ORGANIC CHEMISTRY FRONTIERS

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2026, **13**, 2599

Enantioselective synthesis of atropisomeric biaryls and heterobiaryls *via* transition metal-catalyzed cyclization

Shibo Lin, *[a] Ya Zou,[a] Yiwen Chu,[b] Junfeng Deng[b] and Lifeng Zhao[b]

Received 29th October 2025,
Accepted 24th February 2026

DOI: 10.1039/d5qo01492a

rsc.li/frontiers-organic

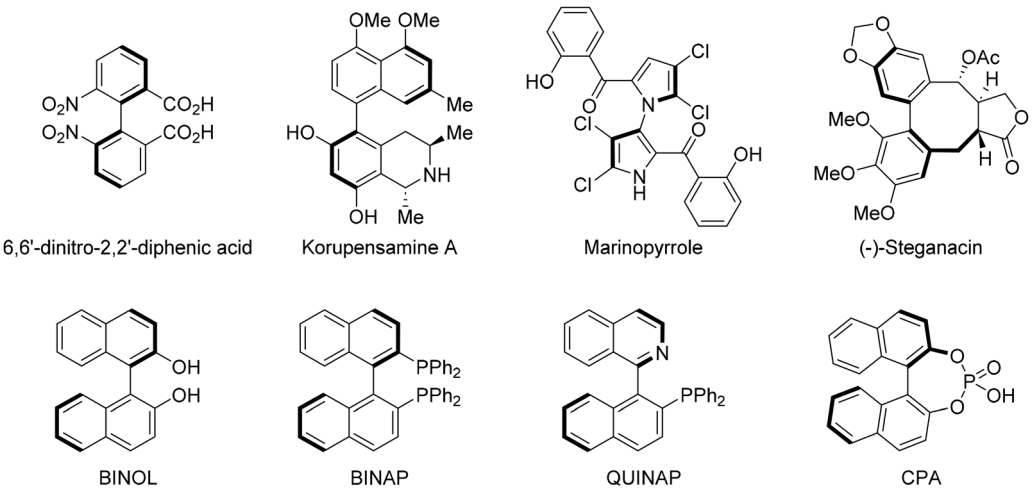
Atropisomeric architectures with a chiral axis are prevalent in biologically active molecules and natural products, and they are widely put to use in privileged catalysts and chiral ligands. Axially chiral biaryls and heterobiaryls are a fundamental category of atropisomeric compounds with inherent barriers caused by rotational restrictions around carbon–carbon, carbon–nitrogen or nitrogen–nitrogen axes. In this regard, the synthesis of biaryls/hetero-biaryls has witnessed substantial progress, despite the generally complicated traditional synthetic methods. Recent developments in the transition metal-catalyzed substrate activation and subsequent annulation reaction offer a straightforward approach to the preparation of various cyclic (hetero)biaryl atropisomers. In this review, we would like to present recent research advancements in transition metal-catalyzed enantioselective annulation reactions towards (hetero)biaryls featuring atropisomeric optical activity. The focus will be on mechanistic investigations, reaction limitations, and synthetic applications. Additionally, the combination of developing synthetic strategies and representative frameworks is discussed, along with some insights into the developing trend.

1. Introduction

Axial chirality, commonly originating from sterically impeded rotation around a stereogenic axis, has become a distinct category of stereoisomerism.[1] First successfully identified by Kenner and Christie in 1922, axially chiral 6,6′-dinitro-2,2′-diphenic acid, featuring a carbon–carbon chiral axis between two phenyl residues, has been synthesized and has sparked further research into atropisomers.[2] These molecules are commonly found in pharmaceuticals and natural products, such as korupensamine A, marinopyrrole and (−)-steganacin.[3–7] Atropisomers could also serve as privileged frameworks for diverse organocatalysts as well as chiral ligands such as CPAs (chiral phosphoric acids), BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] and BINOL (1,1′-binaphthyl-2,2′-diol).[8–11] Additionally, they are effectively used in functional materials, including fluorescent sensors and host–guest chemistry (Scheme 1).[12,13] The growing recognition of the significance of axially chiral compounds has sped up the development of efficient asymmetric synthetic approaches for their production. Moreover, a wealth of axially chiral biaryls and nonbiaryls have been designed and synthesized. These include styrenes, amides, anilides, and even atropisomeric N–N and C–B architectures, which have found use in multidisciplinary fields.[14–19]

Axially chiral biaryls, characterized by a stereogenic axis and aromatic rings, are typically sought-after synthetic target products.[20–22] It is worth noting that various chiral molecules bearing biaryl moieties display multi-functional properties across different fields.[7,23,24] Compared to atropisomeric biaryls, cyclic (hetero)biaryl atropisomers present more complicated architectures with multiple reactive sites, which makes their formation particularly challenging.[25,26] The primary obstacles include: (a) the dynamic behavior of steric hindrance, (b) the occurrence of competing side reactions, and (c) the difficulty in achieving high selectivity in reactions. Despite these difficulties, cyclic (hetero)biaryl-decorated atropisomers have a promising future with significant potential to generate structurally diverse frameworks as a result of the versatile reaction activities of substituents attached to aryl groups, as exemplified by the efficiency of chiral phosphoric acids.[27–29] Hence, significant efforts in academia have focused on developing innovative asymmetric synthesis, mainly through transition-metal catalysis, organocatalysis and enzymatic catalysis. Due to the distinct features of being more sustainable and facile, transition metal-catalyzed annulation strategies have emerged as powerful and straightforward methods for accessing axial chirality and addressing sophisticated atroposelec-

[a]*Department of Pharmacy, West China School of Medicine, Sichuan University, Sichuan University Affiliated Chengdu Second People's Hospital, Chengdu Second People's Hospital, Chengdu 610021, China.*
E-mail: lin0741028@yeah.net
[b]*Antibiotics Research and Re-Evaluation Key Laboratory of Sichuan Province, School of Pharmacy, Chengdu University, Chengdu 610021, China*



Scheme 1 Representative atropisomers in bioactive compounds and asymmetric synthesis.

tive issues.[26,30,31] These approaches exhibit notable advantages in forming chiral axes by activating inert substrates and enabling annulation, thus facilitating the energy-efficient and atom-economical production of valuable cyclic (hetero)biaryl atropisomers.

