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Recent advances in the synthesis of axially chiral biaryls *via* transition metal-catalysed asymmetric C–H functionalization

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Axially chiral biaryl motifs are widely present in natural products and pharmaceuticals. Moreover, they have been broadly used as privileged ligands in asymmetric catalysis. Over the past few decades, the efficient synthesis of axially chiral biaryls has been a research topic of great interest. This feature article will provide an overview of recent advances in the synthesis of these chiral skeletons *via* transition metal-catalysed asymmetric C–H functionalization.

1. Introduction

The axial chirality of biaryls is caused by the restricted rotation of the aryl–aryl bond (the so-called atropisomerism) resulting from the nonplanar arrangement of four *ortho*-substituents about the biaryl axis.¹ During the past few decades, axially chiral biaryls have received considerable attention due to their widespread presence in natural products and pharmaceuticals such as the glycopeptide antibiotic vancomycin, (+)-kinpholone, and (–)-gossypol (Scheme 1a).² In addition, axially chiral biaryls could be used as privileged ligands in asymmetric catalysis (Scheme 1b),^{3,4}

as highlighted by the well-known BINAP, BINOL and its derived phosphoric acids.

Because of the importance of these privileged scaffolds, substantial efforts have been devoted to the asymmetric synthesis of axially chiral biaryl skeletons.⁵ Accordingly, various catalytic systems involving metal-catalyzed approaches and organocatalyzed approaches have been developed for these asymmetric transformations. However, these methods usually suffer from several drawbacks such as the use of stoichiometric chiral auxiliaries, the requirement of prefunctionalization of starting materials and the poor efficiency of chiral induction. The growing demand for enantiopure axially chiral biaryl compounds in asymmetric catalysis and pharmaceutical industries has accelerated the development of efficient strategies for these useful structural motifs.

Recently, asymmetric C–H bond functionalization reactions have attracted much attention for their great promise as an

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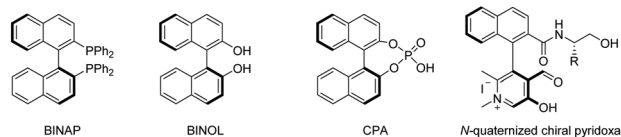
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a) Atropisomerism in natural products and pharmaceuticals



b) Atropisomerism in ligands



Scheme 1 Atropisomerism in natural products and ligands.

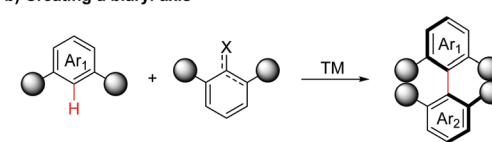
efficient and straightforward approach to access chiral molecules.⁶ With this regard, transition-metal-catalysed asymmetric C–H activation would provide synthetic chemists a novel disconnection of retrosynthetic analysis logic to introduce new stereocenters to organic molecules, enabling the rapid generation of structural complexity in a single step. However, it is a formidable challenge to chemists due to the difficulty in finding suitable ligands or catalysts to control enantioselectivity during the asymmetric C–H activation process.

Although the creation of central and/or planar chirality *via* asymmetric C–H activation has been well investigated, methods for the asymmetric synthesis of axially chiral compounds *via* C–H functionalization have remained a barely explored field until recently, likely due to the possible racemization of atropisomers under typically elevated reaction temperatures of C–H activation reactions.⁶ With significant advances of C–H activation reactions under mild conditions, some elegant strategies have been realized to address the bottleneck of axial

a) Locking a preformed axis



b) Creating a biaryl axis



Scheme 2 Transition-metal-catalyzed atroposelective C–H functionalization strategies towards axially chiral biaryls.

chirality control. This feature article thus aims to provide an up-to-date overview of recent advances in the synthesis of axially chiral biaryls through C–H activation. We will focus exclusively on the generation of axially chiral biaryl skeletons by means of asymmetric C–H activation reactions with transition metal catalysis. That said, atroposelective C–H functionalization reactions using other organocatalysts such as peptides, and quinidine derivatives will not be discussed here.⁷

In general, two main strategies utilizing transition-metal-catalysed atroposelective C–H functionalization have been developed in the synthesis of axially chiral biaryls. In the first case, axially chiral biaryls were synthesized by locking a preformed axis *via* (dynamic) kinetic resolution or desymmetrization processes (Scheme 2a). Accordingly, this section can be further classified into four subsections: catalytic asymmetric C–H functionalization by chiral ligands, atroposelective C–H functionalization catalysed by a preformed chiral catalyst, diastereoselective C–H functionalization directed by a chiral auxiliary and enantioselective C–H functionalization enabled by a transient directing group. The second category is the creation of a biaryl axis *via* C–H activation/asymmetric coupling (Scheme 2b).



