphine ligand PQXphos



More recently, the same group described the asymmetric SM cross-coupling by using an achiral ligand PQXphos (i.e., removing the chirality on the chain of the spacer) and an additive as a source of chirality.[87] First, they showed that the use of (*R*)-or (*S*)-limonene as chiral solvent could allow the formation of biaryl phosphonates in a high level of chiral induction by favoring the screw-sense of the helical polymer (Scheme 18A). In another distinctive work, they employed chiral protected amino acids to induce the screw-sense of the macromolecular catalyst bearing achiral PQXphos ligand **L26**.[88] Using this additive, the asymmetric SM reaction could be performed in water to afford binaphthyl phosphonates in high enantioselectivities (Scheme 18B). This work on macromolecular catalyst showed a great potential in terms of catalyst recycling and very mild reaction conditions.

Based on aforementioned results, the asymmetric SM reaction can be accomplished with very high level of stereoinduction in the presence of chirality on the spacer, inducing the sense of the helical polymer ligand. The recent advances also showcased the potential of the PQXphos ligand where the chirality of the helical macromolecular catalyst can be induced by an additive or solvent.

Asymmetric SM cross-couplings catalyzed by transition-metals other than Pd

Enantioselective SM reactions catalyzed by nickel

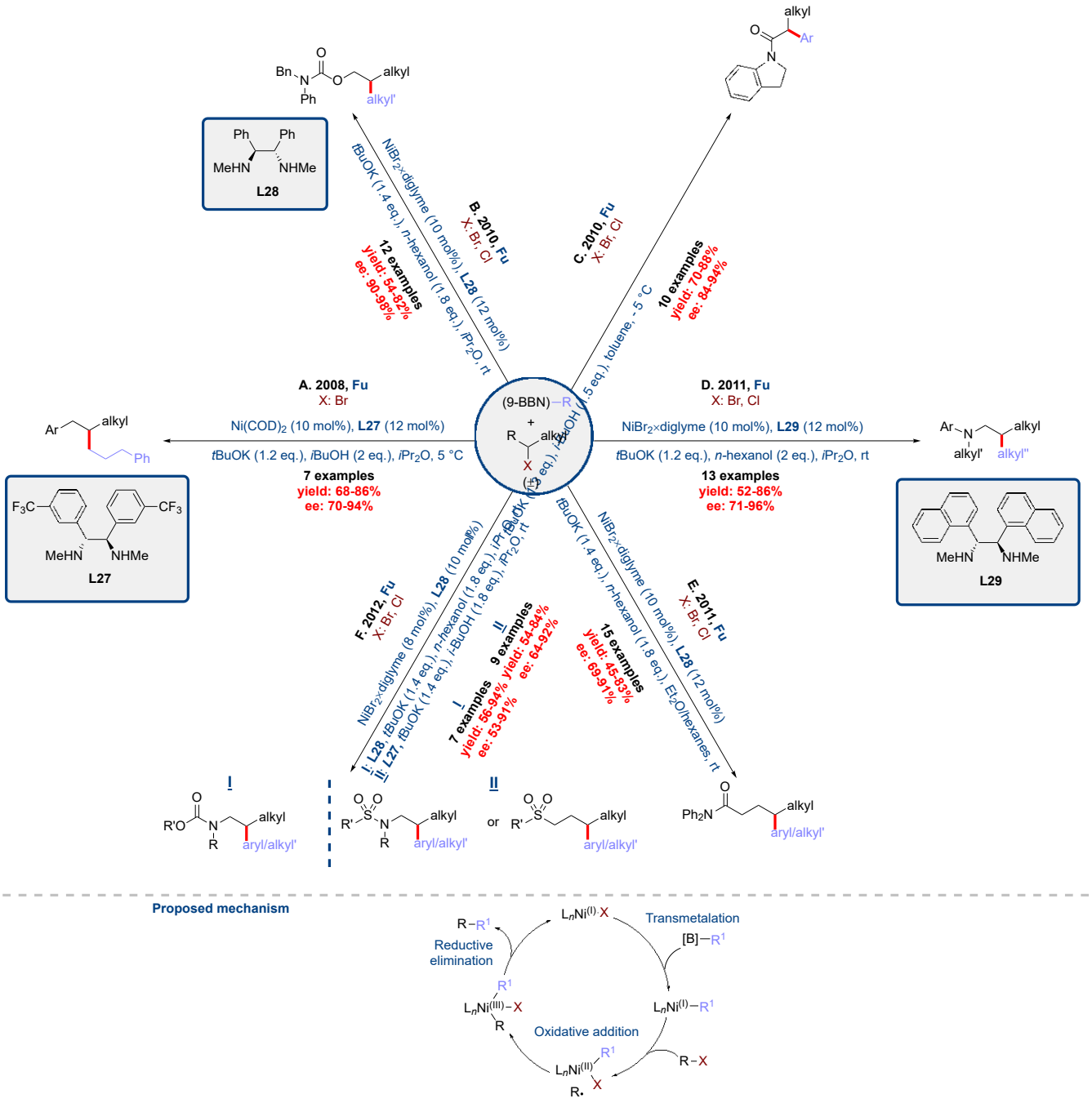
No doubt, the Pd-catalyzed asymmetric SM reaction is a powerful tool to build new atroposelective C(sp^2)-C(sp^2) bonds. However, the asymmetric formation of C(sp^2)-C(sp^3) or C(sp^3)-C(sp^3) bonds has been scarcely reported. Unfortunately, these Pd-catalyzed reactions are not efficient enough. For example, a modified approach for intramolecular couplings has been reported by Morken and co-workers to construct carbocyclic products but in modest-to-good level of enantioinduction, and it is very substrate-dependant.[89]

The nickel (Ni)-catalyzed asymmetric SM reactions of alkyls halides and organoboron compounds have emerged as an appealing solution to enable asymmetric C(sp^3)-C(sp^3) bonds formation. Compared to Pd, Ni is abundant and cheaper.[90,91] The pioneering work on Ni-catalyzed asymmetric SM reactions has been mainly reported by Fu's group, showcasing alkyl-alkyl cross-coupling using accessible chiral diamine ligands. After the seminal work on achiral Ni-catalyzed Suzuki-Miyaura cross-coupling of secondary halides with alkylborons,[92] Fu and coworkers described the first enantioselective SM cross-coupling of secondary racemic bromides with alkyl-9-borabicyclo[3.3.1]nonane (alkyl-(9-BBN)) for the preparation of new alkyl-alkyl bonds.[93] With an affordable chiral diamine ligand and a catalyst loading of 10 mol%, the authors achieved the first Ni-catalyzed asymmetric SM reaction catalyzed by Ni with quite good enantioselectivities (Scheme 19A).

After demonstrating the potential of Ni-catalyzed radical asymmetric SM reactions, the same group demonstrated that the secondary bromohydrins bearing carbamate protecting group can participated in the asymmetric SM reaction, yielding the coupling products in excellent enantioselectivities (Scheme 19B).[94] Interestingly, α-chloroamides could also undergo Ni-catalyzed asymmetric SM reactions to form chiral amides in good enantioselectivities (Scheme 19C).[95] Besides, the asymmetric SM reactions of secondary alkyl chlorides bearing proximal amine moiety has been accomplished to form chiral amines in good optical purities (Scheme 19D).[96]

Such catalytic method has also been developed using directing groups (such as amides) on the secondary alkyl bromide or chloride,[97] carbamates, sulfonamides, and sulfones, enabling the coupling product formation in good-to-excellent enantioselectivities (Scheme 19E, F).[98] Furthermore, the authors proposed a catalytic cycle starting with transmetalation by the boronic species on Ni(I) salt, followed by oxidative addition, contrary to the classical Pd-catalyzed SM reaction. The reductive elimination on the Ni(III) intermediate delivers the desired product. These Ni systems demonstrated a promising efficiency for the C(sp^3)-C(sp^3) and C(sp^2)-C(sp^3) cross-couplings of secondary bromide or chloride electrophiles with 9-BBN boron nucleophiles for alkylation or arylation, tolerating various directing groups. The products were generally obtained in good enantioselectivities under mild conditions.