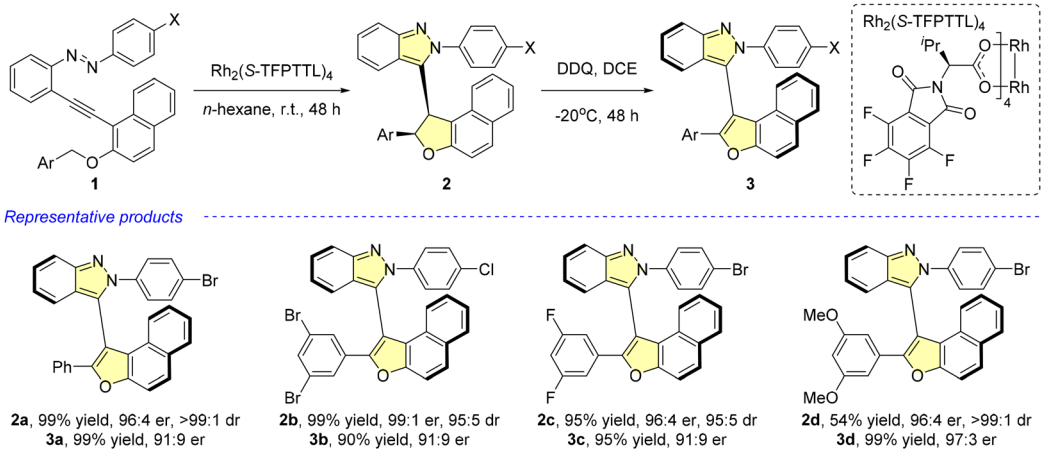
While several fascinating reviews, such as the synthesis of biaxially chiral compounds, the synthesis of molecules featuring multiple stereogenic elements, and the construction of axial chirality *via* benzannulation, have been reported,[32–34] there is currently no review dedicated specifically to the efficient catalytic systems for constructing atropisomeric biaryls and heterobiaryls. In this review, we aim to offer a systematic overview of contemporary advances in transition metal-catalyzed atroposelective ring manipulations of biaryls and heterobiaryls. To clarify these reaction systems, this article is organized based on the catalyst types, emphasizing methodological differences, potential applications and mechanistic insights. We also highlight the axially chiral frameworks that often appear in reviews, showcasing the fascinating discoveries related to the study of atropisomeric scaffolds. We wish this work could provide timely inspiration for organic chemists and guide the development of more practical and sustainable protocols.

2. Rhodium catalysis

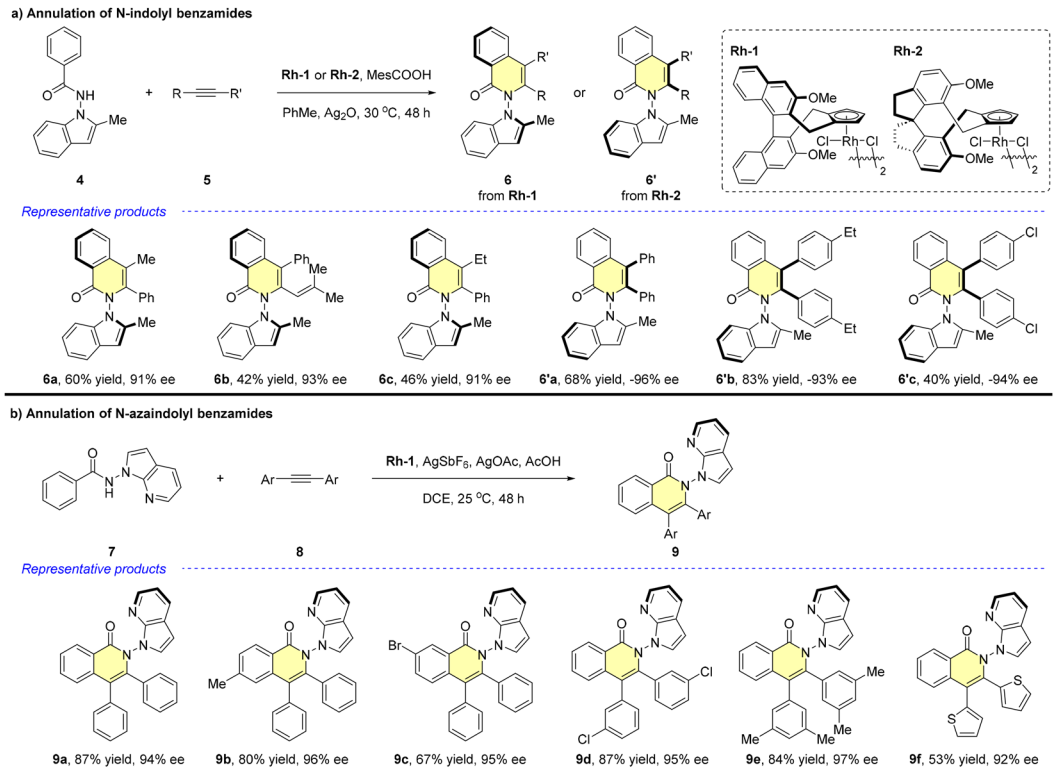
Over the past decade, metallic rhodium has become a focus of interest in chemistry due to its stable chemical properties and exceptional catalytic capabilities.[35–38] Beginning with the rhodium-catalyzed carbonylation of methanol by Paulik and Roth in 1968,[39] rhodium catalysis has significantly advanced the efficient synthesis of diverse organic molecules. Rhodium forms various metal complexes with good catalytic activity and selectivity, accelerating reactions by lowering their energy barriers, which enables milder conditions and broader functional group tolerance.[40,41] The azaenyne group was found to be a suitable reagent serving as an effective directing group to facilitate regioselective ring-closing and generate annulation products through rhodium catalysis. In 2021, Zhu and colleagues combined C–H functionalization with tandem cycloaddition through an intramolecular atroposelective cycloisomerization of azaenynes **1** (Scheme 2).[42] The well-designed naphthyl-fused dihydrofurans **2** were obtained in the presence of a dirhodium(II) catalyst. Upon oxidative dehydrogenation with DDQ, the centrally chiral frameworks was transferred to the conformationally stable isoindazole derivatives **3**. This two-step protocol provided a modular and efficient way to access heterobiaryls with a wide variety of substituents on aromatic rings. Moreover, late-stage modification of the products demonstrated the potential usefulness of this cycloisomerization strategy. This work represented the first example of catalytic asymmetric cycloisomerization of unactivated internal azaenynes.

More recently, this atroposelective arene-forming approach was further extended to the assembly of chiral fused isoquinolin-1(2*H*)-ones with rotationally limited N–N bonds in 2023.[43] By the catalysis of a chiral $Cp^{X}Rh(III)$ catalyst, *N*-indolyl benzamides **4** containing an N–N directing group smoothly underwent an oxidative annulation procedure with internal alkynes **5** to produce the desired indoles **6** (Scheme 3a). Remarkably, changing the orientation of the chiral catalysts allowed the formation of products with the opposite configurations. DFT calculations revealed that the insertion of alkyne into the Rh–C bond was both the rate-limiting and enantio-determining step of the overall process. This approach could also enable the easy transformation of *N*-azaindolyl benzamides **7**, leading to a series of N–N axial atropisomers **9** with high stability (Scheme 3b). Encouragingly, most products were afforded with good to excellent enantioselectivity. Overall, this strategy not only expanded the scope of rhodium-mediated oxidative annulations but also set the stage for subsequent development in the construction of N–N axially chiral frameworks.