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2. Locking a pre-existing biaryl axis *via* (dynamic) kinetic resolution or desymmetrization

2.1 Catalytic asymmetric C–H functionalization cooperatively catalysed by transition metals and chiral ligands

The designation and discovery of efficient ligands for achieving high enantioselectivity has been a central topic in catalytic asymmetric synthesis. In the field of atroposelective C–H functionalization, several types of chiral ligands have already been applied for asymmetric induction of axial chirality.^{8–13} In 2000, the atroposelective alkylation of 2-(1-naphthyl)pyridine or 1-(1-naphthyl)isoquinoline by Rh(I)-catalysed C–H alkylation using chiral ferrocenyl phosphine as the ligand was reported by Murai and co-workers (Scheme 3).⁸ The low inversion barriers of biaryl substrates enabled the interconversion easily during the dynamic kinetic process. The alkylation products, however, are produced with the rise of inversion barriers to restrict the rotation. The biaryl compound *rac-1* reacted with ethylene using the $[\{\text{RhCl}(\text{coe})_2\}_2]/(R),(S)\text{-PPFOMe}$ (**L1**, *coe* = *cis*-cyclooctene) catalytic system obtaining the coupling product **2** in 37% yield with 49% ee. In the case of quinoline derivative **3**, the efficiency and enantioselectivity were slightly lower, giving the product **4** in 33% yield and 22% ee.

Since the pioneering work of Yu and co-workers, mono-*N*-protected amino acids (MPAAs) have been identified as privileged ligands for a wide variety of enantioselective C–H functionalization reactions.⁹ This MPAA catalytic system has also been adopted for atroposelective C–H activation. In 2014, You and co-workers achieved the first Pd-catalysed C–H iodination for the synthesis of axially chiral biaryls *via* kinetic resolution (Scheme 4a).¹⁰ In their report, *N*-iodosuccinimide (NIS) was used as an iodinated reagent and *N*-monoprotected phenylalanine (**L2**) was used as the most effective ligand to control the stereoselectivity. A selectivity factor could be reached up to 27. The iodination products could be easily converted to aryl-substituted pyridine *N*-oxides by Suzuki–Miyaura coupling, which was used as a catalyst in asymmetric allylation of benzaldehyde with allyltrichlorosilane. They proposed that the asymmetric C–H



Scheme 3 Rh(I)-Catalysed asymmetric C–H alkylation using a chiral ferrocenyl phosphine ligand (Murai *et al.*, 2000).⁸



Proposed Mechanism



b) Yang *et al.*, 2017



Scheme 4 Pd-Catalysed atroposelective C–H functionalization using MPAA ligands (You *et al.*, 2014;¹⁰ Yang, *et al.*, 2017¹¹).

bond cleavage of *rac-5* may occur *via* a concerted metathesis deprotonation mechanism (CMD) pathway with the aid of an MPAA ligand. The Pd(II) intermediate **6a** was oxidized by NIS to form a reactive Pd(IV) intermediate **6b**, which then underwent reductive elimination to release the desired product (S)-**7** with the regeneration of Pd(II) species.

In 2017, Yang and co-workers developed a P(O)R₂-directed enantioselective C–H olefination for the synthesis of axially chiral phosphine–olefin biaryls (Scheme 4b).¹¹ The reaction used Boc-L-Val-OH (**L3**) as the chiral ligand and Pd(OAc)₂ as the catalyst. Electron-withdrawing and electron-donating substituents on the substrates were both well tolerated in this transformation. The racemic biaryl phosphine oxides underwent a dynamic kinetic resolution process in the presence of olefin, giving the corresponding chiral biaryl phosphine–olefin compounds with up to 99% yield and up to 96% ee (Scheme 4).

