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Perspective

Synthesis of Atropisomers by Transition-Metal-Catalyzed Asymmetric C−H Functionalization Reactions

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ABSTRACT: Transition-metal-catalyzed enantioselective C−H functionalization has become a powerful strategy for the formation of C−C or C−X bonds, enabling the highly asymmetric synthesis of a wide range of enantioenriched compounds. Atropisomers are widely found in natural products and pharmaceutically relevant molecules, and have also found applications as privileged frameworks for chiral ligands and catalysts. Thus, research into asymmetric routes for the synthesis of atropisomers has garnered great interest in recent years. In this regard, transition-metal-catalyzed enantioselective C−H functionalization has emerged as an atom-economic and efficient strategy toward their synthesis. In this Perspective, the approaches for the synthesis of atropisomers by transition-metal-catalyzed asymmetric C−H functionalization reactions are summarized. The main focus here is on asymmetric catalysis via Pd, Rh, and Ir complexes, which have been the most frequently utilized catalysts among reported enantioselective C−H functionalization reactions. Finally, we discuss limitations on available protocols and give an outlook on possible future avenues of research.

1. INTRODUCTION

Atropisomers are defined as stereoisomers formed due to sterically induced rotational restriction around single bonds, thus making their isolation possible. During the past several decades, biaryls with axial chirality have been recognized as an important structural unit with multiple applications, such as in materials science, as chiral recognition reagents, and as fluorescence enhancement sensors (Scheme 1a).[1] In addition, the importance of axially chiral biaryls in pharmaceuticals and natural products due to their biological activity is increasingly being recognized, with prominent examples being observed in the glycopeptide antibiotic vancomycin, murrastifoline-F, sotorasib, and steganone (Scheme 1b).[2] Meanwhile, they have also been utilized as privileged frameworks for chiral ligands and catalysts, as highlighted by BINOL, BINAP, phosphoramidite ligands, chiral phosphoric acids (CPAs), quaternary ammonium salts, and chiral cyclopentadienyl rhodium (CpRh) catalysts (Scheme 1c).[3] Hence, owing to their significance, numerous methodologies have been developed for the synthesis of axially chiral compounds, including enzyme-catalyzed kinetic resolutions, asymmetric cross-coupling reactions, asymmetric cycloaddition reactions, asymmetric reduction reactions, and organocatalytic reactions.[4]

Great progress has been made in transition-metal-catalyzed enantioselective C−H functionalization,[5] providing novel disconnections for target-oriented synthesis. New stereocenters can be introduced with simple C−H bond-containing molecules, thereby quickly generating complex structures. Although methods for generating central or planar chirality are well documented,[6] significant advances in the enantioselective synthesis of axially chiral compounds through C−H functionalization have only been made more recently, likely due to the facile racemization of atropisomers under relatively vigorous conditions. In addition, the steric hindrance inherently encountered during the synthesis of compounds with stable axial chirality makes the C−H functionalization process more difficult. Nevertheless, these difficulties have been addressed thanks to the elegant strategies developed for innovative syntheses of compounds with axis chirality. In this Perspective, we will concentrate on the generation of axially chiral biaryl skeletons by means of transition-metal-catalyzed asymmetric C−H functionalization reactions.

Three main strategies for the synthesis of axially chiral biaryl skeletons have been developed. The first strategy involves the (dynamic) kinetic resolution or desymmetrization process of axially chiral biaryls (Scheme 2a). Relevant examples are discussed involving catalytic metal complexes, focusing on the transition metals palladium, rhodium, and iridium. Second, the creation of a biaryl axis by aryl−aryl cross-coupling is described according to the type of metal catalyst employed (Scheme 2b). Third, we describe the formation of axially chiral biaryl skeletons by *de novo* arene formation, with a major focus on rhodium catalysis (Scheme 2c).

2. SYNTHESIS OF ATROPISOMERS BY (DYNAMIC) KINETIC RESOLUTION OR DESYMMETRIZATION

The enantiomeric pairs of biaryl compounds with low conversion barriers can be rapidly interconverted. By employing a chiral transition metal complex, the difference in the activation energies for conversion to each atropisomer leads to

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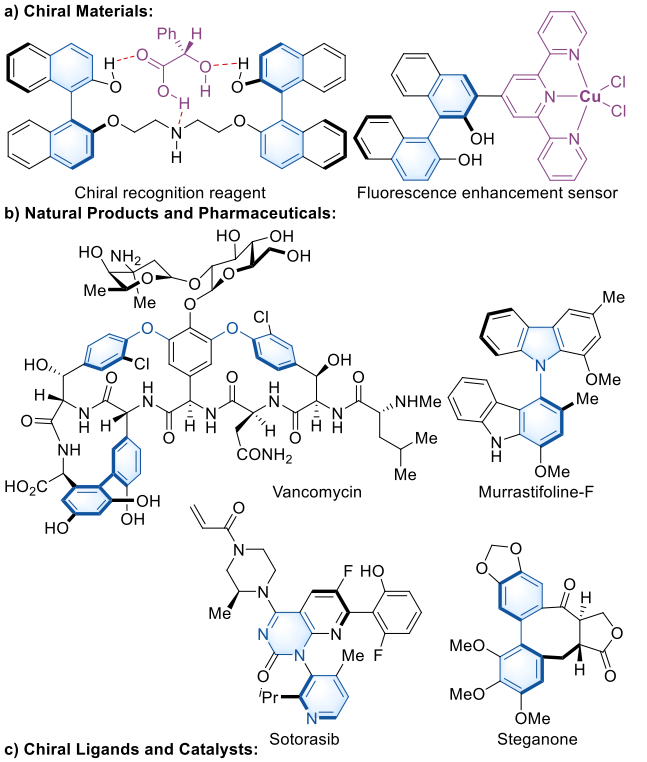
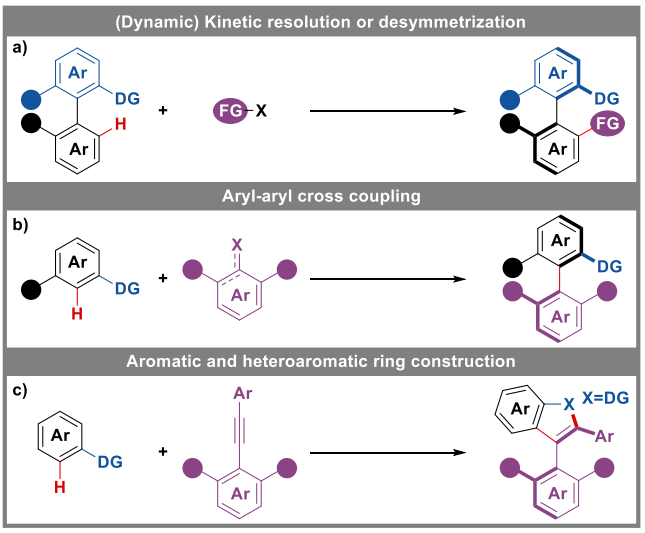
Scheme 1. Atropisomers in Chiral Materials, Natural Products, Chiral Ligands, and Catalysts



Scheme 2. Three Main Strategies for the Synthesis of Atropisomers by Transition-Metal-Catalyzed Asymmetric C−H Functionalization Reactions



the preferential formation of the product with the most favorable energetic barrier in the transition state. Therefore, (dynamic) kinetic resolution or desymmetrization leads to the formation of the most energetically favorable axially chiral biaryl with a specific chirality due to the restricted rotation around the single bond of axial chirality.

2.1. Pd Catalysis. Diastereoselective C−H functionalization has been established as an effective method to afford axially chiral biaryls.[7] The strategy relies on the use of chiral auxiliaries in the substrates, such as sulfoxides and chiral phosphine oxides. In 2013, the Colobert group reported a palladium-catalyzed diastereoselective oxidative Heck-type C−H alkenylation reaction of biaryls **1** with acrylates, with chiral sulfoxide as a directing group, providing a series of axially chiral biaryls **2** with moderate to good diastereoselectivities (Scheme 3a).[7a] Subsequently, Wencel-Delord, Colobert, and co-workers extended this elegant strategy to acetoxylation (Scheme 3b),[7b] iodination (Scheme 3c),[7b] and arylation (Scheme 3d)[7d] reactions of **1**. Notably, the acetoxylation reaction could be carried out at room temperature with high efficiency, promoted by the addition of a small amount of water and using ammonium persulfate as the oxidant. Meanwhile, with the aid of HFIP, the reaction was insensitive to both air and moisture. Compared with the previous oxidative Heck alkenylation, this catalytic system showed better diastereoselective control.

In 2015, Yang et al. reported a menthyl phosphonite-directed palladium-catalyzed diastereoselective C−H alkenylation reaction, yielding a series of functionalized axially chiral biphenyl compounds bearing a phosphine oxide group (Scheme 3e).[7e] For instance, in the presence of 5 mol% palladium acetate and 10 mol% Ac-Gly-OH, menthyl arylphosphonite esters **7** could be obtained in up to 73% yield and >95:5 dr. Meanwhile, the presence of the menthyl phosphonite chiral auxiliary was also compatible with acetoxylation (**8**), iodination (**9**), and acylation (**10**) reactions.

In 2008, Yu et al. reported the first Pd(II)-catalyzed enantioselective C(sp^2)−H functionalization reaction via the desymmetrization of triarylmethane compounds, employing a monoprotected amino acid (MPAA) as an efficient chiral ligand.[8] This pioneering report triggered a surge in further investigations of Pd(II)/MPAA-catalyzed enantioselective C−H functionalization reactions. Using pyridine *N*-oxide as the directing group, in 2014 You et al. achieved a Pd-catalyzed asymmetric C(sp^2)-H iodination reaction (Scheme 4).[9] With (*S*)-**L1** as the chiral ligand, the kinetic resolution of pyridine *N*-oxides (±)-**11** afforded their corresponding axially chiral iodobiaryls **12** with moderate *S* values (4.1−27). At the same time, an axially chiral phenylpyridine *N*-oxide (**13**) could be obtained through an enantiospecific coupling reaction and was used as a Lewis base catalyst in an asymmetric addition reaction of allyltrichlorosilane (**15**) to benzaldehyde (**14**).