In another development, Li and co-workers developed a series of rhodium-catalyzed atroposelective cycloaddition reactions of benzamides with sterically hindered alkyne substrates



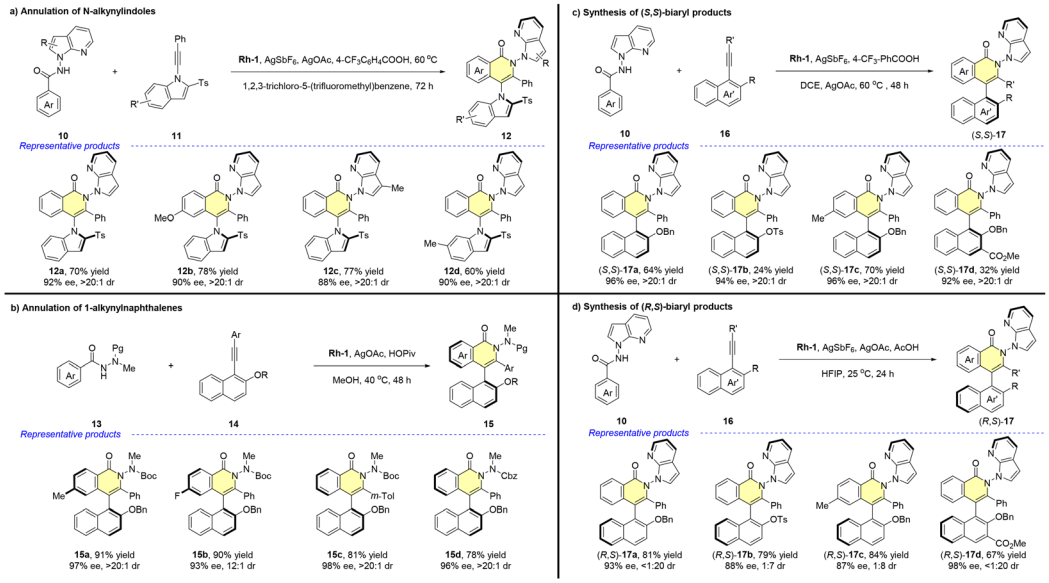
Scheme 2 Atroposelective intramolecular cycloisomerization of azaenynes.



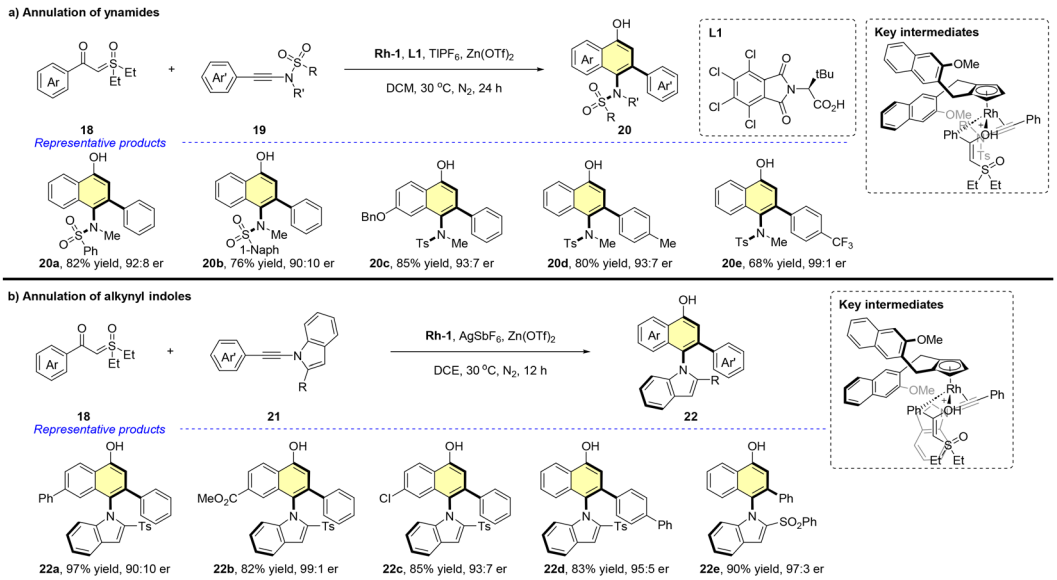
Scheme 3 Atroposelective intermolecular annulation of benzamides and alkynes.

(Scheme 4).[44] The Lewis acidic silver(I) facilitated the bridge connection of the directing group with the 2-OR moiety to insert alkynes in well-defined orientations. Regio- and stereodivergence were endowed by a steric barrier at the less-hindered C–H site. A large array of reagents participated effectively in this diastereodivergent annulation, including *N*-alkynylindoles, 2-substituted 1-alkynylnaphthalenes and benzamides. Computational studies and reaction monitoring suggested that the N–N axial chirality was determined upon the C–H bond activation–cyclometallation procedure, and the solvent exerted a great impact on the alkyne insertion pathway. This protocol laid the groundwork for diversity-oriented synthesis of diaxially chiral heterobiaryls. Additionally, the representative products could be transformed into functionalized molecules, making them versatile synthetic tools for biaryl modification.

Given that the asymmetric coupling of ylide directing groups was still in its early stages, Li, Wang and colleagues reported Rh(III) catalysis for asymmetric annulative coupling reactions intended for their use (Scheme 5).[45] The enantioselective C–H functionalization of sulfoxonium ylides **18**



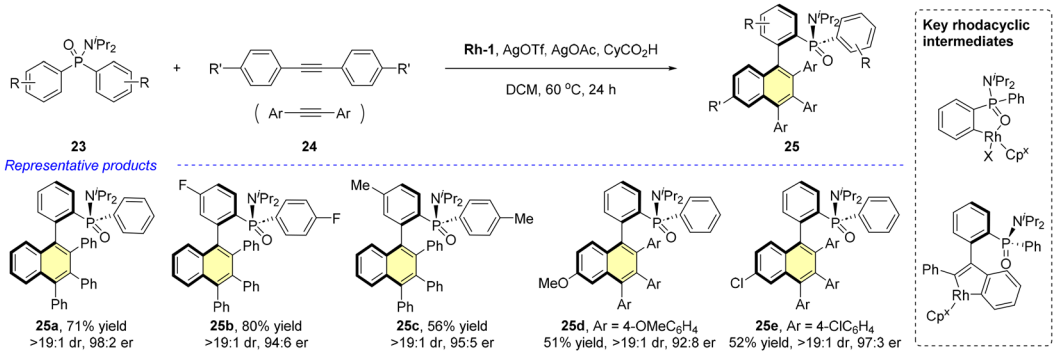
Scheme 4 Rhodium-catalyzed asymmetric approach to access diaxially chiral heterobiaryls.



Scheme 5 Rhodium-catalyzed synthesis of C–N axially chiral naphthols.

enabled atroposelective [4 + 2] cycloaddition with ynamides **19**, resulting in the formation of C–N axially chiral naphthols **20**. Moreover, by simply replacing ynamides with alkynyl indoles **22** as the coupling partners, the researchers were able to produce a series of C–N axially chiral heterobiaryls **23** under similar catalytic conditions. Mechanistically, the ylide motif was inclined to be pushed outward due to steric exclusion. Then, the alkyne with a bulky substituent approached with the group pointed downward, leading to the *R*-configured cyclized product. Importantly, this method also offered an applicable strategy for preparing axially chiral ligands and synthetic frameworks with biological interest.

Despite the progress, the arylating source is restricted to several types of bulky and reactive reagents. The construction of axial chirality requires the development of more convenient arylating agents. Twofold C–H activation also offered attractive opportunities for the enantio- and diastereoselective synthesis of C–C atropisomeric molecules. In 2021, the Li and Wang group demonstrated a stereoselective naphthylation reaction of alkynes for the asymmetric preparation of biaryls bearing both axial and P-central chirality (Scheme 6).[46] It was worth noting that the naphthylation reaction might proceed *via* carboxylate-assisted concerted metalation–deprotonation events, generating rhodacyclic intermediates. KIE experiments also indicated



Scheme 6 CpRh-catalyzed atropo-enantioselective C–H arylation.

that the C–H activation step was the turnover-limiting step, as thermodynamically and kinetically stable rhodacycles were formed in all procedures.