Indoles are a kind of important structural motif widely occurring in natural products and bioactive molecules. Very recently, Gu *et al.* reported enantioselective synthesis of indole-based biaryl atropisomers *via* palladium-catalysed intramolecular C–H arylation (Scheme 5).¹² A modified TADDOL-phosphoramidite was used as an efficient ligand for the intramolecular C–H cyclization reaction. The thermal stability of the indole-based atropisomers was also investigated.



Scheme 5 Palladium-catalyzed intramolecular dynamic kinetic C–H cyclization (Gu et al., 2017).¹²

Very recently, our group reported a Pd(II)-catalysed C–H olefination of quinoline-derived biaryls using chiral spiro phosphoric acids (SPAs) as chiral ligands (Scheme 6).¹³ (*R*)-STRIP (L5) was utilized as a superior ligand for the first time in atroposelective C–H functionalization and exhibited better stereocontrol than BINOL-derived phosphoric acids, probably due to the better steric interaction with the substrates. A wide range of quinoline-derived biaryls and olefins could be employed in this enantioselective transformation. In general, electron-deficient biaryls showed better reactivity than electron-rich ones. The computational results suggested that the enantioselectivity was dominated by the CMD type C–H bond cleavage step, which showed good agreement with the experimental result.

2.2 Atroposelective C–H functionalization catalysed by a preformed chiral catalyst

In contrast to atroposelective C–H functionalization catalysed by chiral metal catalysts that were *in situ* generated *via* replacement of achiral ligands in the precatalysts with chiral ligands, asymmetric synthesis catalysed by a preformed chiral catalyst has also been realized, in the case that the achiral ligands are less easily displaced from the precatalysts. Although a preformed chiral catalyst needs extra step(s) to prepare, it could also obviate the competitive background reactions caused by achiral precatalysts.



Scheme 6 Pd-Catalyzed C–H olefination using chiral (*R*)-STRIP as a chiral ligand (Shi et al., 2019).¹³

In 2012, Cramer and co-workers first introduced a series of C₂-symmetric chiral [Cp^xRh^{III}] catalysts for asymmetric C–H functionalization, which were found to be highly promising catalysts for various enantioselective C–H functionalizations to create central chirality.¹⁴ In 2014, the You group elegantly adopted this type of chiral catalyst for the creation of axial chirality. They reported that the preformed chiral [Cp^xRh^{III}] catalyst (**Cat1**) was capable of enabling the enantioselective C–H alkenylation of isoquinoline-derived biaryls (Scheme 7).¹⁵ The formation of a five-membered cyclometalated intermediate enabled by C–H activation *via* dynamic kinetic resolution is challenging due to the need of two sterically hindered arenes to be coplanar. You and co-workers realized that the preformed chiral [Cp^xRh^{III}] catalyst could overcome this challenge and enhance both good reactivity and high selectivity. In this reaction, a variety of biaryl substrates and alkenes were tolerated in the presence of 5 mol% of catalyst, 5 mol% of (BzO)₂ and a mixture of Cu(OAc)₂ and Ag₂CO₃ as oxidants leading to the corresponding axially chiral biaryls in moderate to excellent yields and enantioselectivities. The potential utility of the resulting axially chiral olefinated products was further demonstrated by their application as *N*/olefin ligands in Rh-catalysed conjugate addition of phenylboronic acid with cyclohexanone.

You and co-workers took this innovative study one step further. In 2016, they disclosed a novel class of spirobiindane-derived Cp ligands (SCps) and found that the corresponding Rh-complexes were excellent chiral catalysts in asymmetric oxidative coupling of biaryls with alkenes (Scheme 7).¹⁶ The axially chiral biaryls were obtained in 19–97% yields with up to 96% ee. Compared to their previous studies using Cramer's C₂-symmetric Cp^x complexed Rh-catalyst, the newly developed [SCpRh^{III}] catalyst behaved as a superior catalyst and gave higher enantioselectivity.