Scheme 19: Ni-catalyzed asymmetric SM reactions of secondary alkyl halides

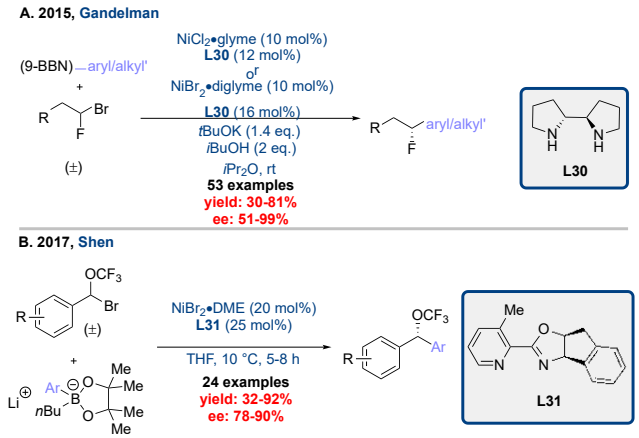


The catalyst loading is sometimes relatively high, which could be compensated by the easy availability of the chiral ligand.

Based on these achievements, a few other groups also accomplished the Ni-catalyzed enantioselective SM couplings of secondary halides. Gandelman's and co-workers developed a methodology for the generation of chiral fluoroalkanes containing a variety of functional groups, such as ketone, sulfonamide, benzylic moieties.[99,100] These functional groups also serve as the directing groups, assisting in the cross-coupling chemistry. This allows the delivery of a broad scope of fluoroalkanes in good-to-excellent enantioselectivities (Scheme 20A). Shen's group described the enantioselective SM cross-coupling of benzyl bromides bearing trifluoromethoxy substituent, allowing the construction of newly trifluoromethoxy-substituted stereogenic centers.[101] Employing pinacol borate lithium salts, arylation of benzyl bromides was achieved smoothly in good enantioselectivities; however, the catalyst loading is high (Scheme 20B).

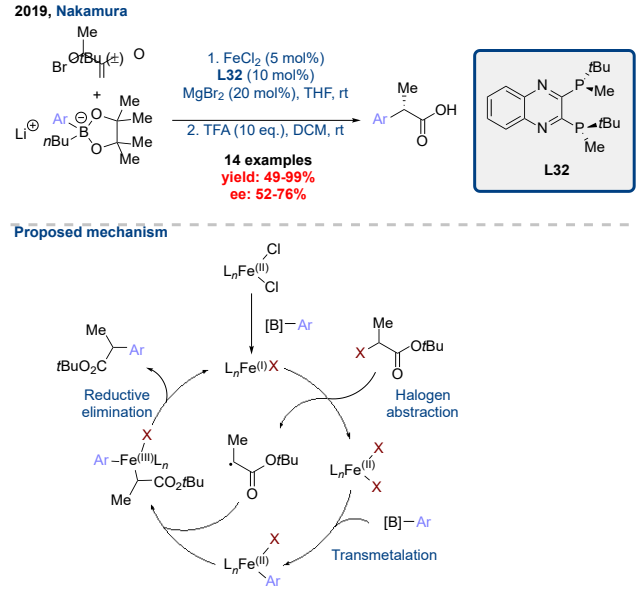
A more recent application has been recently disclosed by Zhang, Feng, and coworkers to achieve the Ni-catalyzed arylation of 3-bromo-phthalides with boronic acid, under mild conditions and in good enantioselectivities.[102]

Scheme 20. Ni-catalyzed asymmetric SM couplings of alkyl or benzyl bromides to build new fluoro or trifluoromethoxy substituted stereogenic centers



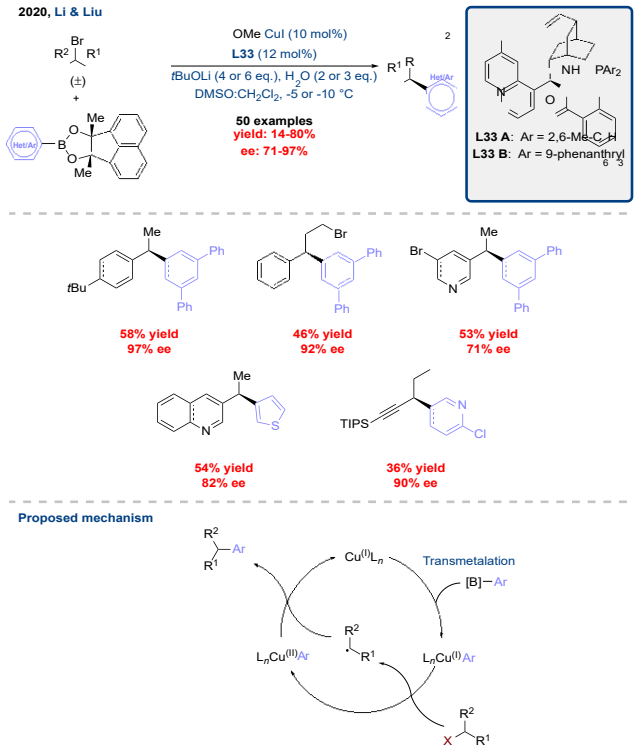
Other first-row transition-metal based catalysts for asymmetric SM reactions

Scheme 21. Fe-catalyzed Asymmetric SM reaction of *α*-bromopropionates



Among the diverse transition-metal catalyzed asymmetric SM reactions, other first-row transition-metals, such as copper (Cu) and iron (Fe) have recently been reported for radical asymmetric SM reactions. Nakamura and coworkers reported the Fe-catalyzed enantioselective SM couplings of racemic alkyl bromides through a Fe-bound *P*-stereogenic chiral ligand **L32**.[103] Unfortunately, the arylation of these *α*-bromopropionates occurred with moderate enantioselectivities, although the authors demonstrated the potential of this methodology to prepare several pharmaceutically relevant compounds. Nevertheless, this Fe-catalyzed technology could be a promising alternative. The catalytic cycle potentially starts with Fe(I) salt being the active species (Scheme 21). First, halogen abstraction generates an alkyl radical and a di-halogenated Fe(II) intermediate. Subsequently, the transmetalation and the addition of the alkyl radical allows the formation of an Fe(III) species, which undergoes reductive elimination to afford the product and regenerate the catalyst.

Scheme 22. Cu-catalyzed asymmetric SM coupling of secondary bromides



Li, Liu and co-workers reported the first example of Cu-catalyzed enantioselective Suzuki-Miyaura cross-couplings.[104] The enantioconvergent C(sp^3)-C(sp^2) coupling of aryl- or heteroarylboronates with secondary alkyl halides delivers a broad range of new chiral scaffolds with high enantioselectivities. Cu ligated with the cinchona alkaloid derived ligand **L33** was used as the catalyst. In contrast to the most of the enantioselective SM couplings discussed above, this method is amenable to heteroaromatics either on the electrophile or the boron nucleophile. Arylbenzyl alkynes can also be built by this radical asymmetric SM reaction using the corresponding halide source. The catalytic cycle potentially starts with the transmetalation of the Cu(I). The halogen abstraction facilitated by Cu(I) generates an alkyl radical and the Cu(II). The reaction between Cu(II)-containing aryl group reacts with the alkyl radical, forms the desired product and regenerates the Cu(I) to be used for the next catalytic cycle (Scheme 22).