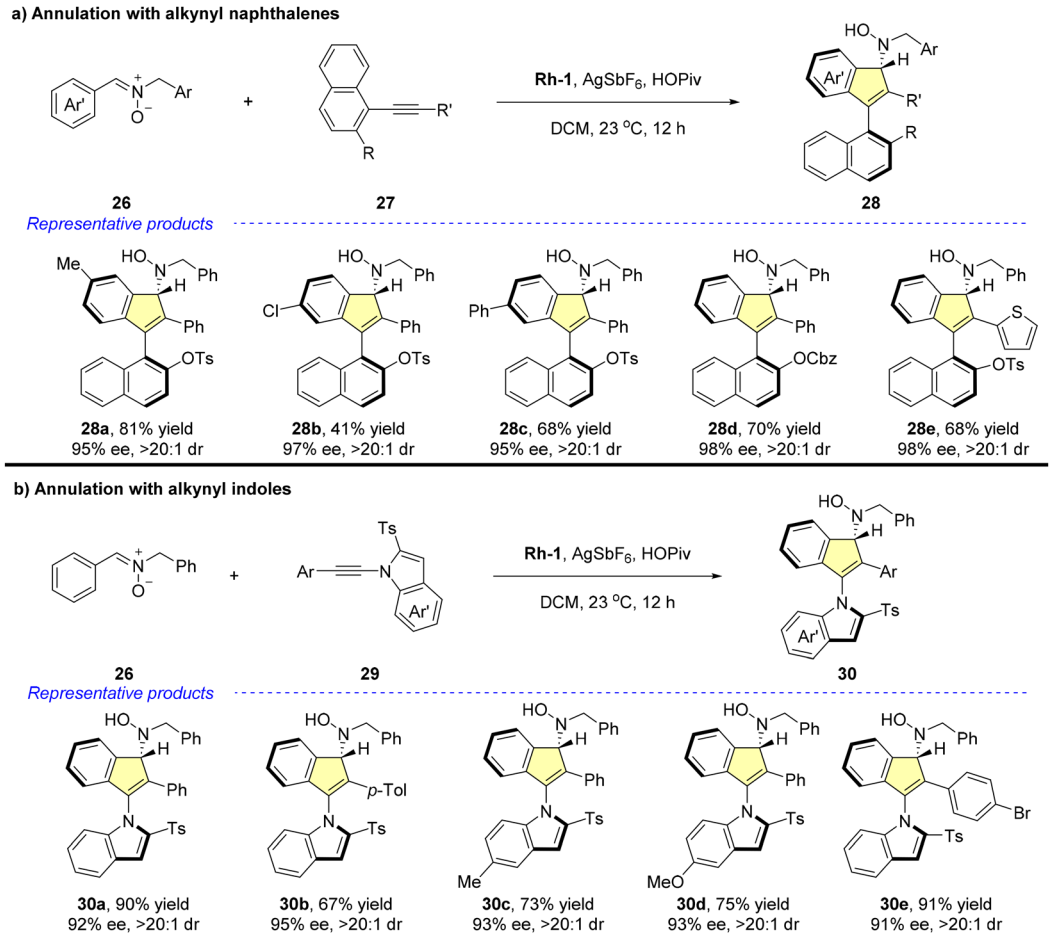
It was very challenging to construct multiple discrete chiralities in a one-pot reaction without mutual impact, especially when they were distal to each other. In 2021, adopting a similar rhodium-catalyzed C–H activation strategy, Li and co-workers developed a straightforward approach to assemble axially chiral pentatomic indenes efficiently (Scheme 7).[47] This protocol involved [3 + 2] annulation and encompassed various reaction pathways. Asymmetric coupling reactions with highly hindered alkyne substrates produced C–N axially chiral products, which were divided into two categories. These products exhibited good diastereo- and enantioselectivity, primarily due to the powerful **Rh-1** catalyst, which enabled two separate stereocontrol procedures. In addition, the same catalyst was used to couple less hindered alkynes with *N*-benzylnitrones, yielding indenyl hydroxyamines with a tertiary chiral center. The diversified structures, high diastereoselectivity control and concise enantiodivergent synthesis of the C–N or C–C atropisomeric platform provided valuable insights for investigating value-added axially chiral architectures through asymmetric C–H activation.

Building on the above insights, Li's group expanded the coupling system to employ *N*–*O*-substituted benzamides for atroposelective [4 + 2] cycloaddition with alkynes (Scheme 8).[48] Initially, the authors realized an atroposelective annulation involving benzamides **31** and 2-substituted 1-alkynylnaphthalenes **32**. This transformation utilized **Rh-3** as the chiral catalyst, along with AgOAc as the oxidant, leading to the generation of axially chiral isoquinolones **33** in good yields with high enantioselectivity (up to 95% yield and 99% ee). KIE measurements suggested that the atroposelective C–H bond activation might participate in the turnover-limiting step. Moreover, the authors proposed that atroposelectivity was induced by minimizing steric interactions between the amide directing group and the naphthalene moiety. The successful compatibility of Ru/AgOAc catalysis inspired the development of atroposelective cycloaddition with other coupling partners such as sterically hindered diarylacetylenes **35**. However, no improvement in enantioselectivity was achieved until the **Rh-1** catalyst, assisted by NaOAc as an additive, was employed. This protocol enabled the synthesis of axially chiral annulated isoquinolones **36** with excellent enantioselectivities. Furthermore, this one-pot cascade C–H activation–cyclization sequence provided efficient access to structurally diverse isoquinolones, valuable frameworks in pharmaceutical chemistry.

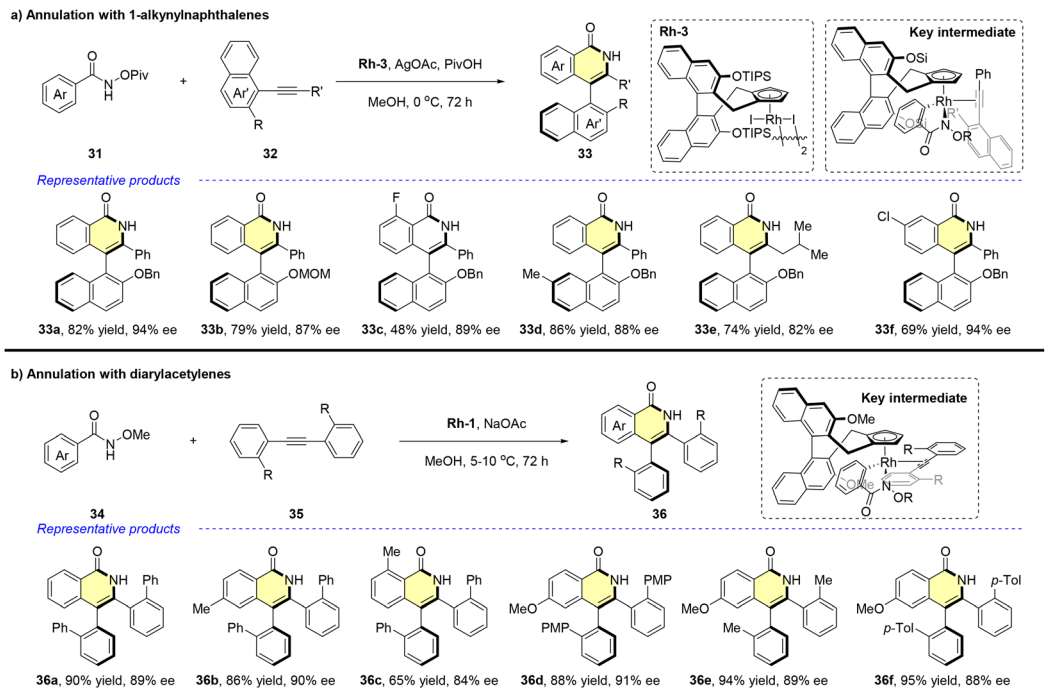
Besides constructing C–N axially chiral indole skeletons from alkynes, some strategies focus on using ynamines as available atropisomer partners. Xie *et al.* then reported the directing ability of the Bpin group under Rh(III)/Phos catalysis through an integration of previous achievements and experimental research.[49] A novel chiral phosphoramidite ligand, XiePhos, was created for the enantioselective [4 + 2] annulation of 2-(cyanomethyl)phenylboronates **38** and indolyl-ynamines **37** (Scheme 9). This approach allowed for the efficient creation of C–N axially chiral indole-based derivatives **39** with reasonable yields (36–47%) and enantiomeric excesses (81–91%). This innovative method demonstrated benefits like mild conditions, easy operation and scalability.