A plausible catalytic cycle is depicted in Scheme 4. In the presence of Pd(II)/MPAA complex, the asymmetric C−H bond cleavage takes place via concerted metalation−deprotonation (CMD) to generate Pd(II) intermediate **A**, while conserving the stereochemistry of (R_a)-**11a**. This is followed by oxidative addition of *N*-iodosuccinimide (NIS) to the Pd(II) intermediate **A** generating the highly reactive Pd(IV) intermediate **B**. Next, the reductive elimination of Pd(IV) intermediate **B** affords the target product (S_a)-**12a**, thereby regenerating the Pd(II) species.

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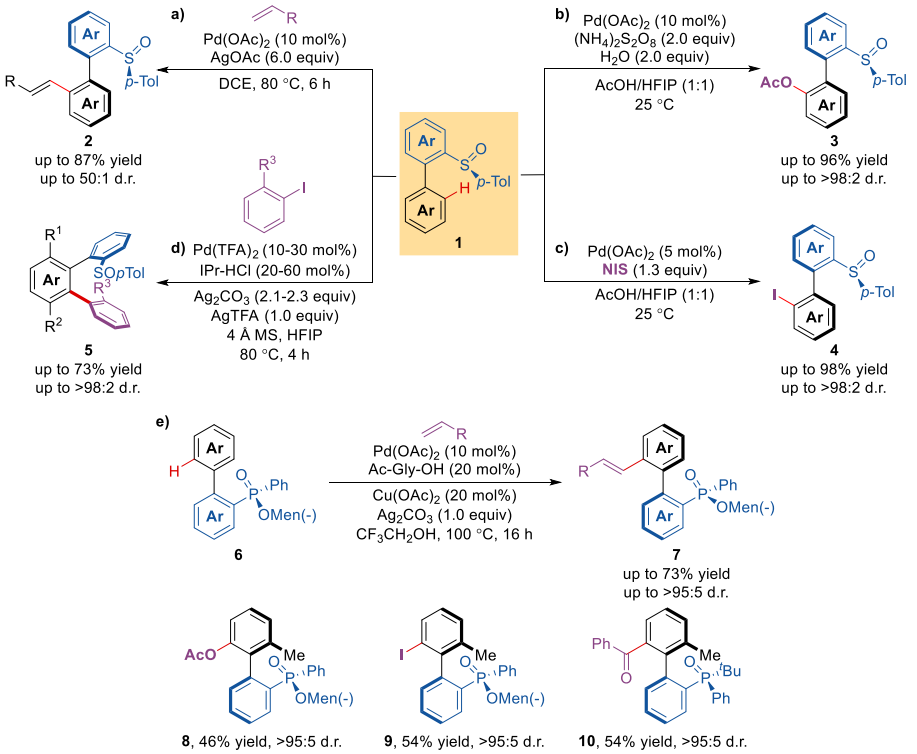
Scheme 3. Pd-Catalyzed Diastereoselective C−H Functionalization Reactions



Success in the synthesis of axially chiral compounds has been achieved using the Pd(II)/MPAA catalytic system.[10] In 2017, Yang et al. reported the utilization of phosphine oxide as a directing group in Pd-catalyzed enantioselective C−H olefination reactions, elegantly demonstrated by the synthesis of axially chiral biaryl phosphine oxides **18** (Scheme 5a) using palladium acetate/Boc-L-Val-OH under mild conditions in up to 73% yield and 96% ee.[10a] Additionally, axially chiral phosphine ligands could be obtained easily after reduction of phosphine oxides **18**.

Besides biaryl compounds, other types of compounds exhibiting atropisomerism such as chiral styrene derivatives, have also gained increased attention. However, the asymmetric synthesis of such compounds is rendered more difficult by their flexible structures. In 2018, Xu et al. developed an oxime ether directed Pd-catalyzed enantioselective C−H oxidative olefination reaction, efficiently constructing axially chiral alkenyl-substituted 2-arylcyclohex-2-enone oxime ether derivatives **20** (Scheme 5b).[10b] With Ac-L-Ala-OH as the chiral ligand and silver acetate as the oxidant, the reaction could be carried out under mild conditions, affording chiral styrenes in up to 87% yield and >99% ee. This promising methodology was further extended in 2021 to asymmetric alkynylation reactions, which yielded a series of highly enantioenriched alkynylated 2-arylcyclohex-2-enone oxime ethers.[10c] In 2020, Shi et al. developed a pyridine directed Pd-catalyzed C−H alkenylation reaction, with L-*p*Glu-OH as the chiral ligand, affording axially chiral styrenes in up to 99% yield and 99% ee (Scheme 5c).[10d] Notably, with alkynyl bromide as substrate the reaction was also amenable to C−H alkynylation. A similar approach was used by Wang et al. in 2021 to synthesize axially chiral cinnamic acid esters through the Pd-catalyzed C−H olefination or arylation of α-phenylcinnamic acid.[10e] After screening various ligands, it was found that Boc-L-*tert*-leucine led to optimal results, forming axially chiral products in up to 99% yield and 99% ee.

Another interesting class of atropisomers are axially chiral aniline derivatives bearing a C−N chiral axis, widely present in pharmaceuticals, natural products, chiral catalysts, and molecular devices. However, the lower rotation barriers of such compounds makes their enantioselective synthesis more challenging with only limited successful examples shown thus far. An interesting example is provided by the enantioselective Pd-catalyzed C−H alkenylation carried out by Shi et al. in 2020 using pyridine as the directing group, which led to the formation of aniline derivatives **24** bearing axial chirality in up to 99% yield, >20:1 *E*:*Z*, and >99% ee (Scheme 5d).[10f] It is noteworthy that these products could be used as effective ligands in the Rh-catalyzed asymmetric Michael addition reaction of an arylboronic acid to cyclohex-2-en-1-one with good enantioselective control. The same approach was used recently by the same group in order to construct various isolable N-aryl peptoid atropisomers via a Pd(II)-catalyzed asymmetric C−H alkynylation using commercially available L-*p*Glu-OH as the chiral source.[10g]

The type of efficient ligand in the Pd-catalyzed asymmetric C−H functionalization reaction has extended to chiral phosphates.[11] For example, in 2019, Shi et al. reported an atroposelective C−H alkenylation reaction of 8-arylquinolines (Scheme 6a),[12a] with SPINOL-derived chiral phosphate (from (*R*)-**CPA1**) as the optimal ligand, which afforded axially chiral quinoline derivatives **26** in up to 99% yield and 98% ee. More recently, this catalytic system was extended to an atroposelective C−H olefination under mild conditions directed by an unprotected aniline, generating atropisomeric 2-aminodiphenyl derivatives **28** in up to 91% yield and 97% ee (Scheme 6b).[12b] Furthermore, methacrylate compounds could also be used as effective electrophiles in a transition-metal-catalyzed C−H allylation. With silver sulfate as oxidant, the

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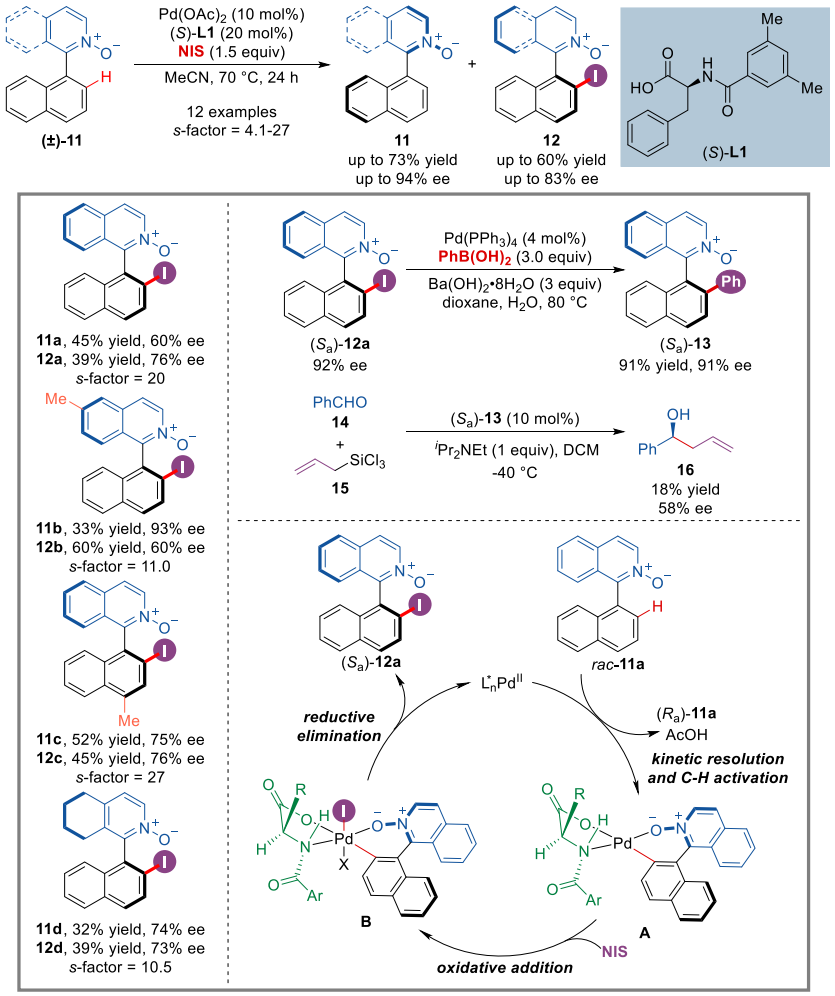
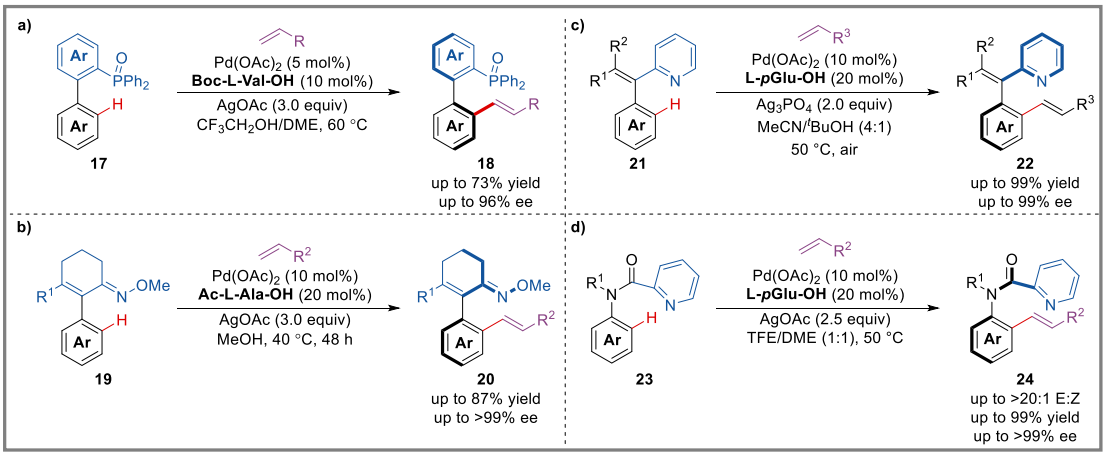
Scheme 4. Pd(II)-Catalyzed Enantioselective Intermolecular C−H Iodination by Kinetic Resolution