To conclude on the use of first-row transition metals for the asymmetric SM reaction, the development of earth-abundant and inexpensive metals-based catalysts opens new doorways for future sustainable asymmetric SM cross-couplings, anticipating a goal of high efficiency, functional group tolerance, and enantioselectivity.

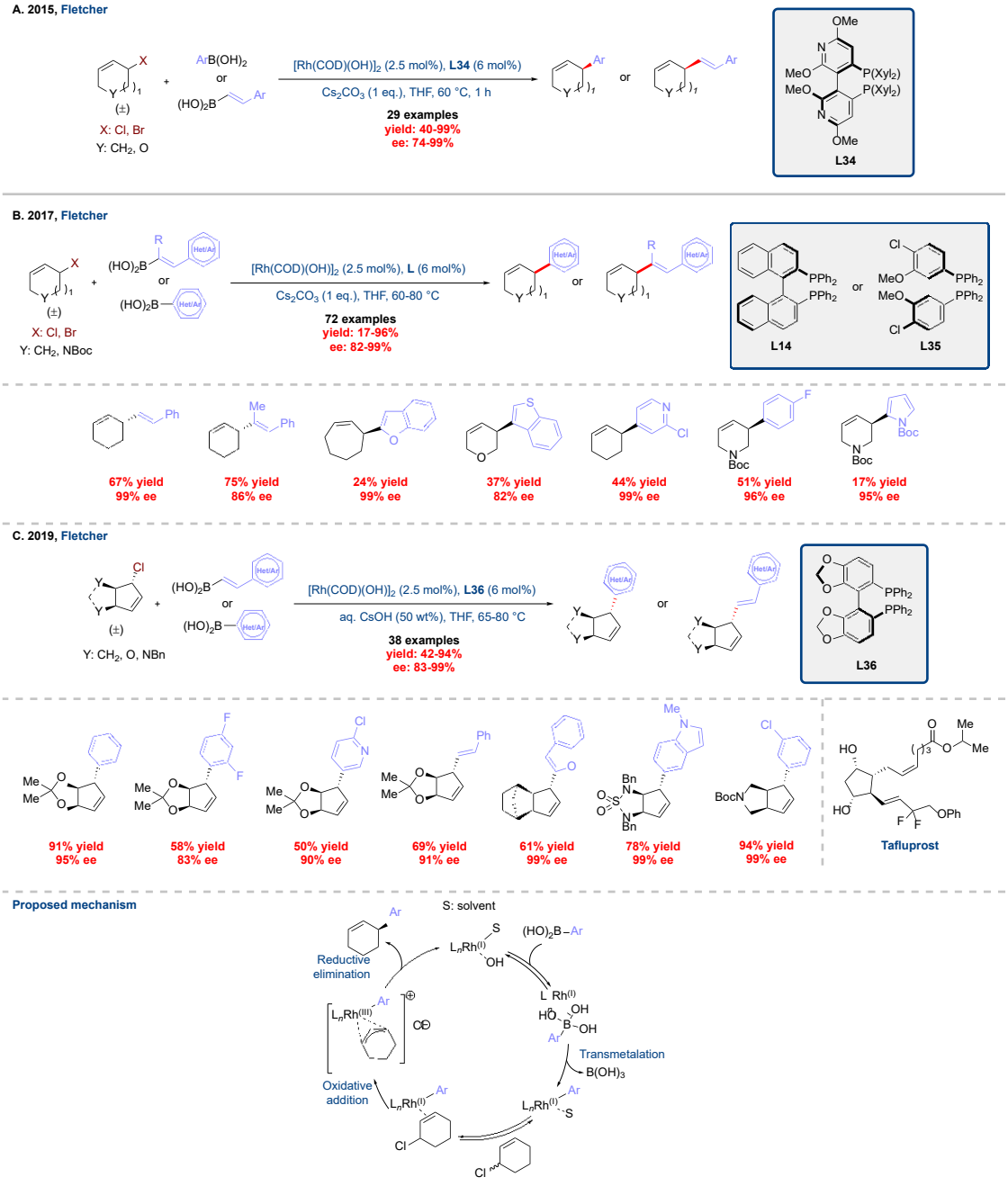
Enantioconvergent Rh-catalyzed cross-couplings

Rhodium (Rh)-catalyzed asymmetric SM couplings have recently emerged as a novel opportunity to build new chiral components starting from racemic allylic halides. At the first glance, this reaction could also be considered as an allylic functionalization. Fletcher group, a pioneer in this field, first described this coupling for the formation of unexplored building blocks. In the

seminal work described by Fletcher in 2015, the Rh-catalyzed enantioselective arylation of cyclic allylic halides is accomplished using a P-Phos ligand **L34**.[105] The carbocyclic compounds are obtained in almost perfect enantioselectivities under mild conditions through a dynamic-kinetic asymmetric transformation (DYKAT) process. Unfortunately, the scope was limited to electron-rich boron nucleophiles, and no examples of heterocyclic scaffolds were reported (Scheme 23A).

A few years later, the aforementioned limitations were overcome by the same group by using non-heterocyclic ligand. The methodology was showcased by a broad substrate scope in terms of the nature of nucleophile and electrophile along with excellent level of stereoinduction.[106,107] Milder reaction conditions and BINAP or **L35** ligand was used (Scheme 23B). Later, the same group extended this methodology to the enantio- and diastereoselective SM couplings of racemic bicycles using a standard diphosphine nonracemic SEGPHOS ligand **L36**.[108] The versatile carbocyclic scaffolds were obtained with high levels of diastereoselectivity and enantioselectivity (Scheme 23C). This original approach has been further highlighted by the total synthesis of Tafluprost, a prostaglandin analog.[109]

Scheme 23. Rh-catalyzed asymmetric SM reaction of cyclic allylic halides



Recent mechanistic studies have been conducted by the groups of Fletcher[110] and Sunoj[111] to gain more mechanistic insights, which involves a dynamic-kinetic asymmetric transformation (DYKAT), allowing the access to a single enantiomer starting from a racemic substrate. First, the Rh(I) undergoes transmetalation, followed by solvent coordination and oxidative addition of the allyl chloride to generate a Rh-allyl intermediate, which upon reductive elimination, delivers the enantioenriched product. This recent Rh-catalyzed variant of asymmetric SM reactions allows and tolerates the formation of unexplored skeletons and permits to densify the portfolio of molecules accessible via this transformation in general.

Conclusion

In summary, the ligand, metal, and solvent play a critical role in asymmetric SM coupling reactions. Besides significant developments, the asymmetric SM couplings remain challenging to date. Many studies on the design of novel chiral ligands have been reported to help understand the underlying factors governing enantioselectivity. Since most of the protocols have employed toxic chiral phosphorus (phosphine) ligands and phosphorus-containing hybrid ligands, novel axially chiral benign ligands are still desirable. Although chiral NHC ligands have been widely used in metal-catalyzed asymmetric reactions to achieve many satisfactory results,[112] their use in asymmetric SM couplings is still rare.[54,55] Compared to the modifications in other chiral ligands, there is a better opportunity for fine-tuning the steric bulk in NHC backbones to achieve optimal chiral induction in the catalytic cycle.