In contrast, Xu and co-workers used 1,6-diynes **40** containing a heteroatom (nitrogen and oxygen) after oxidative cyclization for rhodium-catalyzed coordination with ynamides **41** to produce C–N axially chiral indolyl products **42** (Scheme 10).[50] The ester groups on the indole rings imparted the regioselectivity by blocking reactive sites and enhanced the stability of the stereogenic axis. This well-established protocol demonstrated great potential for broad application in the domain of atroposelective indole-based framework synthesis, chiral catalysis and related research fields. This tandem procedure addressed longstanding challenges in asymmetric cycloaddition, especially achieving 100% atom economy.

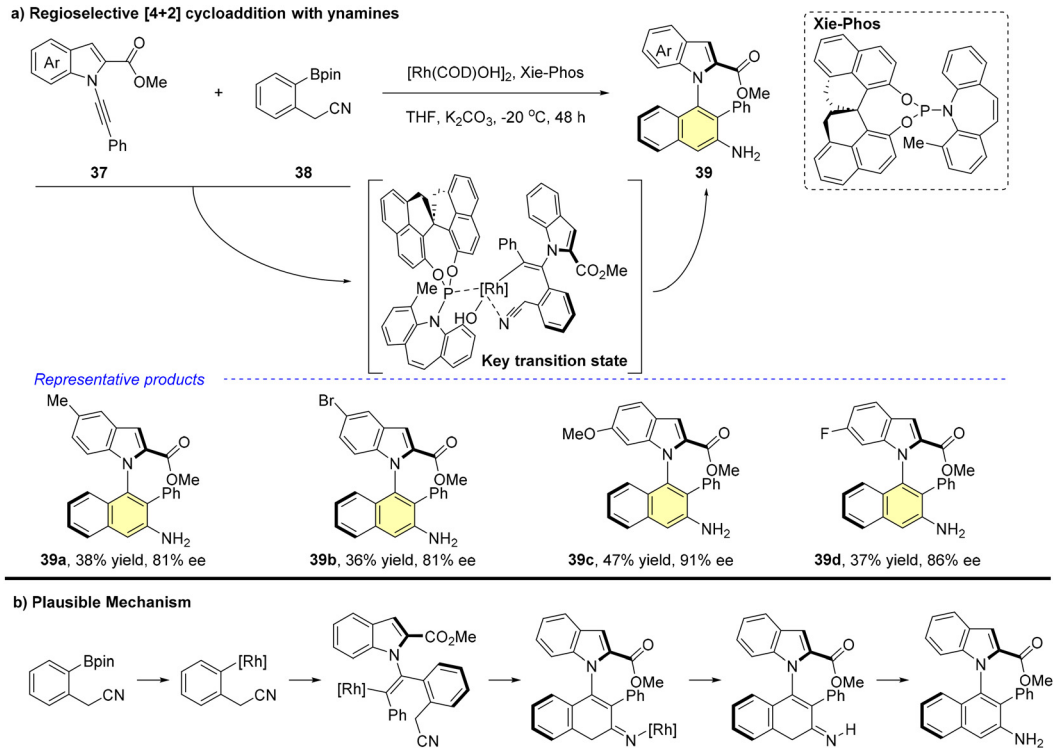
Atroposelective assembly for constructing benzo-fused five-membered heterocycles remained a challenge for chemists. This might be attributed to the significant impediments that exist in such axially chiral frameworks, including complex structures and stereochemical control, which were highly desired to be overcome. Also for instance, Tanaka and co-workers initiated the construction of axially chiral hydroxy esters **45** through Rh-catalyzed enantioselective coupling of diynes **43** and monoynes **44** (Scheme 11a).[51] The phosphine ligand (*S*)-BINAP bearing axial chirality successfully induced stereospecific control during the generation of functionalized



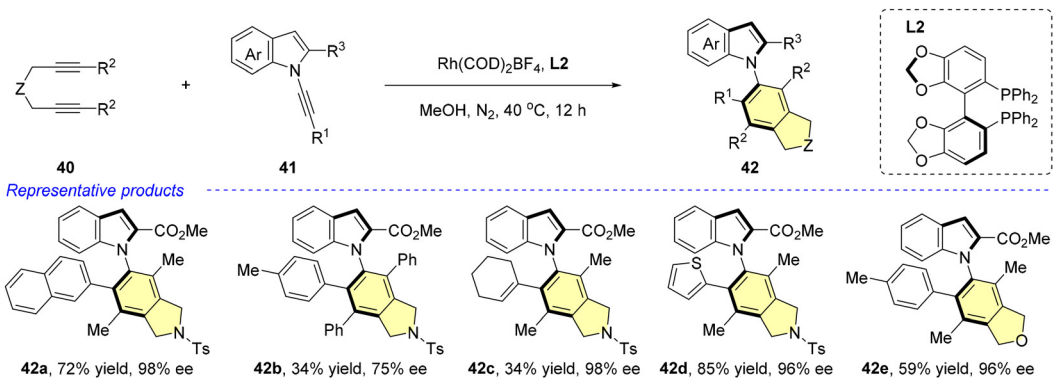
Scheme 7 Nitrone-directed asymmetric annulation to construct pentatomic biaryls.



Scheme 8 Rh-catalyzed preparation of axially chiral isoquinolones.