Scheme 5. Pd(II)-Catalyzed Enantioselective C−H Alkenylations with MPAA as a Ligand



1,1-disubstituted alkene motif could be introduced into 2-aminodiphenyl derivatives **29** to give **30** in up to 96% yield and >99% ee (Scheme 6c).[12c]

However, the necessity of directing groups such as pyridine, pyridine *N*-oxide, and phosphine oxide that need to be introduced and later removed for the C−H functionalization reaction to proceed efficiently has greatly reduced the practicability of these methods developed over the past several decades. To address these issues, Yu et al. ingeniously introduced a transient chiral directing group strategy, which has proven to be a powerful tool in asymmetric C−H functionalization reactions.[13] Using this strategy, Shi et al. has made impressive contributions to synthesize a variety of axially chiral biaryls. For example, the Pd-catalyzed atroposelective dehydrogenative Mizoroki−Heck coupling of 2-biphenylcarboxaldehyde derivatives **31** with terminal alkenes was carried

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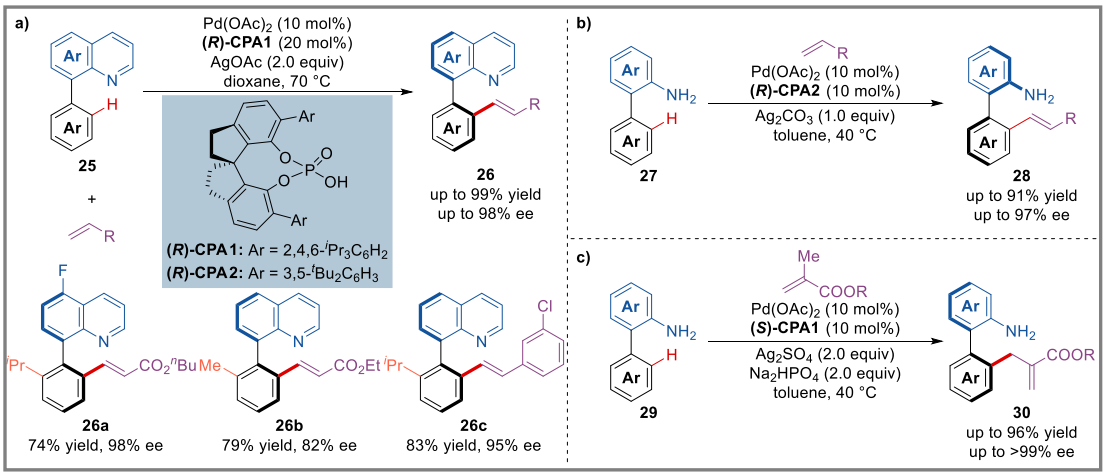
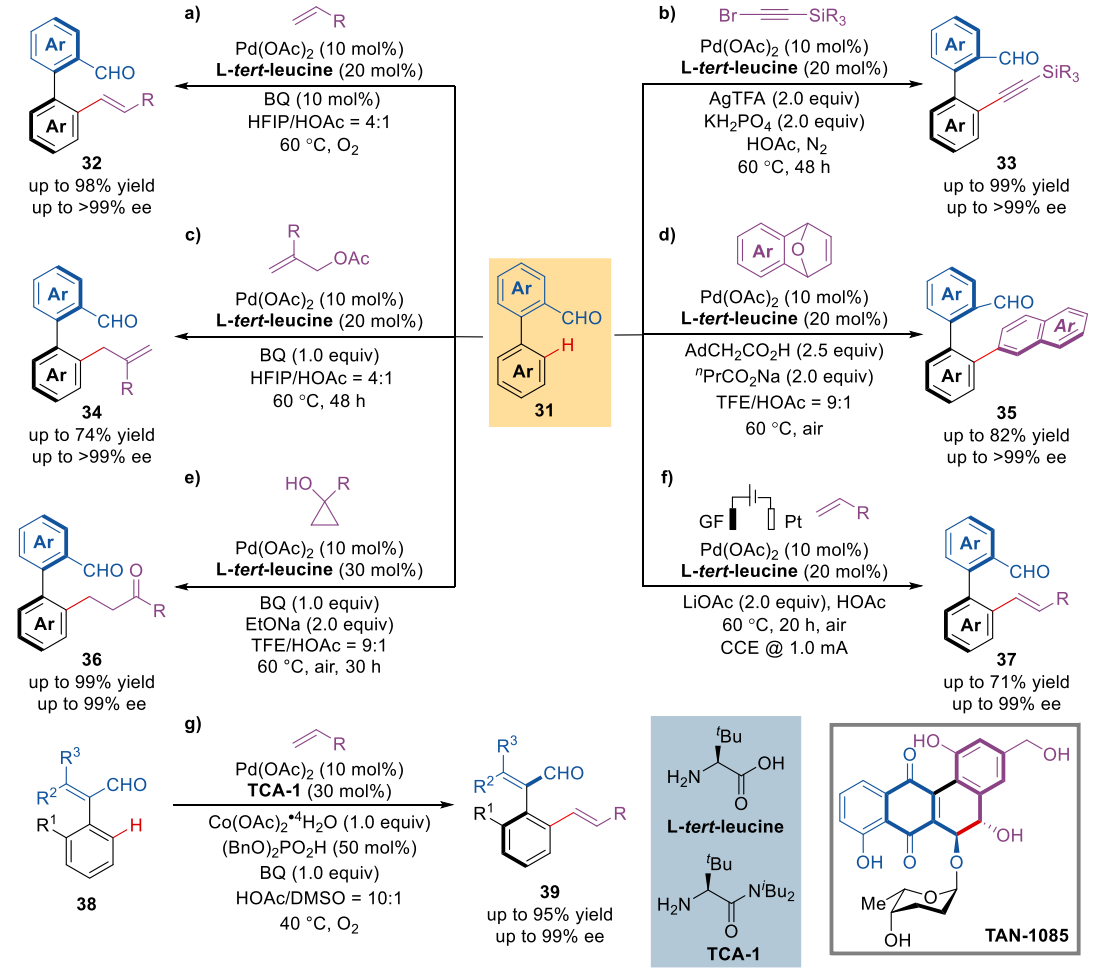
Scheme 6. Pd(II)-Catalyzed Enantioselective C−H Functionalizations with Chiral Phosphate Ligand



Scheme 7. Pd(II)-Catalyzed Atroposelective C−H Functionalizations Using Transient Directing Groups



out in 2017 using L-*tert*-leucine as the optimal transient chiral auxiliary, forming the products in excellent yields and enantioselectivity (up to 98% yield and >99% ee, Scheme 7a).[14a] Soon after, atroposelective C−H alkynylation (Scheme 7b),[14b] allylation (Scheme 7c),[14c] arylation (Scheme 7d),[14d] and alkylation (Scheme 7e)[14e] reactions were realized with the same substrates by employing alkynyl bromide, Morita−Baylis−Hillman (MBH) acetate, 1,4-dihydronaphthalene-1,4-oxide, and cyclopropanol as electrophiles, respectively. An interesting modification for the alkenylation reaction was carried out by Ackermann et al., who employed electrochemistry to avoid oxidant use, generating the products in comparable enantioselectivity (Scheme 7f).[14f] When L-*tert*-leucine was used as the transient chiral auxiliary, excellent enantioselective control was achieved, demonstrating the reliability of this electrochemical strategy. Using a conventional

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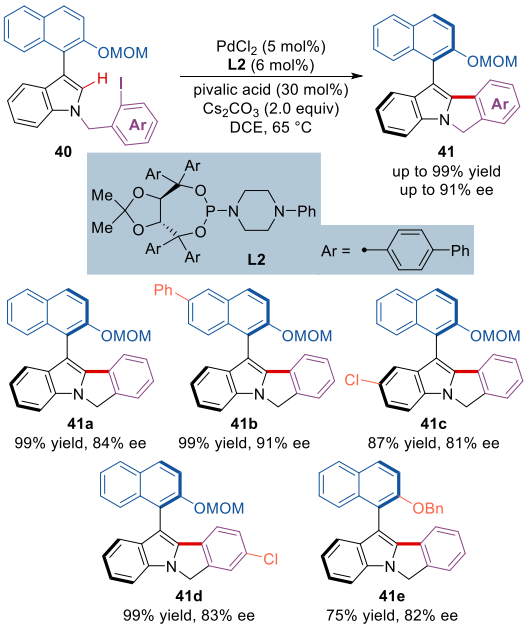
oxidizing strategy, axially chiral styrenes **39** could be obtained in up to 95% yield and 99% ee when **TCA-1** (transient chiral auxiliary) was employed instead of L-*tert*-leucine (Scheme 7g).[14g] Meanwhile, a novel asymmetric catalytic two-fold C−H annulation of aromatic aldehydes with alkynes under Pd(II)/MPAA catalysis was achieved by Xie et al., creating a series of axially chiral aldehydes in good yields and enantioselectivity.[14h] Besides biphenyl compounds, five-membered-ring atropisomeric compounds can also be synthesized through asymmetric C−H alkynylation and alkenylation reactions using the aforementioned transient group strategy, and despite their lower rotation barriers, these biaryl compounds could be obtained with good enantioselectivity.[14i,j] Impressively, the practical utility of this C−H alkenylation methodology has been demonstrated in the asymmetric synthesis of the key intermediate in the total synthesis of TAN-1085.[14k]

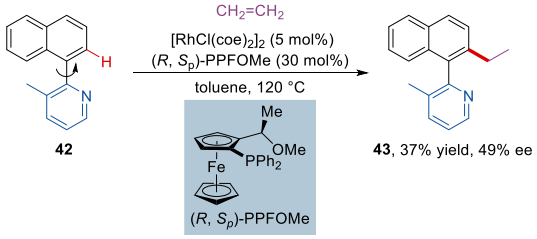
A major breakthrough in the enantioselective intramolecular C(sp^2)-H arylation was achieved in 2009 by Cramer et al. by carrying out the reaction with alkenyl triflate under Pd(0)/Pd(II) catalysis.[15] Subsequently, this strategy was applied to the construction of axially chiral compounds. In 2017, Gu et al. developed the Pd-catalyzed intramolecular atroposelective C−H cyclization to construct axially chiral biaryls in up to 99% yield and 91% ee (Scheme 8).[16] TADDOL-derived phosphoramidite ligand **L2** proved crucial for achieving effective enantiocontrol, while the reaction displayed good functional group compatibility with the indole ring.