So far, Pd catalysts are mainly used in asymmetric SM coupling reactions. However, the first-row transition metals, such as Ni and Cu, have not been well explored for this transformation, although Fu has pioneered the nickel-catalyzed asymmetric alkyl–aryl and alkyl–alkyl coupling reactions.[92-97] Therefore, we envision that the near future will witness a stream of new chiral NHC ligands for efficient Pd- or Ni-catalyzed asymmetric SM coupling to access atropisomers. Moreover, new methodologies implying radical asymmetric SM reactions with first-row transition-metals, including Ni, Cu, and Fe, have recently emerged for opening new perspectives of the SM cross-coupling of racemic sp^3-hybridized carbon. Combined with their abundance and their low toxicity, the use of these metals could also become an appealing solution to substitute the Pd.

Although SM and other cross-couplings in water (a most sustainable solvent) are well-established, the asymmetric SM coupling in water is still rare. Therefore, adopting more environmentally responsible processes, e.g., recycling procedures, use of green solvents, and designing ligands that are not tedious to synthesize, is highly desirable. Since myriads of axially chiral natural products contain multiple heterocyclic residues, we believe that efficient catalyst systems are still needed to achieve cross-couplings of numerous heterocycles-containing substrates in excellent yields and enantioselectivities.

AUTHOR INFORMATION

Corresponding Author

*sachin.handa@louisville.edu

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Miyaura, N.; Suzuki, A. Stereoselective Synthesis of Arylated (E)-Alkenes by the Reaction of Alk-1-Enylboranes with Aryl Halides in the Presence of Palladium Catalyst. *J. Chem. Soc. Chem. Commun.* **1979**, 19, 866–867. https://doi.org/10.1039/C39790000866.

(2) Miyaura, N.; Yamada, K.; Suzuki, A. A New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. https://doi.org/10.1016/S0040-4039(01)95429-2.

(3) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483. https://doi.org/10.1021/cr00039a007.

(4) Jo, Y.-I.; Lee, C.-Y.; Cheon, C.-H. Asymmetric Total Syntheses of Naphthylisoquinoline Alkaloids via Atroposelective Coupling Reaction Using Central Chirality as Atroposelectivity-Controlling Group. *Org. Lett.* **2020**, *22*, 4653–4658. https://doi.org/10.1021/acs.orglett.0c01428.

(5) Yang, H.; Sun, J.; Gu, W.; Tang, W. Enantioselective Cross-Coupling for Axially Chiral Tetra-Ortho-Substituted Biaryls and Asymmetric Synthesis of Gossypol. *J. Am. Chem. Soc.* **2020**, *142*, 8036–8043. https://doi.org/10.1021/jacs.0c02686.

(6) Joncour, A.; Décor, A.; Liu, J.-M.; Tran Huu Dau, M.-E.; Baudoin, O. Asymmetric Synthesis of Antimicrotubule Biaryl Hybrids of Allocolchicine and Steganacin. *Chem. Eur. J.* **2007**, *13*, 5450–5465. https://doi.org/10.1002/chem.200601764.

(7) Bringmann, G.; Menche, D. Stereoselective Total Synthesis of Axially Chiral Natural Products via Biaryl Lactones. *Acc. Chem. Res.* **2001**, *34*, 615–624. https://doi.org/10.1021/ar000106z.

(8) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563–639. https://doi.org/10.1021/cr100155e.

(9) Yang, H.; Tang, W. Efficient Enantioselective Syntheses of Chiral Natural Products Facilitated by Ligand Design. *Chem. Rec.* **2020**, *20*, 23–40. https://doi.org/10.1002/tcr.201900003.

(10) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical

Transformations. *Chem. Rev.* **2015**, *115*, 11239–11300. https://doi.org/10.1021/acs.chemrev.5b00136.

(11) Wu, G.; Liu, Y.; Rouh, H.; Ma, L.; Tang, Y.; Zhang, S.; Zhou, P.; Wang, J.-Y.; Jin, S.; Unruh, D.; Surowiec, K.; Ma, Y.; Li, G. Asymmetric Catalytic Approach to Multilayer 3D Chirality. *Chem. Eur. J.* **2021**, *27*, 8013–8020. https://doi.org/10.1002/chem.202100700.

(12) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent Advances and New Concepts for the Synthesis of Axially Stereoenriched Biaryls. *Chem. Soc. Rev.* **2015**, *44*, 3418–3430. https://doi.org/10.1039/C5CS00012B.

(13) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427. https://doi.org/10.1002/anie.200462661.

(14) Cheng, J. K.; Xiang, S.-H.; Li, S.; Ye, L.; Tan, B. Recent Advances in Catalytic Asymmetric Construction of Atropisomers. *Chem. Rev.* **2021**, *121*, 4805–4902. https://doi.org/10.1021/acs.chemrev.0c01306.

(15) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of Axially Chiral Biaryl Compounds by Asymmetric Catalytic Reactions with Transition Metals. *Coord. Chem. Rev.* **2016**, *308*, 131–190. https://doi.org/10.1016/j.ccr.2015.07.006.

(16) Yang, H.; Yang, X.; Tang, W. Transition-Metal Catalyzed Asymmetric Carbon–Carbon Cross-Coupling with Chiral Ligands. *Tetrahedron* **2016**, *72*, 6143–6174. https://doi.org/10.1016/j.tet.2016.08.042.

(17) Link, A.; Sparr, C. Stereoselective Arene Formation. *Chem. Soc. Rev.* **2018**, *47*, 3804–3815. https://doi.org/10.1039/C7CS00875A.

(18) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534–547. https://doi.org/10.1021/acs.accounts.7b00602.

(19) Zilate, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal.* **2018**, *8*, 2981–2988. https://doi.org/10.1021/acscatal.7b04337.

(20) Frey, J.; Choppin, S.; Colobert, F.; Wencel-Delord, J. Towards Atropoenantiopure N–C Axially Chiral Compounds via Stereoselective C–N Bond Formation. *Chim. Int. J. Chem.* **2020**, *74*, 883–889. https://doi.org/10.2533/chimia.2020.883.

(21) Schmidt, T. A.; Sparr, C. Catalyst Control over Twofold and Higher-Order Stereogenicity by Atroposelective Arene Formation. *Acc. Chem. Res.* **2021**, *54,* 2764-2774. https://doi.org/10.1021/acs.accounts.1c00178

(22) Cammidge, A. N.; Crépy, K. V. L. The First Asymmetric Suzuki Cross-Coupling Reaction. *Chem. Commun.* **2000**, *18*, 1723–1724. https://doi.org/10.1039/B004513F

(23) Yin, J.; Buchwald, S. L. A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052. https://doi.org/10.1021/ja005622z.

(24) Baudoin, O. The Asymmetric Suzuki Coupling Route to Axially Chiral Biaryls. *Eur. J. Org. Chem.* **2005**, 4223–4229. https://doi.org/10.1002/ejoc.200500394.

(25) Zhang, D.; Wang, Q. Palladium Catalyzed Asymmetric Suzuki–Miyaura Coupling Reactions to Axially Chiral Biaryl Compounds: Chiral Ligands and Recent Advances. *Coord. Chem. Rev.* **2015**, *286*, 1–16. https://doi.org/10.1016/j.ccr.2014.11.011.

(26) Li, C.; Chen, D.; Tang, W. Addressing the Challenges in Suzuki–Miyaura Cross-Couplings by Ligand Design. *Synlett* **2016**, *27*, 2183–2200. https://doi.org/10.1055/s-0035-1562360.

(27) Goetzke, F. W.; Dijk, L. V.; Fletcher, S. P. Catalytic Asymmetric Suzuki–Miyaura Couplings. In *PATAI'S Chemistry of Functional Groups*; American Cancer Society, **2019**; pp 1–54. https://doi.org/10.1002/9780470682531.pat0962.