Scheme 7 Rhodium-catalyzed enantioselective C–H alkenylation of biaryls (You et al.).^{15,16}

2.3 Diastereoselective C–H functionalization directed by a chiral auxiliary

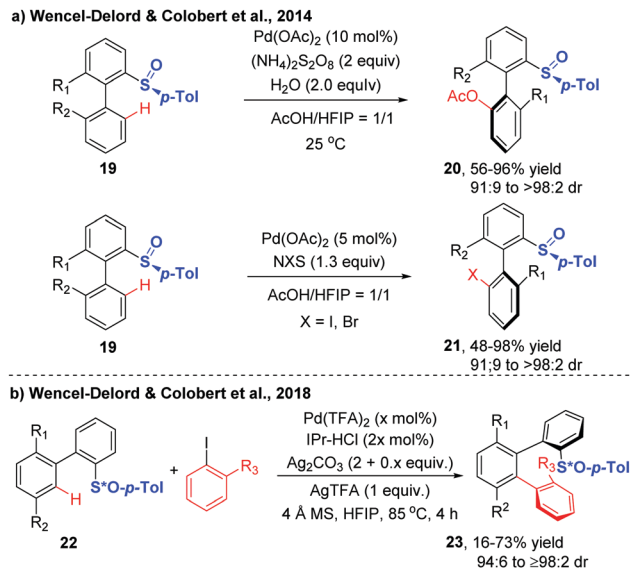
Diastereoselective C–H functionalization has also been realized as an efficient approach to access axially chiral biaryls. This strategy generally relies on the use of substrates containing chiral auxiliaries, such as sulfoxide, and menthyl phenylphosphate.^{17–21}

In 2013, the first atropodiastereoselective palladium(II)-catalyzed oxidative Heck olefination of biaryls using an enantiopure sulfoxide as both the directing group and chiral auxiliary was reported by the group of Colobert (Scheme 8).¹⁷ This reaction showed a perfect control of regioselectivity for the activation of one specific C–H bond. The observation of a total regioselectivity suggests that the soft Pd-catalyst was prone to coordinate with the softer sulfur atom (compared to oxygen), in which a privileged 6-membered palladacycle intermediate was formed. Later, they disclosed that the 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) solvent could drastically improve the efficiency and stereoselectivity of this C–H coupling.¹⁸ Mechanistic studies indicated that a hydrogen-bond was formed between the solvent and the substrate, thus accelerating the cleavage of the C–H bond and improving the stereochemical outcome of the reaction. The traceless nature of the chiral sulfoxide directing group was evidenced by a sulfoxide/lithium exchange and subsequent electrophilic trapping reaction sequence.

Wencel-Delord and Colobert further explored the generality of the atroposelective C–H functionalization through dynamic kinetic resolution directed by a chiral *p*-tolyl sulfoxide auxiliary (Scheme 9).^{19,20} A range of biaryls underwent Pd-catalyzed chiral sulfoxide-directed C–H acetoxylation smoothly at ambient temperature with AcOH using (NH₄)₂S₂O₈ as the stoichiometric oxidant, affording the acetoxylation biaryls in excellent diastereoselectivities. Replacing the above oxidant with *N*-iodosuccinimide (NIS), the catalytic system was shown to be capable of promoting the mild and highly diastereoselective C–H iodination.



Scheme 8 Pd-Catalyzed atroposelective sulfoxide-directed C–H olefination (Colobert et al., 2013).¹⁷



Scheme 9 Chiral sulfoxide-directed diastereoselective C–H acetoxylation, halogenation and arylation (Wencel-Delord and Colobert et al.).^{19,20}

The iodinated biaryls were provided in high yields with diastereomeric ratios ranging from 91:9 to > 98:2. Notably, the brominated product could also be obtained in the presence of NBS under otherwise identical conditions, albeit with a slight decrease in stereocontrol.

Based on these innovative studies, Wencel-Delord and Colobert achieved the synthesis of chiral terphenyl scaffolds containing one or two chiral axes *via* Pd-catalysed atroposelective C–H arylation in 2018.²⁰ Although significant advances have been achieved in chiral sulfoxide-directed C–H functionalization of biaryls, the atroposelective C–H arylation with *ortho*-substituted iodoarenes is extremely challenging, due to the high congestion of two sterically coupled partners as well as the difficulty in the realization of controlling two chiral inductions in one step. Using biaryls bearing a stereogenic sulfoxide moiety as substrates and *ortho*-substituted aryl iodides as coupling partners, the arylation reaction occurred in the presence of Pd(TFA)₂, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr-HCl), Ag₂CO₃, AgTFA and 4 Å MS, at 85 °C in HFIP, delivering the desired products with high diastereoselectivity (Scheme 9b).