Scheme 8. Pd(0)-Catalyzed Intramolecular Asymmetric C−H Cyclization



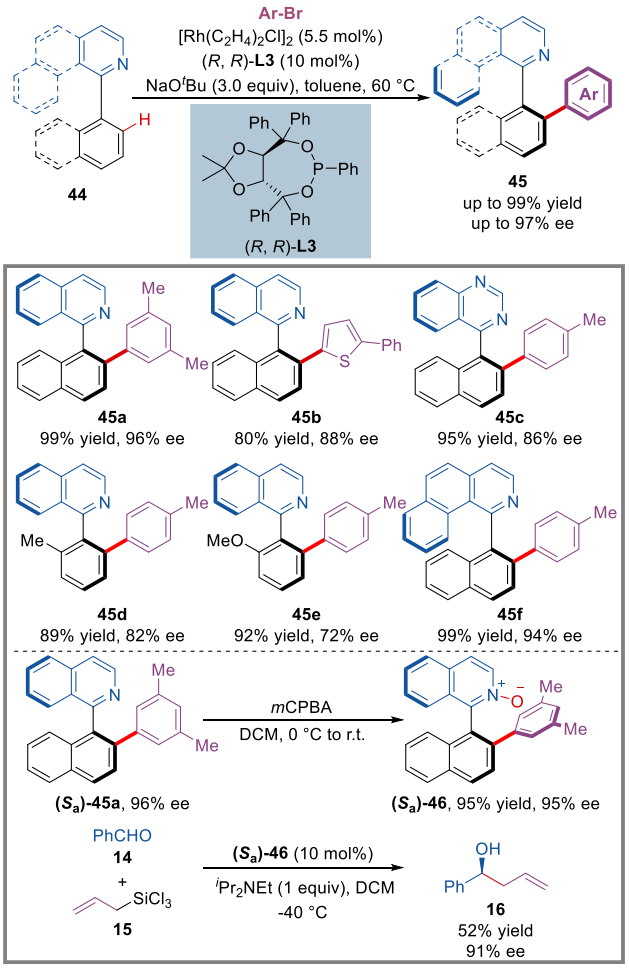
2.2. Rh Catalysis. In 2000, Murai et al. reported the premier atroposelective alkylation of 2-(1-naphthyl)-3-methylpyridine **42** with ethylene to construct axially chiral compounds. Although only moderate yield and enantioselectivity were achieved with this reaction (37% yield and 49% ee) using a $[Rh(coe)_2Cl]_2$ complex and a chiral phosphine ligand [(R,S_p)-PPFOMe], it nevertheless provided a proof-of-concept for the asymmetric C−H functionalization strategy in the synthesis of axially chiral biaryls under Rh(I) catalysis (Scheme 9).[17]

Scheme 9. Rh(I)-Catalyzed Enantioselective C−H Alkylation of Biaryl *N*-Heterocycles



In 2019, the You group realized a highly enantioselective Rh(I)-catalyzed C−H arylation for the synthesis of axially chiral pyridine derivatives. The efficient Rh(I)-catalyzed atroposelective C−H arylation of heterobiaryls depended on the utilization of a $[Rh(C_2H_4)_2Cl]_2$ complex in combination with TADDOL-derived monodentate phosphonite **L3**, affording axially chiral heterobiaryls **45** in up to 99% yield and 97% ee (Scheme 10).[18] The reaction was compatible with aryl bromides substituted at various positions, except for *ortho* substitution, presumably due to steric hindrance. Notably, the substrates could be further extended to heteroaryl bromides such as 2-bromo-5-phenylthiophene, giving the target heterobiaryl product **45b** in 80% yield and 88% ee. However, only moderate stereocontrol was achieved when the less bulky

Scheme 10. Rh(I)-Catalyzed Enantioselective C−H Arylation of Biaryl *N*-Heterocycles



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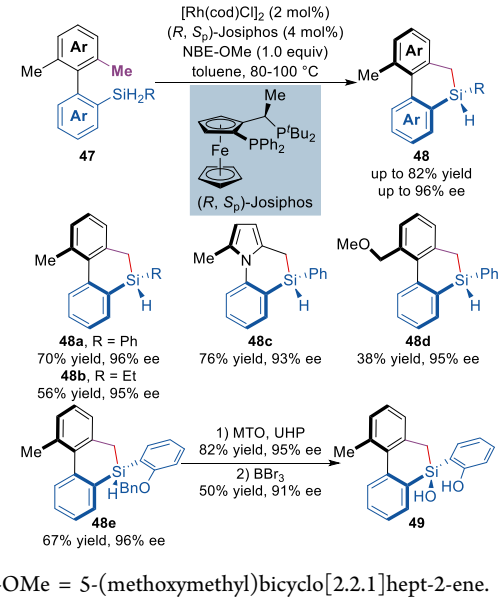
methoxy substituted aryl group was used as substrate, probably due to the low rotational energy barrier (**45e**, 72% ee). Remarkably, aryl benzo[*h*]isoquinolines were also tolerated, and product **45f** was obtained in 99% yield and 94% ee. Moreover, product (S_a)-**45a** was easily oxidized to chiral N-oxide (S_a)-**46**, which acted as a Lewis base catalyst in the asymmetric allylation of benzaldehyde **14** with allyltrichlorosilane **15**, leading to homoallyl alcohol **16** in 52% yield and 91% ee.

In most cases, axial chirality is obtained through C−C bond formation, but scant attention has been paid to approaches involving C−Si bond construction. Recently, He et al. reported an elegant asymmetric synthesis of silicon-stereogenic dihydrodibenzosilines **48** featuring axially chiral six-member-bridged biaryls via desymmetrization. Various dihydrodibenzosiline analogues **48** containing both axial and silicon-central chiralities were conveniently constructed in up to 82% yield and 96% ee via a dehydrogenative C(sp^3)−H silylation (Scheme 11).[19] The dihydrodibenzosiline **48e** could be effectively converted into chiral diol **49** in two steps.

Scheme 11. Rh(I)-Catalyzed Enantioselective C−H Silylation of Biaryls[a]



[a]NBE-OMe = 5-(methoxymethyl)bicyclo[2.2.1]hept-2-ene.

Much progress has been carried out since the pioneering work in 2012 using chiral CpRh complexes as suitable catalysts in asymmetric C−H functionalization reactions.[20] The C_2-symmetric chiral [Cp^xRh^{III}] catalyst was applied in oxidative Heck reactions by You et al. in 2014 to construct axially chiral compounds. Using 5 mol% **Rh-1**, various arylbenzoisoquinoline derivatives underwent an asymmetric oxidative Heck reaction with olefins, creating axially chiral biaryls in up to 99% yield and 86% ee (Scheme 12).[21a] Subsequently, the same group developed a novel class of 1,1′-spirobiindane-derived chiral Cp (SCp) ligands, and among SCpRh complexes, **Rh-2** performed as an excellent catalyst in this asymmetric oxidative Heck reaction, in terms of substrate scope, enantioselectivity, and milder reaction temperature (room temperature).[21b] A comparison between the skeletons of these chiral CpRh catalysts (**Rh-1** and **Rh-2**) showed that the methoxy group at the 6,6′-position in **Rh-2** lies in closer proximity to the rhodium center, thus enhancing the chiral environment as a result of the smaller Rh−O distance, following the steric model suggested by Cramer et al. To demonstrate the practical utility of the axially chiral products generated by this Rh(I)-catalyzed reaction, (*S*)-**50b** was chosen as an N/olefin ligand in the Rh-catalyzed conjugate addition of phenylboronic acid with cyclohexenone, affording **52** in 77% yield and 68% ee.

A combination of a chiral SCpRh(III) complex and a chiral carboxylic acid was disclosed by You and co-workers in 2020 for a Rh(III)-catalyzed enantioselective oxidative C−H/C−H cross-coupling reaction. The reaction was feasible with aryl isoquinoline derivatives bearing various substituents, which underwent direct coupling reactions with electron-rich heteroarenes, such as (benzo)thiophenes, (benzo)furans, and indole, leading to the corresponding axially chiral compounds **53** in up to 99% yield and 99% ee (Scheme 13).[22] However, sterically demanding directing groups were required to achieve effective stereocontrol, as evidenced by the very low enantioselectivity observed in **53f** (97% yield, 17% ee). A plausible catalytic cycle was proposed based on mechanistic experiments. Intermediate **C** is initially formed via carboxylate-assisted CMD of **44a** and subsequent enantioselective C−H bond cleavage. After undergoing electrophilic C−H substitution (S_EAr), rhodacycle intermediate **C** reacts with electron-rich heteroarenes, such as thiophene, generating intermediate **D**. Next, in the presence of an oxidative Ag(I) salt, the hypervalent intermediate **E** can form cross-coupling product **53a** together with the low oxidation state SCpRh complex by oxidation-induced reductive elimination. However, the direct reductive elimination of rhodacycle intermediate **II** through path **b** cannot be completely excluded as a plausible mechanism.

The enantioselective Satoh−Miura-type reaction was reported by Wang et al. in 2019 of *N*-aryloxindoles **54** with alkynes, yielding a series of C−N axially chiral compounds **55** via a dual C−H functionalization process. Using the optimal SCpRh catalyst allowed the annulated products to be formed in up to near quantitative yield and with near complete stereocontrol (99% yield and 99% ee, Scheme 14).[23] The reaction was compatible with other substrates, and products indoline-2-thione **55c** (80% yield and 99% ee) and quinolinone **55d** (70% yield and 77% ee) could also be formed with this catalytic system with satisfactory results.

2.3. Ir Catalysis. An *in situ*-formed [Ir^I/Tol-SDP] complex was developed by Lassaletta et al. as the catalyst for the hydroarylation of electron-rich acyclic olefins, 2,3-dihydrofuran, and norbornene with configurationally labile heterobiaryls, which simultaneously constructed axial chirality and central chirality in up to >99% yield, > 20:1 dr, and 99% ee (Scheme 15).[24] Additionally, the corresponding mechanistic studies suggested that the reaction took place through a modified Chalk−Harrod-type mechanism, where the fast migratory insertion of the alkene moiety into the Ir−$C_{(aryl)}$ complex was the selectivity-determining step.