(28) Kamikawa, K.; Watanabe, T.; Uemura, M. Stereoselective Synthesis of Both Enantiomers of Axially Chiral Biaryls Utilizing Planar Chiral Tricarbonyl(Arene)Chromium Complexes. *J. Org. Chem.* **1996**, *61*, 1375–1384. https://doi.org/10.1021/jo951404q.

(29) Uemura, M.; Kamikawa, K. Stereoselective Induction of an Axiel Chirality by Suzuki Cross Coupling of Tricarbonyl(Arene)Chromium Complexes with Arylboronic Acids. *J. Chem. Soc. Chem. Commun.* **1994**, 23, 2697–2698. https://doi.org/10.1039/C39940002697.

(30) Nelson, S. G.; Hilfiker, M. A. Asymmetric Synthesis of Monodentate Phosphine Ligands Based on Chiral H6-Cr[Arene] Templates. *Org. Lett.* **1999**, *1*, 1379–1382. https://doi.org/10.1021/ol990929s.

(31) Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Bräse, S.; Rübsam, F. Total Synthesis of Vancomycin—Part 1: Design and Development of Methodology. *Chem. Eur. J.* **1999**, *5*, 2584–2601. https://doi.org/10.1002/(SICI)1521-3765(19990903)5:9<2584::AID-CHEM2584>3.0.CO;2-B.

(32) Lipshutz, B. H.; Keith, J. M. A Stereospecific, Intermolecular Biaryl-Coupling Approach to Korupensamine A En Route to the Michellamines. *Angew. Chem. Int. Ed.* **1999**, *38*, 3530–3533. https://doi.org/10.1002/(SICI)1521-3773(19991203)38:23<3530::AID-ANIE3530>3.0.CO;2-W.

(33) Joncour, A.; Décor, A.; Thoret, S.; Chiaroni, A.; Baudoin, O. Biaryl Axis as a Stereochemical Relay for the Enantioselective Synthesis of Antimicrotubule Agents. *Angew. Chem. Int. Ed.* **2006**, *45*, 4149–4152. https://doi.org/10.1002/anie.200600451.

(34) Colobert, F.; Valdivia, V.; Choppin, S.; Leroux, F. R.; Fernández, I.; Álvarez, E.; Khiar, N. Axial Chirality Control During Suzuki−Miyaura Cross-Coupling Reactions: The Tert-Butylsulfinyl Group as an Efficient Chiral Auxiliary. *Org. Lett.* **2009**, *11*, 5130–5133. https://doi.org/10.1021/ol9020755.

(35) Ma, Y.-N.; Yang, S.-D. Asymmetric Suzuki–Miyaura Cross-Coupling for the Synthesis of Chiral Biaryl Compounds as Potential Monophosphine Ligands. *Chem. Eur. J.* **2015**, *21*, 6673–6677. https://doi.org/10.1002/chem.201406554.

(36) Ma, Y.-N.; Yang, S.-D. Asymmetric Synthesis of Chiral Atropisomeric Bis-Aryl Organophosphorus from Menthyl H-Phosphinate. *Chem. Rec.* **2016**, *16*, 977–986. https://doi.org/10.1002/tcr.201500242.

(37) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. Enantioselective Synthesis of Axially Chiral Biaryls by the Pd-Catalyzed Suzuki−Miyaura Reaction: Substrate Scope and Quantum Mechanical Investigations. *J. Am. Chem. Soc.* **2010**, *132*, 11278–11287. https://doi.org/10.1021/ja104297g.

(38) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L. Highly Efficient Synthesis of a Class of Novel Chiral-Bridged Atropisomeric Monophosphine Ligands via Simple Desymmetrization and Their Applications in Asymmetric Suzuki–Miyaura Coupling Reaction. *Org. Lett.* **2012**, *14*, 1966–1969. https://doi.org/10.1021/ol300721p.

(39) Wu, W.; Wang, S.; Zhou, Y.; He, Y.; Zhuang, Y.; Li, L.; Wan, P.; Wang, L.; Zhou, Z.; Qiu, L. Highly Diastereoselective Synthesis of Atropisomeric Bridged P,N-Ligands and Their Applications in Asymmetric Suzuki–Miyaura Coupling Reaction. *Adv. Synth. Catal.* **2012**, *354*, 2395–2402. https://doi.org/10.1002/adsc.201200095.

(40) Zhou, Y.; Wang, S.; Wu, W.; Li, Q.; He, Y.; Zhuang, Y.; Li, L.; Pang, J.; Zhou, Z.; Qiu, L. Enantioselective Synthesis of Axially Chiral Multifunctionalized Biaryls via Asymmetric Suzuki–Miyaura Coupling. *Org. Lett.* **2013**, *15*, 5508–5511. https://doi.org/10.1021/ol402666p.

(41) Zhou, Y.; Zhang, X.; Liang, H.; Cao, Z.; Zhao, X.; He, Y.; Wang, S.; Pang, J.; Zhou, Z.; Ke, Z.; Qiu, L. Enantioselective Synthesis of Axially Chiral Biaryl Monophosphine Oxides via Direct Asymmetric Suzuki Coupling and DFT Investigations of the Enantioselectivity. *ACS Catal.* **2014**, *4*, 1390–1397. https://doi.org/10.1021/cs500208n.

(42) Li, Y.; Pan, B.; He, X.; Xia, W.; Zhang, Y.; Liang, H.; Reddy, C. V. S.; Cao, R.; Qiu, L. Pd-Catalyzed Asymmetric Suzuki–Miyaura Coupling Reactions for the Synthesis of Chiral Biaryl Compounds with a Large Steric Substituent at the 2-Position. *Beilstein J. Org. Chem.* **2020**, *16*, 966–973. https://doi.org/10.3762/bjoc.16.85.

(43) Ji, W.; Wu, H.-H.; Zhang, J. Axially Chiral Biaryl Monophosphine Oxides Enabled by Palladium/WJ-Phos-Catalyzed Asymmetric Suzuki–Miyaura Cross-Coupling. *ACS Catal.* **2020**, *10*, 1548–1554. https://doi.org/10.1021/acscatal.9b04354.

(44) Jensen, J. F.; Johannsen, M. New Air-Stable Planar Chiral Ferrocenyl Monophosphine Ligands: Suzuki Cross-Coupling of Aryl Chlorides and Bromides. *Org. Lett.* **2003**, *5*, 3025–3028. https://doi.org/10.1021/ol034943n.

(45) Patel, N. D.; Sieber, J. D.; Tcyrulnikov, S.; Simmons, B. J.; Rivalti, D.; Duvvuri, K.; Zhang, Y.; Gao, D. A.; Fandrick, K. R.; Haddad, N.; Lao, K. S.; Mangunuru, H. P. R.; Biswas, S.; Qu, B.; Grinberg, N.; Pennino, S.; Lee, H.; Song, J. J.; Gupton, B. F.; Garg, N. K.; Kozlowski, M. C.; Senanayake, C. H. Computationally Assisted Mechanistic Investigation and Development of Pd-Catalyzed Asymmetric Suzuki–Miyaura and Negishi Cross-Coupling Reactions for Tetra-Ortho-Substituted Biaryl Synthesis. *ACS Catal.* **2018**, *8*, 10190–10209. https://doi.org/10.1021/acscatal.8b02509.

(46) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J. J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. Efficient Chiral Monophosphorus Ligands for Asymmetric Suzuki–Miyaura Coupling Reactions. *Org. Lett.* **2012**, *14*, 2258–2261. https://doi.org/10.1021/ol300659d.

(47) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 570–573. https://doi.org/10.1021/ja409669r.