These terphenyls with two chiral axes exhibited a new tridimensional structure and thus had potential as unique chiral bidentate ligands. For example, treatment of **23a** with *tert*-BuLi followed by PPh₂Cl led to the corresponding diphosphine ligand **24** in 54% yield. **BiaxPhos 24** was applied in the enantioselective rhodium-catalysed hydrogenation of methyl (*Z*)- α -acetamidocinnamate (**25**), giving **26** with excellent yield and enantioselectivity. In another case, the *S/N*-**Biax** ligand **27** was synthesized in two steps from **23b**, which showed good efficiency in asymmetric 1,2-addition of Et₂Zn to aldehyde (Scheme 10).

In 2015, the Yang group reported the synthesis of chiral biaryl phosphates *via* Pd(II)-catalysed asymmetric C–H alkenylation using an enantiopure menthylphenylphosphate group as the



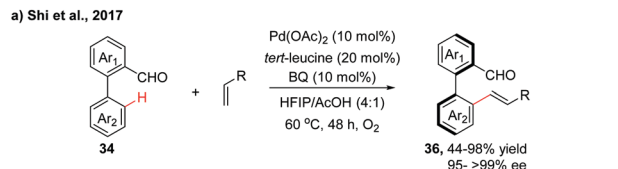
Scheme 10 Synthesis and application of BiaxPhos and S/N-Biax ligands.

Scheme 11 Pd(II)-Catalysed menthylphenylphosphate-directed C–H activation/dynamic kinetic resolution for the synthesis of chiral biaryl phosphates (Yang et al., 2015).²¹

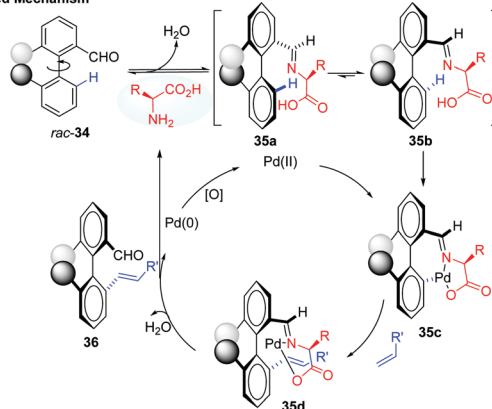
directing group (Scheme 11).²¹ Exploring Pd(OAc)₂ and *N*-acyl glycine as the catalyst system, various axially chiral phosphine oxide compounds were obtained in excellent diastereomeric ratios with moderate to good yields. The asymmetric C–H functionalization can also be extended to acetoxylation and iodization using the same substrates.

2.4 Atroposelective C–H functionalization enabled by a transient chiral auxiliary

Over the past few decades, a variety of functionalities have been employed as directing groups for site-selective C–H activations.²² Recently, a transient directing group strategy has emerged as an efficient and powerful tool to functionalize the inert C–H bond for the obviation of the steps for installation/removal of the directing group.²³ A breakthrough in this field was made by Yu and co-workers, who developed a transient chiral auxiliary approach for the creation of point chirality.²⁴ Inspired by the elegance of this strategy, our group achieved several examples of Pd(II)-catalysed atroposelective C–H functionalization for the synthesis of axially chiral biaryls. Compared to the chiral ligand or chiral auxiliary enabled catalytic asymmetric C–H functionalization, as illustrated in Sections 2.1 and 2.3, this transient directing group could reversibly link with the substrate to form a better σ -donor motif, thus playing a dual role as a catalytic directing group and chiral ligand. With commercially available