3. SYNTHESIS OF ATROPISOMERS BY ARYL−ARYL CROSS-COUPLING

Compared with (dynamic) kinetic resolution or desymmetrization, direct aryl−aryl cross-coupling is a straightforward but challenging strategy for the synthesis of atropisomers. The utilization of sterically hindered aryl reagents generally requires higher temperature to complete the reaction and often renders effective enantiocontrol more difficult.

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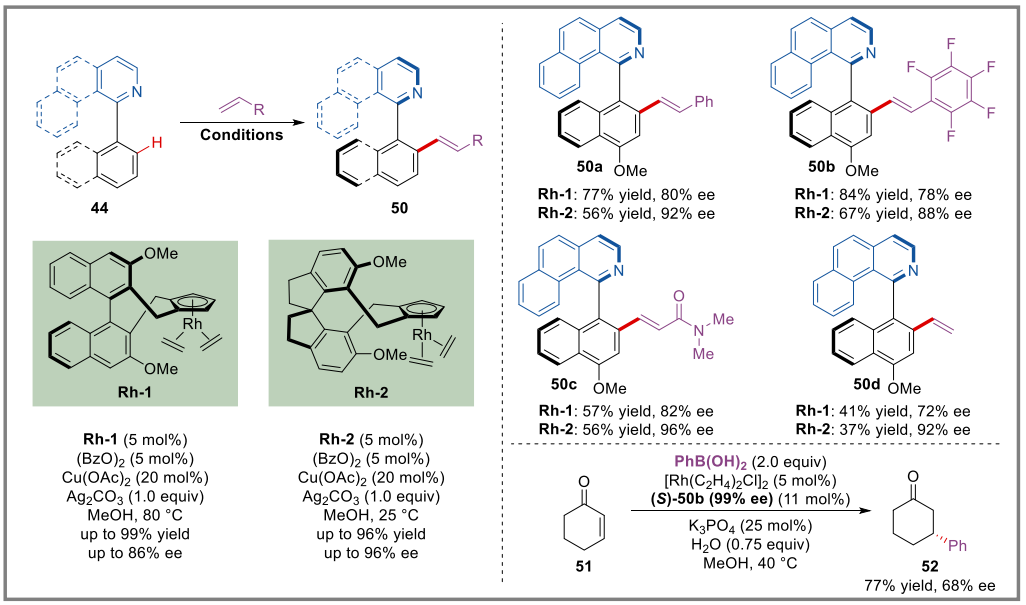
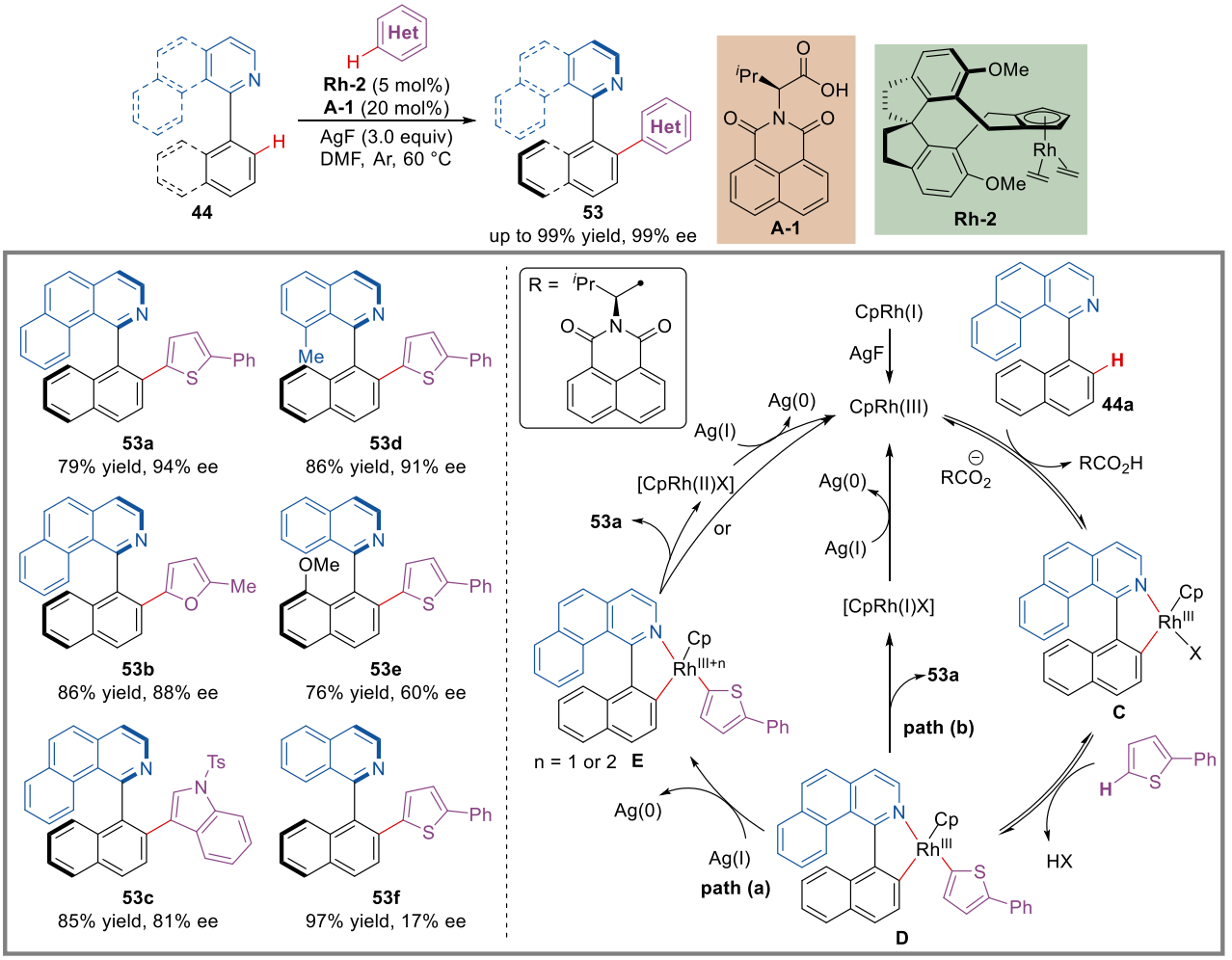
Scheme 12. Rh(III)-Catalyzed Enantioselective C−H Alkenylation of Biaryl *N*-Heterocycles



Scheme 13. Rh(III)-Catalyzed Enantioselective C−H Arylation of Biaryl *N*-Heterocycles



3.1. Pd Catalysis. Yamaguchi, Itami, and co-workers reported in 2012 a Pd-catalyzed asymmetric C−H arylation reaction of thiophene with aryl boronic acids (Scheme 16).[25a] With bisoxazoline ligand and 2,2,6,6-tetramethylpiperidine-nitrogen-oxide (TEMPO) as oxidant, axially chiral thiophene **59a** was obtained in 63% yield and 41% ee. However, while

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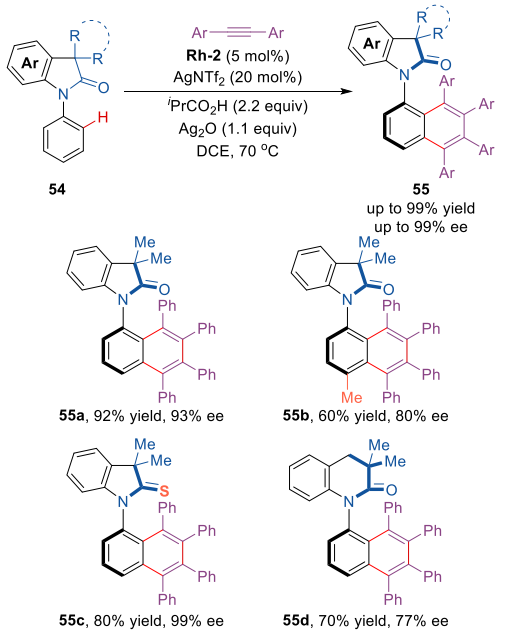
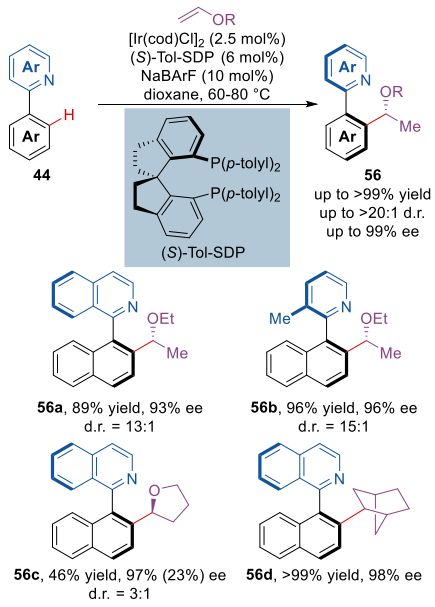
Scheme 14. Rh(III)-Catalyzed Enantioselective Dual C−H Annulation of *N*-Aryloxindoles



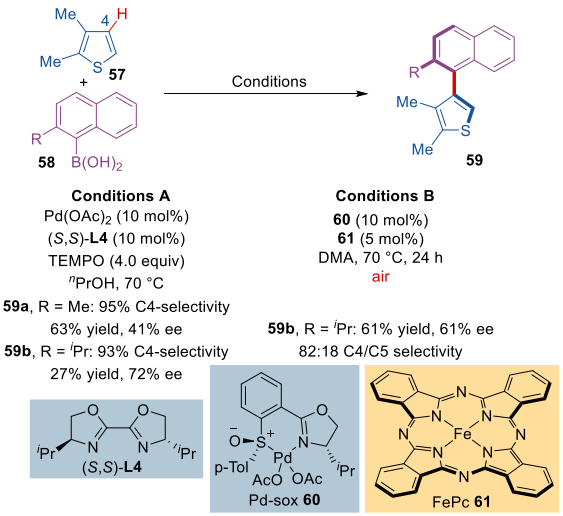
Scheme 15. Ir(I)-Catalyzed Enantioselective C−H Alkylation of Biaryl *N*-Heterocycle



increasing the steric hindrance in **58** from Me to ^{i}Pr led to an improvement in the enantioselectivity, the yield was severely negatively affected (**59b**, 27% yield, 72% ee). Further research enhanced the utility of this methodology and led to the discovery in 2013 that excess TEMPO oxidant could be replaced by a simpler air oxidation procedure using a chiral sulfoxide-oxazoline (sox) ligand, further taking advantage of the synergistic effect between palladium and iron phthalocyanine catalysts.[25b]

Despite the challenge of constructing axially chiral biaryls via the direct atroposelective C−H arylation approach, through the rational design of amide substrates **62**, Cramer et al. achieved an efficient atroposelective reaction forming various biphenyl derivatives (Scheme 17a).[26a] The Pd(0)-catalyzed

Scheme 16. Pd(II)-Catalyzed Enantioselective Intermolecular C−H Coupling of Thiophene with Hindered Arylboronic Acids



intramolecular C−H arylation was performed with the aid of TADDOL-derived phosphoramidite, generating atropisomerically enriched dibenzazepinones **63** in 96% yield and 96% ee. Further studies demonstrated that the presence of an *ortho* substituent was crucial to prevent racemization of axially chiral products, as evidenced by the formation of a racemic mixture of **63b**. Remarkably, when the substrate bore a prochiral carbon substituted with two phenyl groups, desymmetrization proceeded leading to good diastereo- and enantioselectivities.