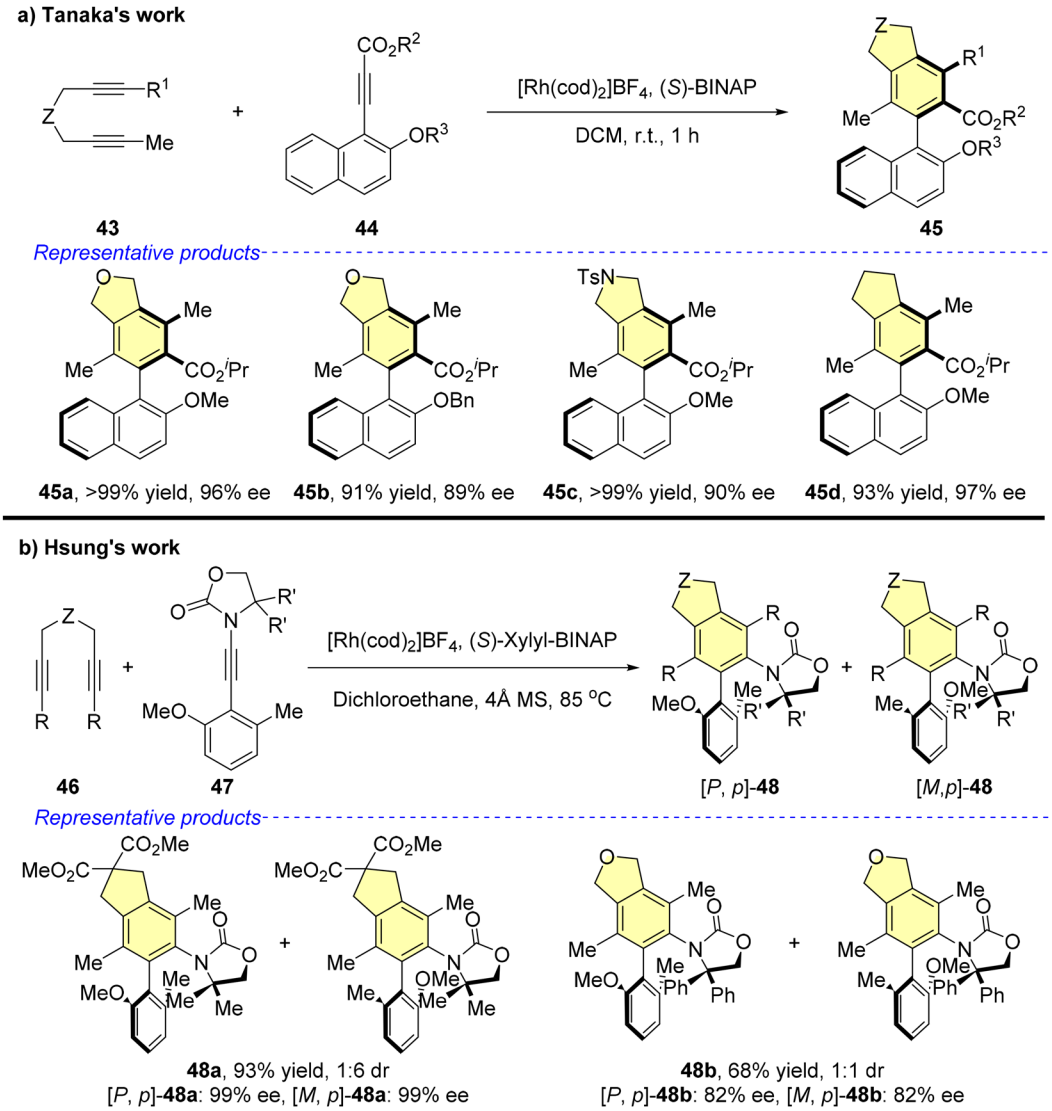
Scheme 9 Neighboring group-directed synthesis of indole-based derivatives.



Scheme 10 Rh-catalyzed asymmetric [2 + 2 + 2] cycloaddition with diynes.

axially chiral biaryl compounds. In another report, the Hsung group developed a similar Ru catalysis protocol to atroposelectively produce chiral *N*,*O*-biaryls **48** from readily available achiral ynamides **46** and diynes **47**, using a chiral auxiliary (Scheme 11b).[52] Notably, this process involved enantioselective C–H activation of ynamides through bidentate rhodium(III) chelation.

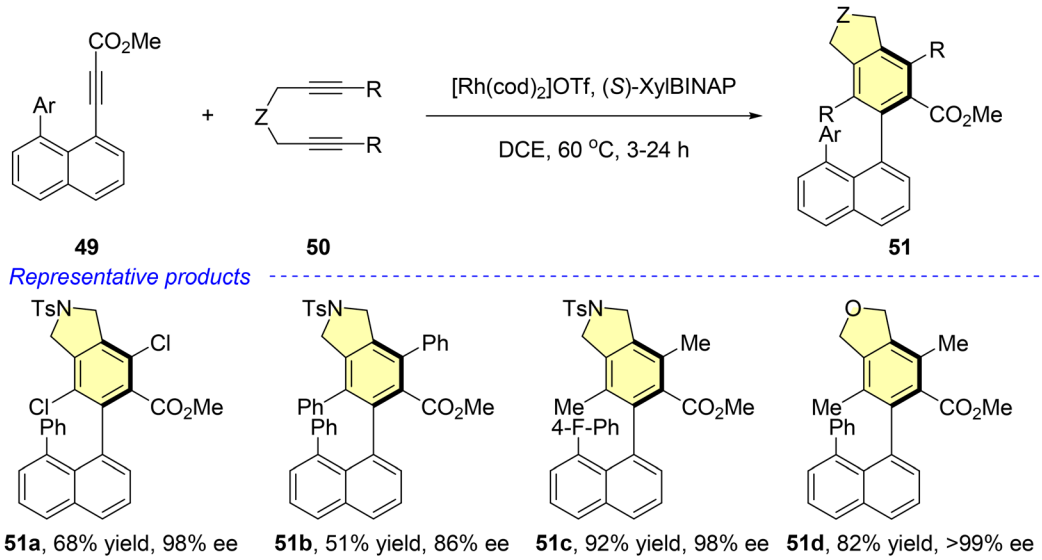
1,8-Diarylnaphthalenes have attracted considerable attention lately owing to their distinctive arrangement of *peri*-aryl rings, which enables multipurpose applications, such as luminescent materials and dyes. Nevertheless, the classic approach to their preparation involved the coupling of diiodonaphthalene with Grignard reagents. Aiming to investigate the chiral bisphosphine ligand, Shibata and colleagues employed a bulky XylBINAP ligand that facilitated the enantioselective [2 + 2 + 2] cycloaddition for synthesizing atropisomeric 1,8-diarylnaphthalenes **51**, with $[Rh(cod)_2]OTf$ as the catalyst (Scheme 12).[53] The key influencing factor contributing to the effective asymmetric induction was the presence of an ester group on the alkyne terminus, whose carbonyl moiety could coordinate with the rhodium catalyst. This method was notable for its excellent reactivity and mild conditions, which allowed for the tolerance of various functional groups and aromatic rings. Importantly, the resulting 1-pyrene-substituted products were first demonstrated to be potential CPL-emitting materials due to their good chiroptical properties.