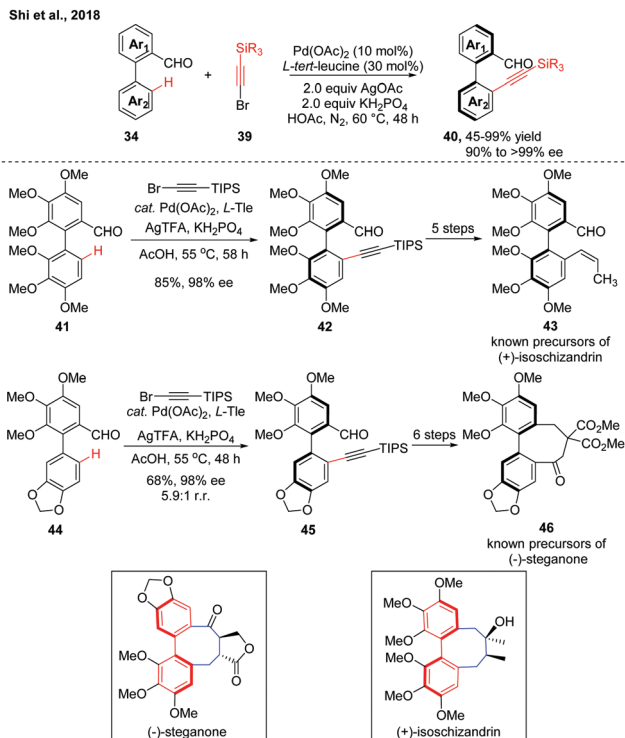
Proposed Mechanism

Scheme 12 Pd-Catalyzed atroposelective C–H olefination of biaryl aldehydes using Tle as a transient chiral auxiliary (Shi et al., 2017, 2019).^{25,26}

tert-Leucine (Tle) as a transient chiral auxiliary, we first achieved the atroposelective C–H olefination of biaryl aldehydes *via* a Pd(II)/Pd(0) catalytic cycle, affording the desired olefinated biaryls in good yields (up to 98%) with excellent enantioselectivities (95 to >99% ee) (Scheme 12a).²⁵ The reaction was proposed to form the imines **35** by the dehydration of biaryl aldehydes with the chiral amino acids. Owing to steric factors, one of the imine diastereomers preferentially underwent C–H palladation to afford an axially stereo-enriched biaryl palladacycle intermediate **35c**. The resulting seven-membered palladacycle underwent a Heck-type reaction with alkene to form intermediate **35d** followed by hydrolysis to give the desired product **36** with high levels of enantioselectivities. The released Pd(0) species could be reoxidized back to catalytically active Pd(II) by BQ and O₂.

The potential utility of this method was demonstrated by the asymmetric total synthesis of TAN-1085. The key to the success of this total synthesis relies on the construction of the axially chiral biaryl **38** with high levels of enantiopurity *via* Pd-catalyzed asymmetric C–H olefination (Scheme 12b).²⁶ Poor yield and unsatisfactory ee value were obtained using our previously reported conditions, due to the electron-rich properties of the biaryl aldehyde **37**. After fine tuning of the reaction parameters, olefinated product **38** was finally obtained in 75% isolated yield with 99% ee in a 1.2 gram scale.

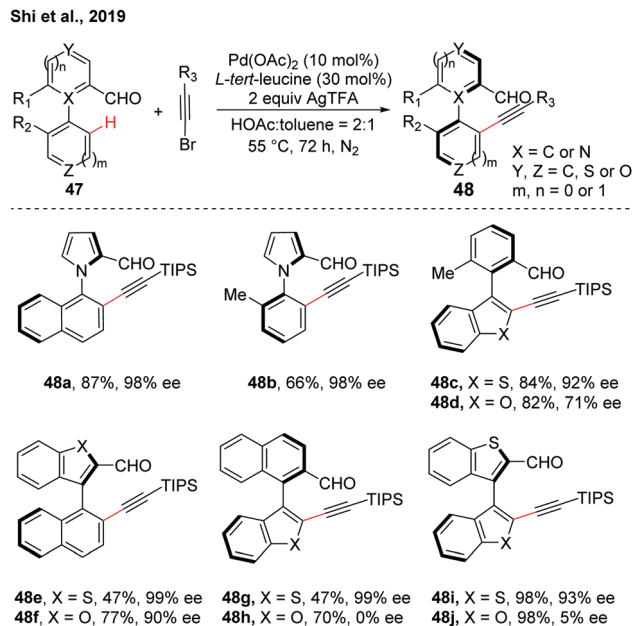
In 2018, we further adopted this strategy to Pd(II)-catalysed atroposelective C–H alkynylation. A variety of alkynylated biaryls