Although Cramer et al. demonstrated the reliability of intramolecular atroposelective C−H arylation, the construction of axially chiral molecules through an intermolecular process is a much more challenging process. However, significant progress in this regard was recently reported by Cramer et al., who reported the C−H atroposelective arylation of 1,2,3-triazoles **65** with 1-bromo-2-alkoxyarenes **64** (Scheme 17b).[26b] The corresponding pyrazole-derived biaryls **66** were obtained with the aid of cesium carbonate as the base. Interestingly, the biaryl dihedral angle of the ligand played a crucial role in affecting efficient enantiocontrol. After screening, H_8-BINAPO was determined as the optimal ligand, yielding biaryl products **66** in up to 95% ee. The reaction was also feasible with pyrazole analog **65** bearing an electron-withdrawing substituent at the 3-position, leading to product **66c** formed with considerable enantioselective control (91% ee). Additionally, when 2-phenylimidazo[1,2-*a*]pyrimidine was used as the substrate, the target product **66d** could be obtained with moderate enantioselectivity (36% ee), along with a small amount of racemic byproduct **66d′** in 11% yield.

The Pd/norbornene-catalyzed Catellani domino reaction allows both *ipso* and *ortho* functionalization of aryl halides.[27] With such a strategy, *ortho* C−H functionalization of aryl halides can be achieved without the introduction of a directing group, and the Catellani reaction has proven to be a powerful strategy in C−H functionalization reactions. Recently, significant contributions on asymmetric Catellani reactions have been made by Dong et al. and Yu et al. using both chiral ligands and chiral norbornenes, providing greater choices for the attainment of efficient enantiocontrol.[28] The synthesis of atropisomerically enriched biphenyl compounds using the

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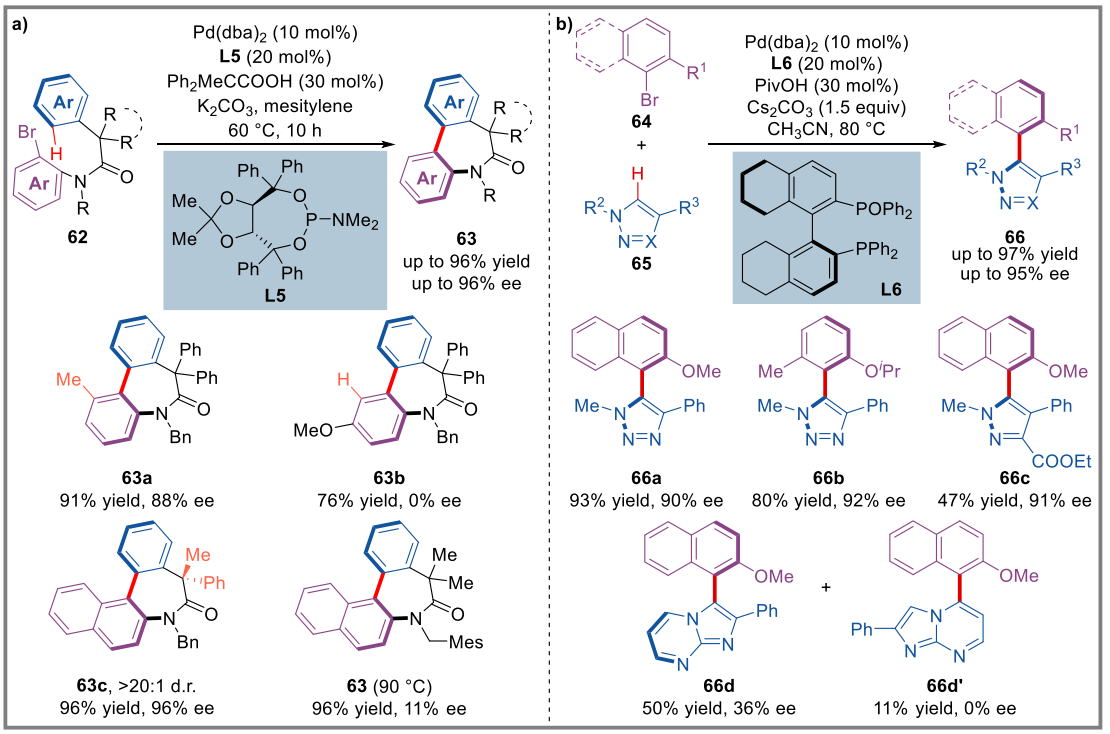
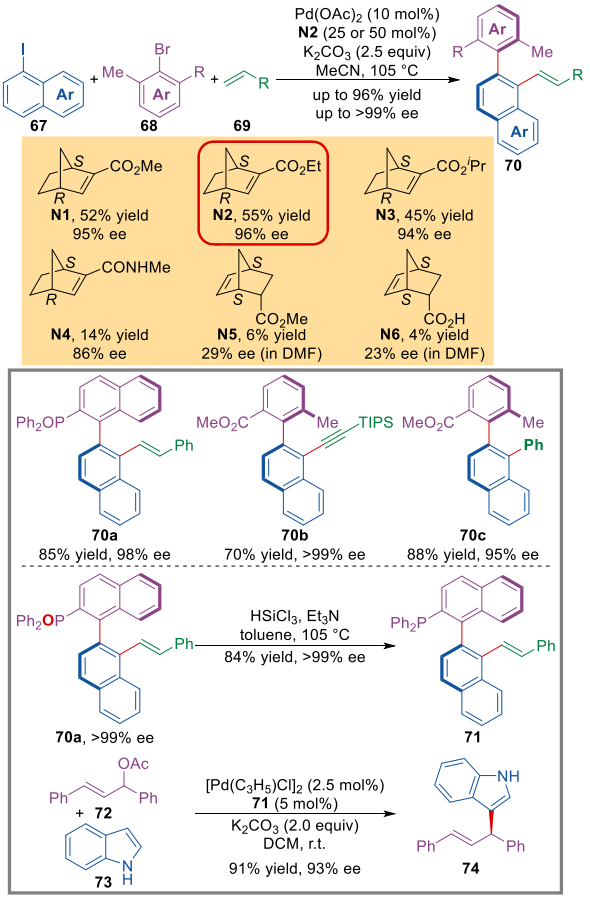
Scheme 17. Pd(0)-Catalyzed Atroposelective C−H Arylations



asymmetric Catellani reaction was first achieved in 2018 by Gu et al.[29a] Enantioselective control was achieved via an asymmetric Suzuki-type termination with the aid of a chiral phosphate ligand. Despite this pioneering work, construction of chiral biaryls by the Catellani reaction via *ortho* C−H functionalization/C−C axial construction with aryl halides remains a significant challenge due to unfavorable steric hindrance. In 2020, Zhou et al. reported the synthesis of a series of chiral biphenyl compounds via the asymmetric Catellani reaction using a palladium/chiral norbornene cooperative catalyst (Scheme 18).[29b] With the optimal chiral norbornene ligand **N2**, excellent enantioselectivities could be achieved. Notably, further reaction with various coupling reagents such as alkene, alkyne, and aryl boronic acid afforded the corresponding biphenyl compounds, in which the increased steric bulk from the introduced groups helped to stabilize the axial chirality. The usefulness of this reaction was demonstrated in the reduction of chiral phosphine **70a** to **71**, which proved to be an efficient ligand in the Pd-catalyzed asymmetric allylic alkylation of indole. Meanwhile, Song et al. used a similar strategy to prepare a variety of axially chiral biaryl-based monophosphine oxides in good yields and excellent enantioselectivities.[29c] In a more recent development, Zhou et al. was able to replace olefins **69** with sterically hindered aryl boronic acids, achieving the assembly of atropisomeric *o*-terphenyls with 1,2-diaxes by axial-to-axial diastereoinduction.[29d] Meanwhile, an axial-to-axial chirality transfer was reported by the Zhou group to generate C−N atropisomers in good yields and enantioselectivities based on palladium/chiral norbornene cooperative catalysis.[29e]

3.2. Rh Catalysis. A novel class of structurally adjustable and readily synthesized chiral *Jas*Cp ligands were developed in 2017 by Waldmann et al. using enantioselective [6+3] cycloaddition reactions. [*Jas*CpRh^{III}] **Rh-3** was successfully used in the enantioselective C−H functionalization of

Scheme 18. Pd/Chiral Norbornene Cooperatively Catalyzed Asymmetric C−H Arylation of Aryl Iodides



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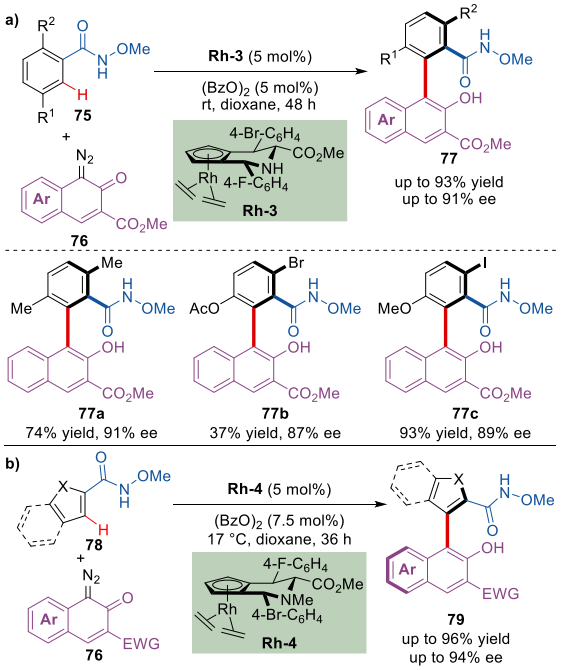
benzamides **75** with diazonaphthoquinones **76** (Scheme 19a).[30a] The reaction was compatible with electron-rich