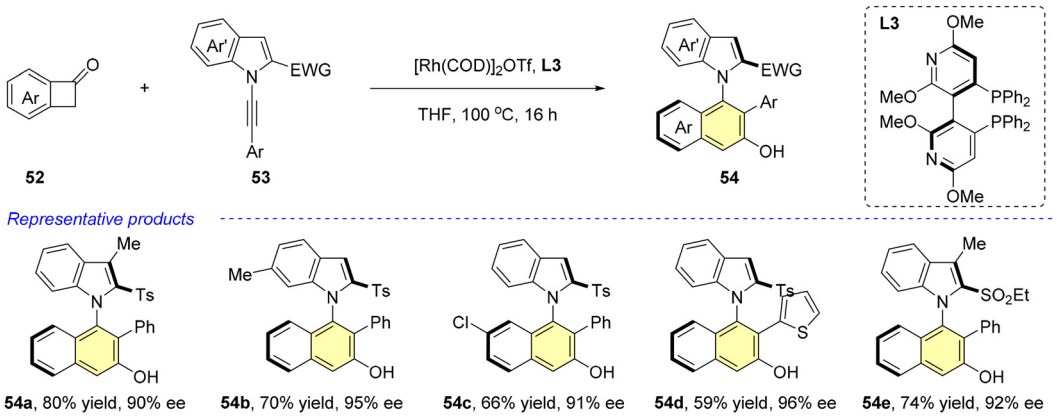
Scheme 11 Rh-promoted cycloaddition to access atropisomeric diaryls.

The diastereoselective synthesis of C–C and C–N atropisomers was further elegantly developed by the Li and Huang group in 2025 (Scheme 13).[54] In this innovative work, the authors judiciously incorporated a strained ring, cyclobutanone, into benzocyclobutenones, thereby enabling the first rhodium-catalyzed enantioselective annulative coupling with alkynes to construct atropisomeric indolylnaphthol products. The computations showed that the reaction was promoted by the transition state generated *in situ via* hydrogen-bonding interactions between the substrates and the chiral ligand. Notably, the cyclobutanone moiety served not only as a key platform for the coordination with the Rh center, but also as an efficient handle for versatile transformations. This approach facilitated the direct, modular building of three-dimensional naphthols under mild conditions, providing a versatile chiral platform for enantioselective C–C activation reactions.

Apart from using monoynes as the coupling partners, in 2015, Ollivier and colleagues prominently developed an efficient enantioselective [2 + 2 + 2] annulation of isocyanates and diynes with the assistance of a combined chiral ligand and chiral counter-ion pair to produce axially chiral adducts (Scheme 14a).[55] This process involved the construction of pyridine skeletons with an Ar–N atropoisomeric axis through double-asymmetric induction. Nevertheless, the employment of hydrogen enabled facile replacement of the cyclooctadiene ligand from rhodium, which favored the generation of active intermediates. This led to a significant improvement in efficiency and enantioselectivity in this challenging cycloaddition at ambient temperature. Notably, the superiority of this matched pair strategy not only improved the substrate compatibility and reaction efficiency but also offered potential possibilities for asymmetric induction.



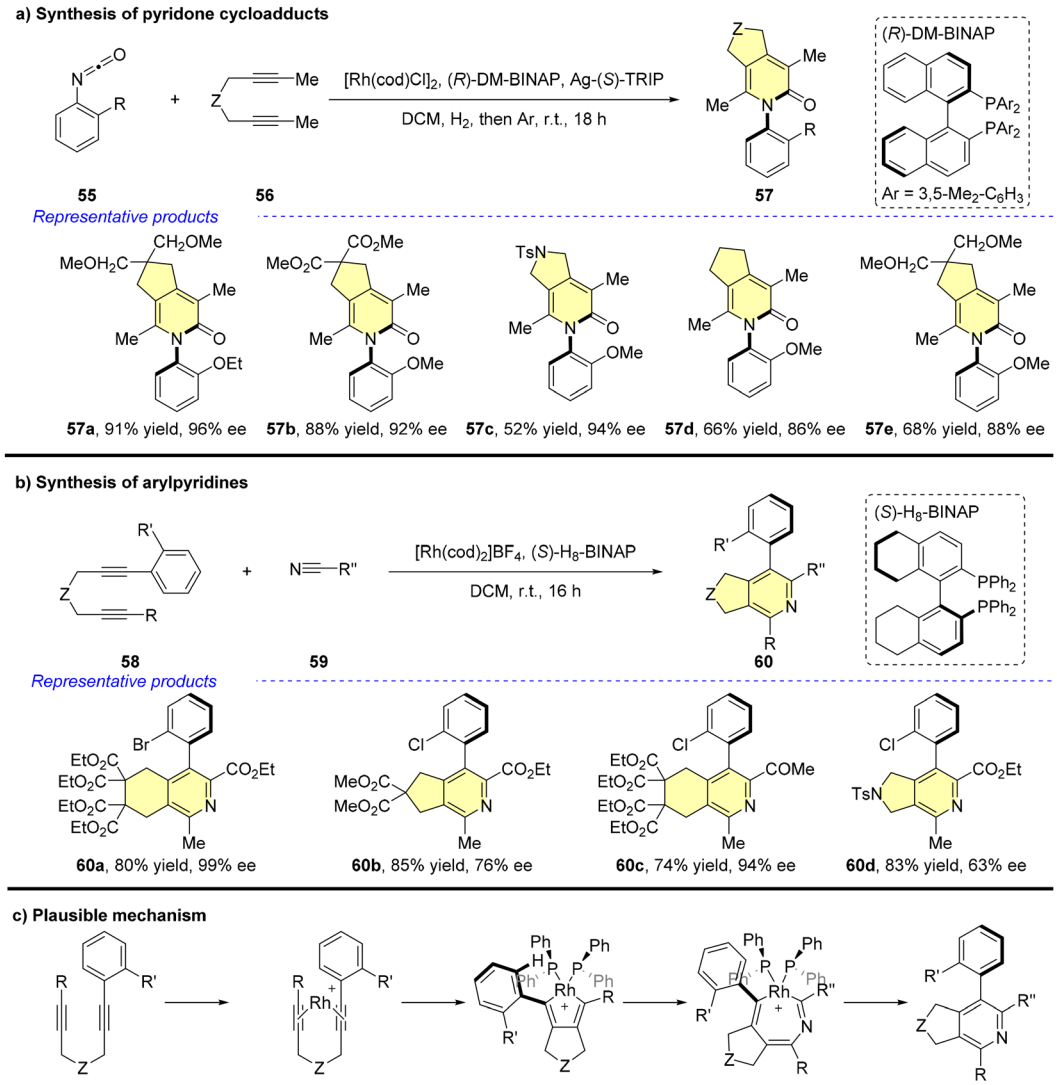
Scheme 12 Synthesis of atropisomeric biaryls through cycloaddition procedure.



Scheme 13 Asymmetric annulation with 1-alkynyl-2-naphthols.

Then, in 2016, Tanaka and co-workers reported a rhodium-catalyzed atroposelective annulation with a unique point-to-axial chiral transfer process.[56] This strategy used readily available phenyl diynes **58** and nitriles **59** as building blocks, establishing the basis of the *ortho* effect in the assembly of diverse arylpyridines **60** (Scheme 14b). A notable feature of this methodology consisted in the remarkable influence of phenylated substituents on the reaction regio- and enantioselectivity. The reaction began with the coordination of rhodium and diyne, yielding the metal complex. Then, the oxidative cyclization of the Ru-complex intermediate afforded a five-membered rhodacycle species, which could determine the axial chirality depending on the steric effect. Subsequent nitrile insertion afforded a seven-membered rhodacycle, which underwent reductive elimination to give the chiral 3-arylpyridine product.