(48) Yang, X.; Xu, G.; Tang, W. Efficient Synthesis of Chiral Biaryls via Asymmetric Suzuki-Miyaura Cross-Coupling of Ortho-Bromo Aryl Triflates. *Tetrahedron* **2016**, *72*, 5178–5183. https://doi.org/10.1016/j.tet.2015.12.051.

(49) Byrne, L.; Sköld, C.; Norrby, P.-O.; Munday, R. H.; Turner, A. R.; Smith, P. D. Enantioselective Synthesis of Atropisomeric Biaryls Using Biaryl 2,5-Diphenylphospholanes as Ligands for Palladium-Catalysed Suzuki-Miyaura Reactions. *Adv. Synth. Catal.* **2021**, *363*, 259–267. https://doi.org/10.1002/adsc.202001211.

(50) Karpus, A.; Yesypenko, O.; Boiko, V.; Poli, R.; Daran, J.-C.; Voitenko, Z.; Kalchenko, V.; Manoury, E. Chiral Phosphinoferrocenyl-Calixarenes. *Eur. J. Org. Chem.* **2016**, *2016*, 3386–3394. https://doi.org/10.1002/ejoc.201600208.

(51) Bermejo, A.; Ros, A.; Fernández, R.; Lassaletta, J. M. C2-Symmetric Bis-Hydrazones as Ligands in the Asymmetric Suzuki−Miyaura Cross-Coupling. *J. Am. Chem. Soc.* **2008**, *130*, 15798–15799. https://doi.org/10.1021/ja8074693.

(52) Ros, A.; Estepa, B.; Bermejo, A.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Phosphino Hydrazones as Suitable Ligands in the Asymmetric Suzuki–Miyaura Cross-Coupling. *J. Org. Chem.* **2012**, *77*, 4740–4750. https://doi.org/10.1021/jo300548z.

(53) Zhang, S.-S.; Wang, Z.-Q.; Xu, M.-H.; Lin, G.-Q. Chiral Diene as the Ligand for the Synthesis of Axially Chiral Compounds via Palladium-Catalyzed Suzuki−Miyaura Coupling Reaction. *Org. Lett.* **2010**, *12*, 5546–5549. https://doi.org/10.1021/ol102521q.

(54) Wu, L.; Salvador, A.; Ou, A.; Shi, M. W.; Skelton, B. W.; Dorta, R. Monodentate Chiral N-Heterocyclic Carbene–Palladium-Catalyzed Asymmetric Suzuki–Miyaura and Kumada Coupling. *Synlett* **2013**, *24*, 1215–1220. https://doi.org/10.1055/s-0033-1338864.

(55) Shen, D.; Xu, Y.; Shi, S.-L. A Bulky Chiral N-Heterocyclic Carbene Palladium Catalyst Enables Highly Enantioselective Suzuki–Miyaura Cross-Coupling Reactions for the

Synthesis of Biaryl Atropisomers. *J. Am. Chem. Soc.* **2019**, *141*, 14983-14945. https://doi.org/10.1021/jacs.9b08578

(56) Haraguchi, R.; Hoshino, S.; Yamazaki, T.; Fukuzawa, S. Chiral Triazolylidene-Pd-PEPPSI: Synthesis, Characterization, and Application in Asymmetric Suzuki–Miyaura Cross-Coupling. *Chem. Commun.* **2018**, *54*, 2110–2113. https://doi.org/10.1039/C7CC09960F.

(57) Wang, T.; Hao, X.-Q.; Huang, J.-J.; Wang, K.; Gong, J.-F.; Song, M.-P. Chiral CNN Pincer Palladium(II) Complexes with 2-Aryl-6-(Oxazolinyl)Pyridine Ligands: Synthesis, Characterization, and Application to Enantioselective Allylation of Isatins and Suzuki–Miyaura Coupling Reaction. *Organometallics* **2014**, *33*, 194–205. https://doi.org/10.1021/om400945d.

(58) Pomarański, P.; Samanta, S.; Roszkowski, P.; Maurin, J. K.; Czarnocki, Z. Enantioselective Synthesis of Axially Chiral 3-Bromo-4-Alkoxy-2,6-Dimethyl-5-(Naphthalen-1-Yl)Pyridines via an Asymmetric Suzuki–Miyaura Cross-Coupling Reaction. *Tetrahedron Lett.* **2016**, *57*, 4713–4717. https://doi.org/10.1016/j.tetlet.2016.09.024.

(59) Haddad, N.; Mangunuru, H. P. R.; Fandrick, K. R.; Qu, B.; Sieber, J. D.; Rodriguez, S.; Desrosiers, J.-N.; Patel, N. D.; Lee, H.; Kurouski, D.; Grinberg, N.; Yee, N. K.; Song, J. J.; Senanayake, C. H. Reengineered BI-DIME Ligand Core Based on Computer Modeling to Increase Selectivity in Asymmetric Suzuki–Miyaura Coupling for the Challenging Axially Chiral HIV Integrase Inhibitor. *Adv. Synth. Catal.* **2016**, *358*, 3522–3527. https://doi.org/10.1002/adsc.201600889.

(60) Xia, W.; Li, Y.; Zhou, Z.; Chen, H.; Liang, H.; Yu, S.; He, X.; Zhang, Y.; Pang, J.; Zhou, Z.; Qiu, L. Synthesis of Chiral-Bridged Atropisomeric Monophosphine Ligands with Tunable Dihedral Angles and Their Applications in Asymmetric Suzuki–Miyaura Coupling Reactions. *Adv. Synth. Catal.* **2017**, *359*, 1656–1662. https://doi.org/10.1002/adsc.201700020.

(61) Xia, W.; Zhang, Z.-W.; Li, Y.; Jiang, X.; Liang, H.; Zhang, Y.; Cao, R.; Qiu, L. Enantioselective Synthesis of Chiral Heterocyclic Biaryls via Asymmetric Suzuki–Miyaura Cross-Coupling of 3-Bromopyridine Derivatives. *Org. Biomol. Chem.* **2019**, *17*, 2351–2355. https://doi.org/10.1039/C8OB03048K.

(62) Pan, C.; Zhu, Z.; Zhang, M.; Gu, Z. Palladium-Catalyzed Enantioselective Synthesis of 2-Aryl Cyclohex-2-Enone Atropisomers: Platform Molecules for the Divergent Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem. Int. Ed.* **2017**, *56*, 4777–4781. https://doi.org/10.1002/anie.201701467.

(63) Ros, A.; Estepa, B.; Ramírez-López, P.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Dynamic Kinetic Cross-Coupling Strategy for the Asymmetric Synthesis of Axially Chiral Heterobiaryls. *J. Am. Chem. Soc.* **2013**, *135*, 15730–15733. https://doi.org/10.1021/ja4087819.

(64) Lou, Y.; Wei, J.; Li, M.; Zhu, Y. Distal Ionic Substrate–Catalyst Interactions Enable Long-Range Stereocontrol: Access to Remote Quaternary Stereocenters through a Desymmetrizing Suzuki–Miyaura Reaction. *J. Am. Chem. Soc.* **2022**, *144*, 123–129. https://doi.org/10.1021/jacs.1c12345.

(65) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. Enantioselective Suzuki Reactions: Catalytic Asymmetric Synthesis of Compounds Containing Quaternary Carbon Centers. *Angew. Chem. Int. Ed.* **2004**, *43*, 1249–1251. https://doi.org/10.1002/anie.200352648.

(66) Sun, C.; Potter, B.; Morken, J. P. A Catalytic Enantiotopic-Group-Selective Suzuki Reaction for the Construction of Chiral Organoboronates. *J. Am. Chem. Soc.* **2014**, *136*, 6534–6537. https://doi.org/10.1021/ja500029w.