Scheme 13 Pd-Catalyzed atroposelective C–H alkylation and its synthetic applications (Shi et al., 2018).²⁶

were obtained in good to excellent yields with excellent enantioselectivities (Scheme 13).²⁷ The potassium dihydric phosphate is a crucial additive for reaction activity, which may serve as a buffer to balance the pH value of the reaction system. Compared to the C–H olefination, this transformation may proceed using a Pd^{II}/Pd^{IV} catalytic cycle. This Pd(II)-catalyzed atroposelective C–H alkylation reaction has also found applications in the gram-scale formal syntheses of (+)-isoschizandrin and (+)-steganone. After optimization of the reaction conditions, the racemic precursors **41** and **44** were subjected to the slightly modified C–H alkylation conditions, giving the desired products **42** and **45**, respectively, in good yields and excellent enantioselectivities in gram-scale. Both intermediates were converted to known precursors of the corresponding natural products in 5–6 steps, thus completing their formal syntheses.

Despite the good investigations of the synthesis of the hexatomic atropisomer, the asymmetric construction of the five-membered atropisomers remains a considerable challenge due to the nature of their lower rotational barriers resulting from the relatively long distances between adjacent substituents *ortho* to the rotation axis.²⁸ By using the transient chiral auxiliary strategy, a rare example of Pd-catalyzed asymmetric C–H alkylation for the synthesis of five-membered heteroatropisomers was reported by our group (Scheme 14).²⁹ Various five-membered heteroarenes such as pyrroles, thiophenes, benzothiophenes, and benzofurans were compatible with the reaction conditions. These atropisomers featuring one or even two five-membered rings connected through C–N or C–C bonds were obtained (up to 98% yield and up to >99% ee). Lower ee values were obtained in



Scheme 14 Pd-Catalyzed enantioselective C–H alkylation for the synthesis of atropisomers featuring pentatomic heteroaryls (Shi et al., 2019).²⁹

biaryls containing benzofuran moieties than benzofuran moieties, which was demonstrated by the calculation of the difference of the rotational barrier and half-life.

As an extension to Pd(II)-catalyzed asymmetric C–H activation reactions using a catalytic transient chiral auxiliary, our group achieved a further advance in accessing more structurally diverse axially chiral biaryls *via* atroposelective C–H allylation (Scheme 15).³⁰ A variety of racemic biaryl aldehydes could be allylated with Morita–Baylis–Hillman (MBH) acetates, affording the enantioenriched biaryls through β -O elimination. 4-Vinyl-1,3-dioxolan-2-one, as a versatile allylic surrogate, was also compatible in this allylation reaction, giving a mixture of *Z/E* isomers instead. The mixture of allylated products was then treated with RANEY[®]-Ni to afford the reduced biaryls with excellent enantioselectivity.



Scheme 15 Pd-Catalyzed atroposelective C–H allylation (Shi et al., 2018).³⁰

3. The creation of biaryl axis *via* C–H activation/asymmetric coupling

Over the past few years, transition metal-catalyzed direct C–H arylation of (hetero)arenes has been among the most attractive strategies for the construction of biaryl motifs.³¹ Despite the significant advances, the synthesis of axially chiral biaryls *via* enantioselective C–H activation remains a daunting challenge. Such an atroposelective biaryl coupling was first reported in 2012 by Yamaguchi and Itami (Scheme 16a).³² The coupling reaction proceeded between substituted thiophenes and sterically hindered naphthylboronic acids in the presence of Pd(OAc)₂/biox (L6), giving the desired biaryl in 27% yield with 72% ee (Scheme 16a). A reactivity–selectivity dilemma was observed, in which the ee value increased at the expense of the reaction yield. In the following year, the same group described a second-generation catalytic system using a chiral Pd(II)-sox (sulfoxide-oxazoline) complex and iron-phthalocyanine (FePc) as a co-catalyst (Scheme 16b).³³ Although this dual catalyst system could furnish the desired product in increased yield, the enantioselectivity remains to be improved. These results described above highlight the difficulty in controlling the axial chirality *via* a direct C–H activation/asymmetric coupling strategy. A major hurdle might be the fact that sterically demanding substituents on both coupling partners are needed to maintain the chirality of the resulting biaryls; however, the reactivity significantly decreased with those sterically hindered coupling partners.

Recently, the Waldmann and Antonchick group developed a general method for gram scale synthesis of a class of novel chiral JasCp ligands, which could be used for Rh(III)-catalyzed enantioselective C–H activation reactions.³⁴ The chiral [JasCpRh^{III}] complexes (CAT3) have proven to be a good catalyst in the enantioselective C–H arylation of benzamides with diazonaphthoquinones (Scheme 17). The reaction proceeded under mild conditions and a broad range of axially chiral biaryls were formed in 37–93% yield and 79–90% ee.