Scheme 19. Rh(III)-Catalyzed Enantioselective C−H Arylation of (Het)arylamide

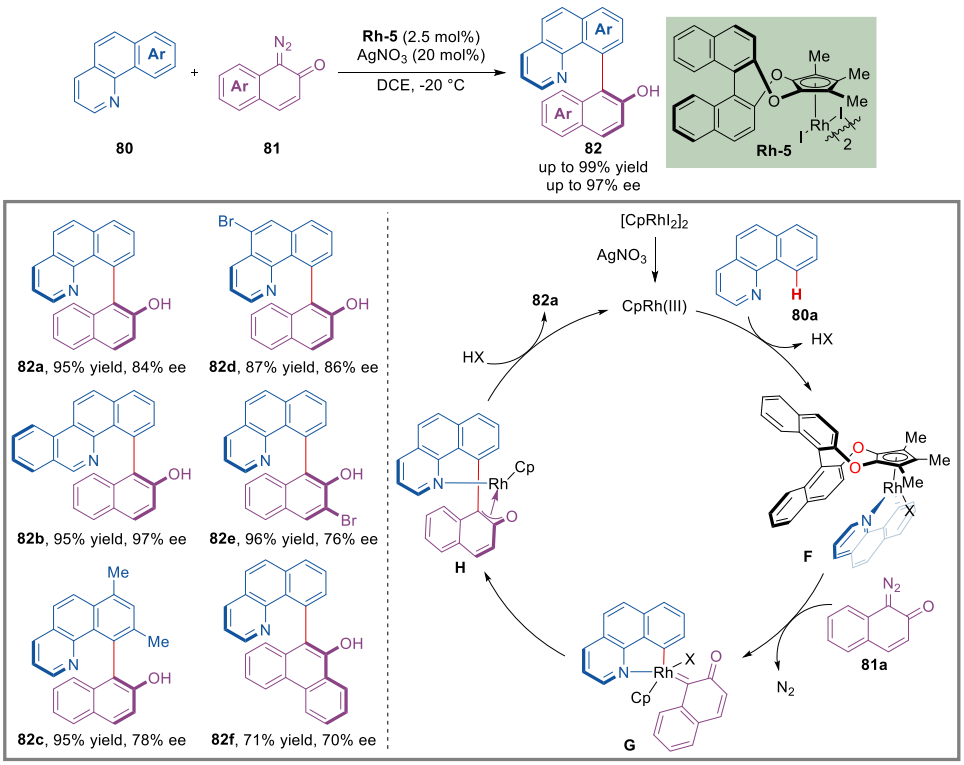


substituents in the *meta* position of the benzamide, leading to a variety of axially chiral biaryls **77** in up to 93% yield and 91% ee. In a further development of the reaction, in 2020 a similar [*Jas*CpRh^{III}] **Rh-4** catalyst was used to construct a series of five-membered ring containing atropisomeric compounds **79** through enantioselective C−H functionalization of (benzo)furan, (benzo)thiophene, and indole derivatives (Scheme 19b).[30b]

Most of the reported chiral cyclopentadienyl ligands used in Rh catalysis are mainly limited to C-linked Cp and are often synthetically challenging. Recently, You et al. developed a novel class of chiral cyclopentadienyl ligands with oxygen linkers (BOCp), and their Rh complexes were proven to be efficient catalysts for the C−H arylation of benzo[*h*]quinolines **80** with 1-diazonaphthoquinones **81**, generating axially chiral heterobiaryls **82** in up to 99% yield and 97% ee (Scheme 20).[31] The reaction conditions were highly tolerant of different substituents in the benzo[*h*]quinolines or 1-diazonaphthoquinones, leading to a variety of axially chiral biaryls. Detailed mechanistic experiments proved that the reaction occurs via initial C−H activation to generate rhodacyclic intermediate **F**, isolated via normal phase column chromatography (silica gel) and structurally determined by X-ray crystallographic analysis. This is followed by coupling with diazonaphthoquinone **81a** to afford the rhodium carbene intermediate **G** with the release of N_2. Migration/insertion of **G** gives the intermediate **H**, generating the biaryl axis. Finally, protonation of the intermediate **H** releases product **82a** and regenerates the rhodium catalyst, thereby completing the catalytic cycle.

3.3. Ir Catalysis. A catalytic phosphine oxide directed enantioselective C−H arylation with *o*-quinone diazides **81** was developed in 2018 by Cramer et al. using an iridium(III) complex bearing a chiral cyclopentadienyl (Cp^x) ligand as the catalyst together with phthaloyl *tert*-leucine as cocatalyst. The corresponding biaryl phosphine oxides **84** containing both central chirality at phosphorus and axially chiral biaryl backbones were formed in up to 96% yield, >20:1 dr, and

Scheme 20. Rh(III)-Catalyzed Enantioselective C−H Arylation of Benzoquinoline



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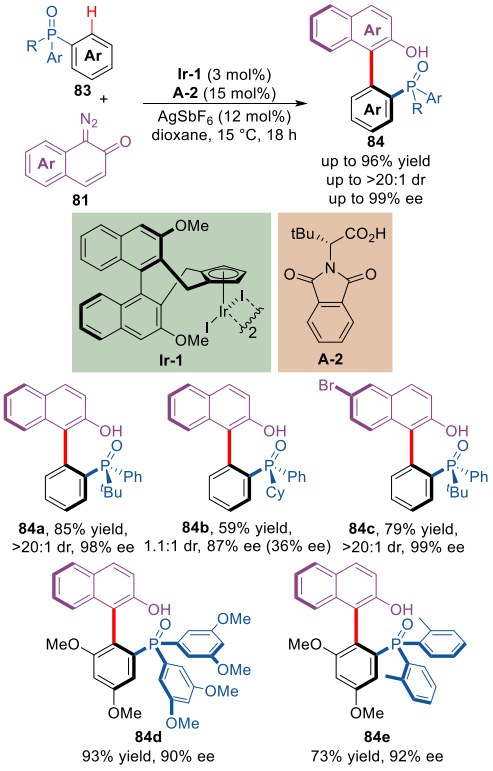
99% ee (Scheme 21).[32] Furthermore, control experiments proved that addition of the chiral acid is crucial for the success

Scheme 21. Ir(III)-Catalyzed Atroposelective C−H Arylation of Phosphine Oxides



of the reaction, and different enantiomers result in starkly different outcomes for the [CpIr^{III}]-catalyzed reaction.

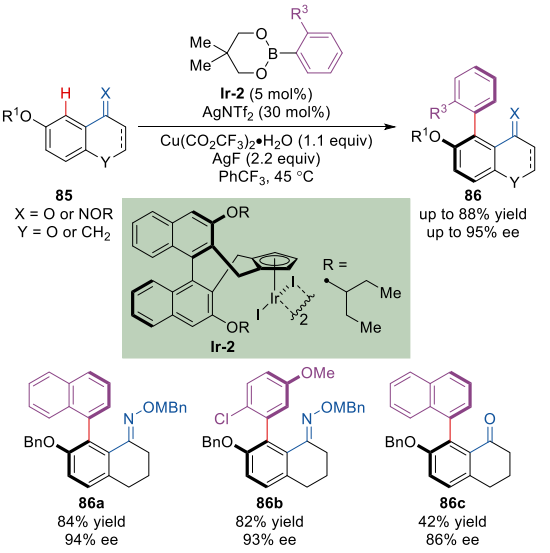
Apart from aryl bromides and diazo derivatives as effective substrates for the construction of axial chirality, Cramer et al. recently applied boronic esters as nucleophilic coupling partners to achieve the CpIr(III)-catalyzed highly atropo-enantioselective C−H arylation of α-tetralone derivatives **85**.[33] Pentan-3-yloxy ether-substituted chiral catalyst **Ir-2** delivered oxime product **86** not only in higher yields but also with better enantioselectivity than other chiral iridium catalysts. Meanwhile, a ketone, rather than an oxime (X = O, Scheme 22), could also be used as a suitable directing group to realize the reaction, albeit with lower conversion and moderate enantioselectivity (42% yield, 86% ee).

4. SYNTHESIS OF ATROPISOMERS BY ARYL AND HETEROARYL RING CONSTRUCTION

Another successfully developed approach for the installation of axial chirality is the *de novo* construction of an aromatic ring, with the chirality being formed once simultaneous ring formation with the coupling partner has been achieved (approach c, Scheme 2), rather than originating after coupling with a pre-existing aryl ring (approach b). In this regard, Rh(III)-catalyzed C−H activation has been a successful approach to effect the annulation of various alkynes for the construction of a diverse array of (hetero)arenes with concomitant formation of axial chirality.

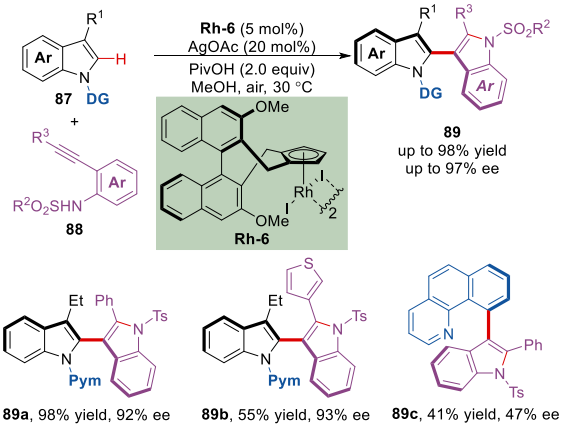
Hence, a highly enantioselective C−H functionalization and concomitant alkyne cyclization process for the synthesis of 2,3′-biindolyls, a class of axially chiral pentatomic biaryls with a

Scheme 22. Ir(III)-Catalyzed Atroposelective C−H Arylation with Aryl Boronic Esters



relatively low rotational barrier, was carried out in 2019 by Li et al. using [CpRh^{III}] complex (**Rh-6**) (Scheme 23).[34]

Scheme 23. Rh(III)-Catalyzed Enantioselective C−H Annulation of *N*-Alkoxybenzamides



Impressively, alkynes bearing alkyl-substituted phenyl and heteroaryl groups were all compatible annulation partners. Additionally, the range of C−H functionalization substrate partners could also be extended to pyrrole, imidate ester, and benzo[*h*]quinolone.