(67) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. Nonracemic Allylic Boronates through Enantiotopic-Group-Selective Cross-Coupling of Geminal Bis(Boronates) and Vinyl Halides. *J. Am. Chem. Soc.* **2014**, *136*, 17918–17921. https://doi.org/10.1021/ja510266x.

(68) Potter, B.; Edelstein, E. K.; Morken, J. P. Modular, Catalytic Enantioselective Construction of Quaternary Carbon Stereocenters by Sequential Cross-Coupling Reactions. *Org. Lett.* **2016**, *18*, 3286–3289. https://doi.org/10.1021/acs.orglett.6b01580.

(69) Liu, X.; Sun, C.; Mlynarski, S.; Morken, J. P. Synthesis and Stereochemical Assignment of Arenolide. *Org. Lett.* **2018**, *20*, 1898–1901. https://doi.org/10.1021/acs.orglett.8b00439.

(70) Sun, H.-Y.; Kubota, K.; Hall, D. G. Reaction Optimization, Scalability, and Mechanistic Insight on the Catalytic Enantioselective Desymmetrization of 1,1-Diborylalkanes via Suzuki–Miyaura Cross-Coupling. *Chem. Eur. J.* **2015**, *21*, 19186–19194. https://doi.org/10.1002/chem.201406680.

(71) Ding, L.; Sui, X.; Gu, Z. Enantioselective Synthesis of Biaryl Atropisomers via Pd/Norbornene-Catalyzed Three-Component Cross-Couplings. *ACS Catal.* **2018**, *8*, 5630–5635. https://doi.org/10.1021/acscatal.8b01037.

(72) Liu, Z.-S.; Hua, Y.; Gao, Q.; Ma, Y.; Tang, H.; Shang, Y.; Cheng, H.-G.; Zhou, Q. Construction of Axial Chirality via Palladium/Chiral Norbornene Cooperative Catalysis. *Nat. Catal.* **2020**, *3*, 727–733. https://doi.org/10.1038/s41929-020-0494-1.

(73) Dong, Y.; Liu, R.; Wang, W. Catalytic Asymmetric Catellani-Type Reaction: A Powerful Tool for Axial Chirality Construction. *Green Synth. Catal.* **2020**, *1*, 83–85. https://doi.org/10.1016/j.gresc.2020.09.002.

(74) Sheldon, R. A.; Woodley, J. M. Role of Biocatalysis in Sustainable Chemistry. *Chem. Rev.* **2018**, *118*, 801–838. https://doi.org/10.1021/acs.chemrev.7b00203.

(75) Carmona, J. A.; Rodríguez-Franco, C.; Fernández, R.; Hornillos, V.; Lassaletta, J. M. Atroposelective Transformation of Axially Chiral (Hetero)Biaryls. From Desymmetrization to Modern Resolution Strategies. *Chem. Soc. Rev.* **2021**, *50*, 2968–2983. https://doi.org/10.1039/D0CS00870B.

(76) Abe, S.; Niemeyer, J.; Abe, M.; Takezawa, Y.; Ueno, T.; Hikage, T.; Erker, G.; Watanabe, Y. Control of the Coordination Structure of Organometallic Palladium Complexes in an Apo-Ferritin Cage. *J. Am. Chem. Soc.* **2008**, *130*, 10512–10514. https://doi.org/10.1021/ja802463a.

(77) Chatterjee, A.; Mallin, H.; Klehr, J.; Vallapurackal, J.; Finke, A. D.; Vera, L.; Marsh, M.; Ward, T. R. An Enantioselective Artificial Suzukiase Based on the Biotin–Streptavidin Technology. *Chem. Sci.* **2016**, *7*, 673–677. https://doi.org/10.1039/C5SC03116H.

(78) Uozumi, Y.; Matsuura, Y.; Arakawa, T.; Yamada, Y. M. A. Asymmetric Suzuki–Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin. *Angew. Chem. Int. Ed.* **2009**, *48*, 2708–2710. https://doi.org/10.1002/anie.200900469.

(79) Uozumi, Y.; Matsuura, Y.; Suzuka, T.; Arakawa, T.; Yamada, Y. M. A. Palladium-Catalyzed Asymmetric Suzuki–Miyaura Cross Coupling with Homochiral Phosphine Ligands Having Tetrahydro-1H-Imidazo[1,5-a]Indole Backbone. *Synthesis* **2017**, *49*, 59–68. https://doi.org/10.1055/s-0036-1589407.

(80) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. Asymmetric Suzuki–Miyaura Coupling Reactions Catalyzed by Chiral Palladium Nanoparticles at Room Temperature. *Angew. Chem. Int. Ed.* **2008**, *47*, 6917–6919. https://doi.org/10.1002/anie.200802174.

(81) Mori, K.; Kondo, Y.; Yamashita, H. Synthesis and Characterization of FePd Magnetic Nanoparticles Modified with Chiral BINAP Ligand as a Recoverable Catalyst Vehicle for the Asymmetric Coupling Reaction. *Phys. Chem. Chem. Phys.* **2009**, *11*, 8949–8954. https://doi.org/10.1039/B910069E.

(82) Yamamoto, T.; Yamada, T.; Nagata, Y.; Suginome, M. High-Molecular-Weight Polyquinoxaline-Based Helically Chiral Phosphine (PQXphos) as Chirality-Switchable, Reusable, and Highly Enantioselective Monodentate Ligand in Catalytic Asymmetric Hydrosilylation of Styrenes. *J. Am. Chem. Soc.* **2010**, *132*, 7899–7901. https://doi.org/10.1021/ja102428q.

(83) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. Highly Enantioselective Synthesis of Axially Chiral Biarylphosphonates: Asymmetric Suzuki–Miyaura Coupling Using High-Molecular-Weight, Helically Chiral Polyquinoxaline-Based Phosphines. *Angew. Chem. Int. Ed.* **2011**, *50*, 8844–8847. https://doi.org/10.1002/anie.201103792.

(84) Suginome, M.; Yamamoto, T.; Nagata, Y.; Yamada, T.; Akai, Y. Catalytic Asymmetric Synthesis Using Chirality-switchable Helical Polymer as a Chiral Ligand. *Pure Appl. Chem.* **2012**, *84*, 1759–1769. https://doi.org/10.1351/PAC-CON-11-08-23.

(85) Akai, Y.; Konnert, L.; Yamamoto, T.; Suginome, M. Asymmetric Suzuki–Miyaura Cross-Coupling of 1-Bromo-2-Naphthoates Using the Helically Chiral Polymer Ligand PQXphos. *Chem. Commun.* **2015**, *51*, 7211–7214. https://doi.org/10.1039/C5CC01074H.

(86) Nagata, Y.; Kuroda, T.; Takagi, K.; Suginome, M. Ether Solvent-Induced Chirality Inversion of Helical Poly(Quinoxaline-2,3-Diyl)s Containing L-Lactic Acid Derived Side Chains. *Chem. Sci.* **2014**, *5*, 4953–4956. https://doi.org/10.1039/C4SC01920B.

(87) Nagata, Y.; Takeda, R.; Suginome, M. Asymmetric Catalysis in Chiral Solvents: Chirality Transfer with Amplification of Homochirality through a Helical Macromolecular Scaffold. *ACS Cent. Sci.* **2019**, *5*, 1235–1240. https://doi.org/10.1021/acscentsci.9b00330.

(88) Ikeda, S.; Takeda, R.; Fujie, T.; Ariki, N.; Nagata, Y.; Suginome, M. Protected Amino Acids as a Nonbonding Source of Chirality in Induction of Single-Handed Screw-Sense to Helical Macromolecular Catalysts. *Chem. Sci.* **2021**, *12*, 8811–8816. https://doi.org/10.1039/D1SC01764K.