Very recently, Cramer and co-workers realized an enantioselective C–H arylation of phosphine oxides with *o*-quinone diazides employing a chiral iridium(III) complex (CAT4) and phthaloyl *tert*-leucine as a co-catalyst (Scheme 18).³⁵ The con-



Scheme 17 Synthesis of axially chiral biaryls by Rh-catalyzed enantioselective C–H arylation (Waldmann and Antonchick *et al.*, 2017).³⁴



a) axial and P-chiral phosphine oxides

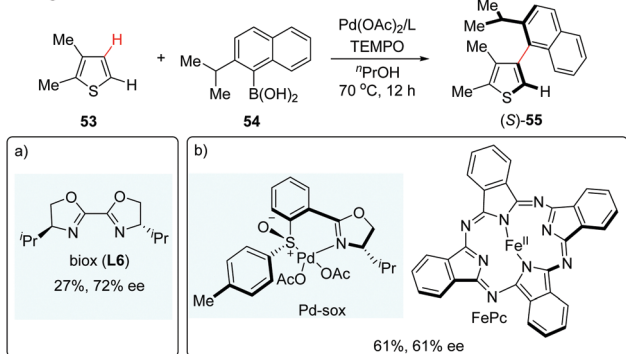


b) axial phosphine oxides



Scheme 18 Cp*Ir^{III}-Catalyzed enantioselective C–H arylations of phosphine oxides (Cramer *et al.*, 2018).³⁵

Yamaguchi & Itami *et al.*



Scheme 16 Enantioselective C–H coupling of thiophene with arylboronic acid (Yamaguchi and Itami *et al.*).^{32,33}

figuration of the chiral amino acid was proved to be essential for achieving satisfactory enantioselectivity. The reaction of diazo reactants bearing sterically demanding substituents in the *ortho* position, afforded the stable axial and P-chiral biaryls in moderate to excellent yields (59–96%) and high enantioselectivities (up to 99% ee) (Scheme 18a). The synthesis of purely axially chiral phosphine oxides has also been investigated using tris-3,5-dimethoxyphenylphosphine oxide as a substrate (Scheme 18b). Enantiospecific reduction of the chiral phosphine oxides gave the synthetically valuable monodentate biaryl phosphorus compounds that could be of great potential as ligands in other types of asymmetric reactions.

In 2018, the asymmetric synthesis of axially chiral dibenzazepinones *via* Pd(0)-catalyzed atropo-enantioselective intramolecular C–H arylation of achiral amides using TADDOL-based phosphoramidite (L7) as a ligand was achieved by Cramer and co-workers



Scheme 19 Pd(0)-Catalyzed atropo-enantioselective intramolecular C–H arylation of achiral amides (Cramer et al., 2018).³⁶

(Scheme 19).³⁶ The acid additive is essential for achieving both excellent reactivity and enantioselectivity. A board range of axially chiral dibenzazepinones were obtained in high yields and impressive enantioselectivities. Computational investigation provides a reliable prediction of the racemization barriers of the chiral axis, which also suggests that configurationally stable eight-membered palladacycles were formed through an enantio-determining CMD step during the C–H functionalization process.

4. Conclusions and outlook

Over the past few years, transition metal-catalysed asymmetric C–H functionalization has gradually matured into a powerful and straightforward tool for the construction of various optically active building blocks. In this review, we have summarized recent advances in the synthesis of axially chiral biaryl compounds *via* transition metal-catalysed asymmetric C–H functionalization.³⁸ Although a range of biaryl backbones bearing axial chirality have become accessible *via* several strategies, this area is still in its infancy. The discovery of new types of chiral ligands or catalysts is still highly demanded. In addition, current studies mainly focused on the use of noble transition metals, such as Pd, Rh, and Ir. The exploration of using earth-abundant, inexpensive 3d transition metals in atroposelective C–H activation would be another promising research area.³⁷ We hope that this review will provide some insights in this emerging field and inspire the discovery of more innovative strategies for the synthesis of axially chiral biaryls.

Conflicts of interest

There are no conflicts to declare.

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