Antonchick et al. described in 2018 the piperidine-fused Cp^{x}Rh complex **Rh-4**-catalyzed enantioselective construction of axially chiral 4-arylisoquinolones **91** in up to 95% yield and 93% ee by an intramolecular C−H annulation (Scheme 24a).[35a] Demonstrating the utility of this reaction, the axially chiral 4-arylisoquinolones exhibit good biological activities as novel non-smoothened binding hedgehog pathway inhibitors. Subsequently, in 2020, Li et al. reported a [Cp^{x}Rh^{III}]-catalyzed intermolecular coupling with sterically hindered alkynes via an atroposelective synthesis that afforded biaryl isoquinolones **94** in up to 95% yield and 99% ee (Scheme 24b).[35b] Notably, the reaction tolerated well a broad range of benzamides with electron-donating, electron-withdrawing, and halogenated groups at different positions of the benzene ring. More

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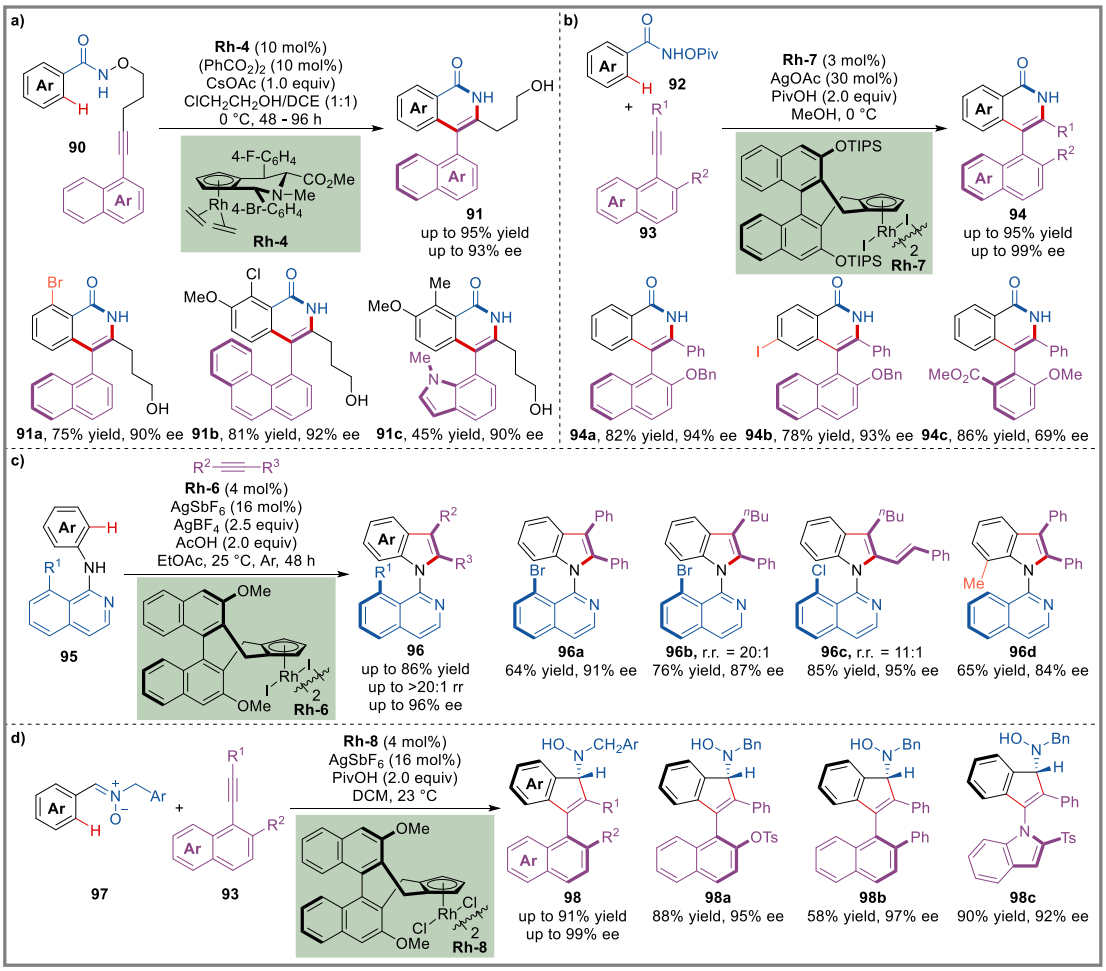
Scheme 24. Rh(III)-Catalyzed Asymmetric C−H Activation and Alkyne Cyclization



recently, the same group developed a Rh(III)-catalyzed enantioselective [3+2] annulation between *N*-isoquinolylanilines **95** and internal alkynes for the atroposelective synthesis of *N*-isoquinolylindoles **96** (Scheme 24c).[35c] Notably, **Rh-6** could effectively control the conformation of the amino-isoquinoline group prior to C−N reductive elimination, thus providing a variety of *N*-isoquinolylindoles in up to 86% yield, >20:1 rr, and 96% ee under mild conditions. The enantioselective [3+2] annulative coupling reaction of nitrones **97** with sterically hindered alkynes **93** via a Rh(III)-catalyzed C−H activation using electrophilic nitrone as the directing group was developed in 2021 by Li et al., affording indenylhydroxylamines **98** bearing a tertiary stereogenic center and C−C or C−N chiral axis with high enantio- and diastereoselection (Scheme 24d).[35d]

In a further development, Li et al. applied *de novo* construction of aromatic rings to achieve the coupling of phosphinamides **99** with two diarylacetylenes for the synthesis of axially chiral biaryls **100** bearing a P-stereogenic center under mild conditions and with high diastereo- and enantioselectivities (up to >19:1 dr and 96% ee, Scheme 25).[36] The reaction first proceeds by C−H activation, likely via carboxylate-assisted CMD and insertion of the first equivalent of diphenylacetylene to give intermediate **I**, which undergoes *cis*−*trans* isomerization to afford Rh(III) vinyl intermediate **J**. A stable rhodacyclic intermediate **K** is generated after the second *ortho* C−H activation, and insertion of a second equivalent of diphenylacetylene followed by reductive elimination leads to the formation of product **100**.

5. CONCLUSIONS AND OUTLOOK

In summary, transition-metal-catalyzed asymmetric C−H functionalization has emerged as a powerful tool for constructing optically active atropisomers with good chemo-, regio-, and enantioselectivities. Compared with traditional synthetic methods, the asymmetric C−H functionalization strategy can be applied to readily available substrates for the construction of diverse axial chirality around biaryl axes, olefin axes, C−N axes, and other novel axially chiral frameworks. Further synthetic transformation of axially chiral compounds can be carried out via convenient transformations to form central or helical chiral molecules. Demonstrating the utility of this approach and its rapid development, axially chiral compounds are increasingly being used as chiral ligands, catalysts, and chiral materials.

Despite the significant breakthroughs made so far, research in the synthesis of optically active atropisomers via asymmetric C−H functionalization remains in its early stages. Future developments include but are not limited to the following possibilities. An improvement in the catalytic efficiency of most reactions is still necessary, as relatively high transition metal catalytic loadings (5−10 mol%) are still generally required, limiting their practical applications. More effective catalytic systems will be expected to drive this field. Furthermore, the

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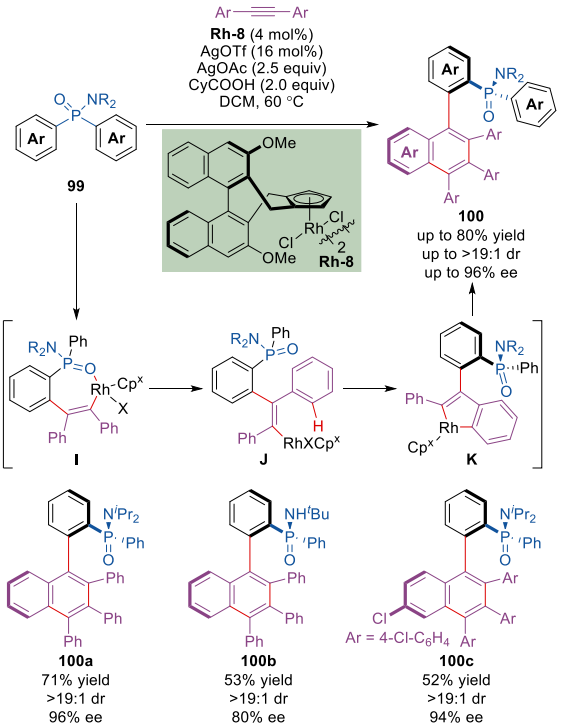
Scheme 25. Rh(III)-Catalyzed C−H Arylation of Phosphinamides with Two Diarylacetylenes



reaction mechanisms still need to be explored in greater detail, which will in turn aid the development of more efficient catalysts, further expanding the reaction possibilities and substrate scope. Additionally, there is an urgent need to expand the scope of metals that can be converted into useful catalyst complexes for the atroposelective C−H functionalization beyond the currently used but expensive Pd, Rh, and Ir metals to include much cheaper and abundant first-row transition metals such as Fe, Co, and Ni. Meanwhile, while the synthesis of axially chiral compounds using diverse electrophiles as the coupling reagents to form C−X bonds such as C−N, C−S, and C−P is highly desirable, the heteroatoms present in both substrates and products in these reactions can lead to problematic catalyst poisoning. The presence of pre-installed directing groups necessary for the efficient synthesis of atropisomers, which usually cannot be effectively removed or transformed, greatly restricts their use in the synthesis of natural products and pharmaceuticals. Hence, the development of reactions with directing groups that can be more easily modified or reactions involving non-directed C−H bond activation to synthesize axially chiral compounds are highly desirable research goals. Finally, along with advances in this field, the development of more applications for these synthetic methodologies and their related products is expected. Given the fast rate of developments in this research area, we expect that novel catalysts and transformations will soon be developed for constructing optically active atropisomers via asymmetric C−H functionalization processes.

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Notes

The authors declare no competing financial interest.

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