(89) Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. Enantioselective Carbocycle Formation through Intramolecular Pd-Catalyzed Allyl–Aryl Cross-Coupling. *Org. Lett.* **2014**, *16*, 4420–4423. https://doi.org/10.1021/ol5019163.

(90) Han, F.-S. Transition-Metal-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions: A Remarkable Advance from Palladium to Nickel Catalysts. *Chem. Soc. Rev.* **2013**, *42*, 5270–5298. https://doi.org/10.1039/C3CS35521G.

(91) Li, Z.; Jiang, Y.-Y.; Fu, Y. Theoretical Study on the Mechanism of Ni-Catalyzed Alkyl–Alkyl Suzuki Cross-Coupling. *Chem. Eur. J.* **2012**, *18*, 4345–4357. https://doi.org/10.1002/chem.201103882.

(92) Saito, B.; Fu, G. C. Alkyl−Alkyl Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603. https://doi.org/10.1021/ja0740081.

(93) Saito, B.; Fu, G. C. Enantioselective Alkyl−Alkyl Suzuki Cross-Couplings of Unactivated Homobenzylic Halides. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695. https://doi.org/10.1021/ja8013677.

(94) Owston, N. A.; Fu, G. C. Asymmetric Alkyl−Alkyl Cross-Couplings of Unactivated Secondary Alkyl Electrophiles: Stereoconvergent Suzuki Reactions of Racemic Acylated Halohydrins. *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909. https://doi.org/10.1021/ja105924f.

(95) Lundin, P. M.; Fu, G. C. Asymmetric Suzuki Cross-Couplings of Activated Secondary Alkyl Electrophiles: Arylations of Racemic α-Chloroamides. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. https://doi.org/10.1021/ja105148g.

(96) Lu, Z.; Wilsily, A.; Fu, G. C. Stereoconvergent Amine-Directed Alkyl–Alkyl Suzuki Reactions of Unactivated Secondary Alkyl Chlorides. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157. https://doi.org/10.1021/ja203560q.

(97) Zultanski, S. L.; Fu, G. C. Catalytic Asymmetric γ-Alkylation of Carbonyl Compounds via Stereoconvergent Suzuki Cross-Couplings. *J. Am. Chem. Soc.* **2011**, *133*, 15362–15364. https://doi.org/10.1021/ja2079515.

(98) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. New Directing Groups for Metal-Catalyzed Asymmetric Carbon–Carbon Bond-Forming Processes: Stereoconvergent Alkyl–Alkyl Suzuki Cross-Couplings of Unactivated Electrophiles. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797. https://doi.org/10.1021/ja301612y.

(99) Jiang, X.; Sakthivel, S.; Kulbitski, K.; Nisnevich, G.; Gandelman, M. Efficient Synthesis of Secondary Alkyl

Fluorides via Suzuki Cross-Coupling Reaction of 1-Halo-1-Fluoroalkanes. *J. Am. Chem. Soc.* **2014**, *136*, 9548–9551. https://doi.org/10.1021/ja504089y.

(100) Jiang, X.; Gandelman, M. Enantioselective Suzuki Cross-Couplings of Unactivated 1-Fluoro-1-Haloalkanes: Synthesis of Chiral β-, γ-, δ-, and ε-Fluoroalkanes. *J. Am. Chem. Soc.* **2015**, *137*, 2542–2547. https://doi.org/10.1021/jacs.5b00473.

(101) Huang, W.; Wan, X.; Shen, Q. Enantioselective Construction of Trifluoromethoxylated Stereogenic Centers by a Nickel-Catalyzed Asymmetric Suzuki–Miyaura Coupling of Secondary Benzyl Bromides. *Angew. Chem. Int. Ed.* **2017**, *56*, 11986–11989. https://doi.org/10.1002/anie.201706868.

(102) Xu, S.-Y.; Zhang, R.; Zhang, S.-S.; Feng, C.-G. Enantioselective Synthesis of 3-Aryl-Phthalides through a Nickel-Catalyzed Stereoconvergent Cross-Coupling Reaction. *Org. Biomol. Chem.* **2021**, *19*, 4492–4496. https://doi.org/10.1039/D1OB00487E.

(103) Iwamoto, T.; Okuzono, C.; Adak, L.; Jin, M.; Nakamura, M. Iron-Catalysed Enantioselective Suzuki–Miyaura Coupling of Racemic Alkyl Bromides. *Chem. Commun.* **2019**, *55*, 1128–1131. https://doi.org/10.1039/C8CC09523J.

(104) Jiang, S.-P.; Dong, X.-Y.; Gu, Q.-S.; Ye, L.; Li, Z.-L.; Liu, X.-Y. Copper-Catalyzed Enantioconvergent Radical Suzuki–Miyaura C(Sp3)–C(Sp2) Cross-Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 19652–19659. https://doi.org/10.1021/jacs.0c09125.

(105) Sidera, M.; Fletcher, S. P. Rhodium-Catalysed Asymmetric Allylic Arylation of Racemic Halides with Arylboronic Acids. *Nat. Chem.* **2015**, *7*, 935–939. https://doi.org/10.1038/nchem.2360.

(106) Schäfer, P.; Palacin, T.; Sidera, M.; Fletcher, S. P. Asymmetric Suzuki-Miyaura Coupling of Heterocycles via Rhodium-Catalysed Allylic Arylation of Racemates. *Nat. Commun.* **2017**, *8*, 15762. https://doi.org/10.1038/ncomms15762.

(107) González, J.; van Dijk, L.; Goetzke, F. W.; Fletcher, S. P. Highly Enantioselective Rhodium-Catalyzed Cross-Coupling of Boronic Acids and Racemic Allyl Halides. *Nat. Protoc.* **2019**, *14*, 2972–2985. https://doi.org/10.1038/s41596-019-0209-8.

(108) Goetzke, F. W.; Mortimore, M.; Fletcher, S. P. Enantio- and Diastereoselective Suzuki–Miyaura Coupling with Racemic Bicycles. *Angew. Chem. Int. Ed.* **2019**, *58* (35), 12128–12132. https://doi.org/10.1002/anie.201906478.

(109) Kučera, R.; Goetzke, F. W.; Fletcher, S. P. An Asymmetric Suzuki–Miyaura Approach to Prostaglandins: Synthesis of Tafluprost. *Org. Lett.* **2020**, *22*, 2991–2994. https://doi.org/10.1021/acs.orglett.0c00745.

(110) van Dijk, L.; Ardkhean, R.; Sidera, M.; Karabiyikoglu, S.; Sari, Ö.; Claridge, T. D. W.; Lloyd-Jones, G. C.; Paton, R. S.; Fletcher, S. P. Mechanistic Investigation of Rh(I)-Catalysed Asymmetric Suzuki–Miyaura Coupling with Racemic Allyl Halides. *Nat. Catal.* **2021**, *4*, 284–292. https://doi.org/10.1038/s41929-021-00589-y.

(111) Pareek, M.; Sunoj, R. B. Energetics of Dynamic Kinetic Asymmetric Transformation in Suzuki–Miyaura Coupling. *ACS Catal.* **2020**, *10*, 4349–4360. https://doi.org/10.1021/acscatal.9b05526.

(112) Wang, F.; Liu, L, J.; Wang, W.; Li, S.; Shi, M. Chiral NHC–metal-based asymmetric catalysis. *Coord. Chem. Rev.* **2012**, *256*, 804-853.

SYNOPSIS TOC: This review critically analyzes the past and the new advancements on homogeneous and heterogeneous asymmetric catalyzed Suzuki-Miyaura cross-couplings.