Axially chiral azaborines with a C–B axis are prevalent in pharmaceuticals and functional materials.[57–60] However, their synthesis remains a significant challenge owing to the lower rotational barrier compared to related compounds with a C–N or C–C axis.[61–63] In 2024, Wang *et al.* developed a method for constructing axially chiral azaborines through rhodium-catalyzed atroposelective C–H activation, using commercially available (*S*)-H8-BINAP as the chiral ligand (Scheme 15).[64] A library of axially chiral pyridylborons **63** were provided in good yields with excellent enantioselectivities (up to 84% yield, 99% ee and >20 : 1 dr). Based on DFT calculations, the authors proposed a mechanism where the catalyst complex formed by BN-diynes and rhodium underwent oxidative cyclization to produce a cyclometallic species, which was identified as the stereo-determining step. The five-membered rhodacycle then coordinated with nitrile to generate a stable intermediate, followed by cyano insertion to produce a seven-membered rhodacycle. Finally, reductive elimination yielded the atroposelective pyridine derivative and regenerated the rhodium catalyst. This protocol provided a promising plat-

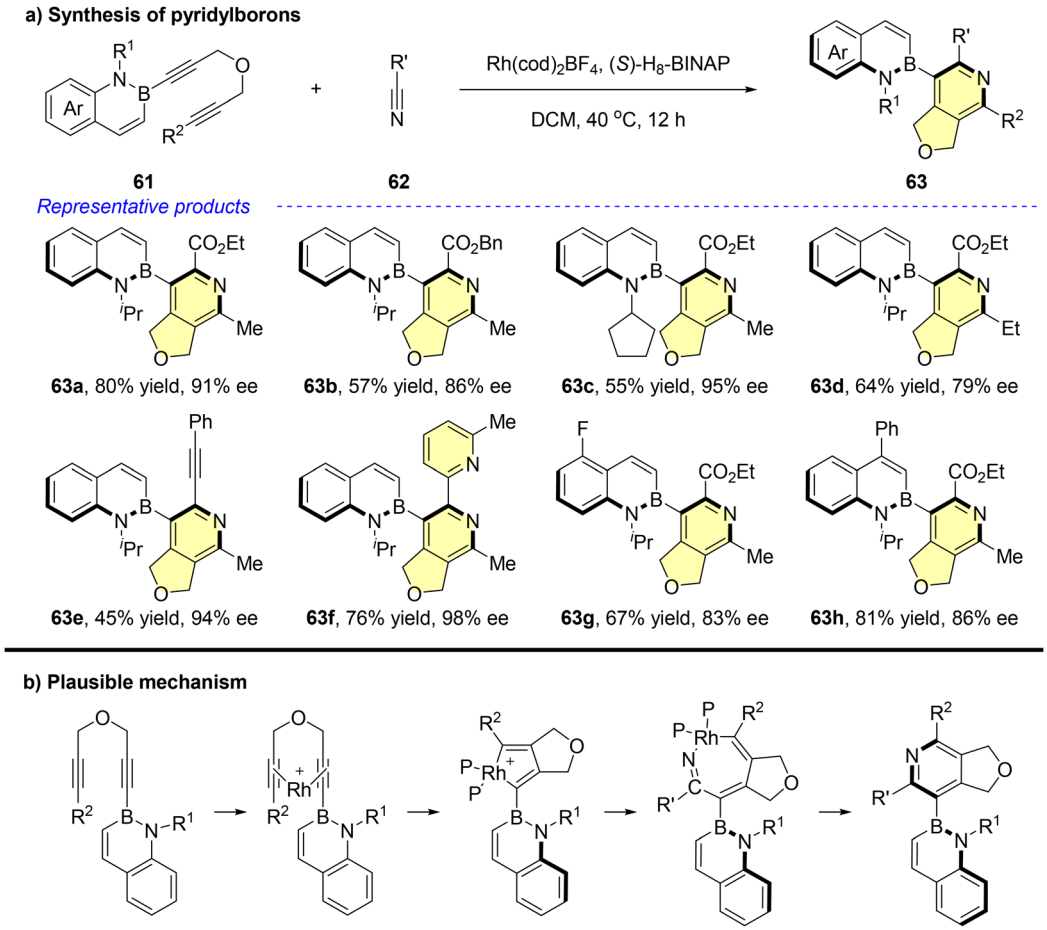


Scheme 14 Rh catalysis for atroposelective intermolecular annulation reactions.

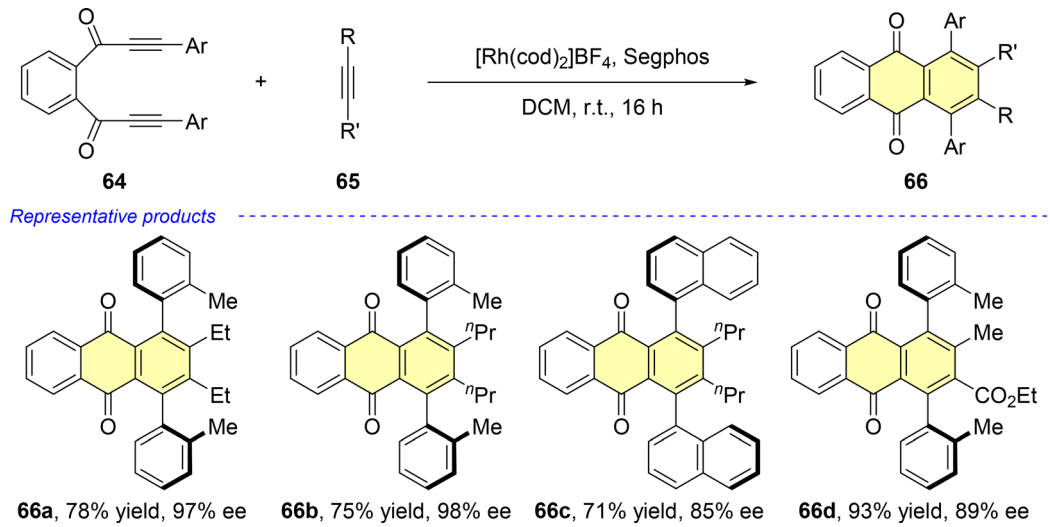
form for achieving pyridylborons with a challenging C–B axis, which showed practical performance in diversified derivatizations.

To construct the C–B axially chiral platform, Ping and co-workers developed a novel catalytic system of cationic rhodium/monodentate phosphine for the preparation of atroposelective arylboron compounds with high optical purity through an intermolecular cycloaddition.[65] Soon later, Li and Huang widened the atroposelective construction of boron-based axial chirality through a Rh(III)-catalyzed C–H activation–annulation of alkynylborons with 2-carboxamide-functionalized indoles.[66] Stereoinduction was facilitated by a chiral rhodium-cyclopentadienyl catalyst. Moreover, photophysical investigations revealed that the representative products exhibited high dissymmetry factors, indicating their potential as photoluminescent materials. In an ongoing effort to build C–C axially chiral frameworks, Tanaka and co-workers sought to investigate an alternative cycloaddition method to overcome the harsh reaction conditions noted in earlier studies.[67] They showed that an effective catalytic system, $[Rh(cod)_2]BF_4$/Segphos, could be employed in the intermolecular cycloaddition of 1,2-bis(arylpropiolyl)benzenes **64** and monoalkynes **65** (Scheme 16). This reaction allowed for the highly enantio- and diastereoselective construction of axially chiral teraryls **66** with impressive efficiency. Its convenient operation and mild conditions offered a practical access to axially chiral organoborons with drug-like properties.

Polycyclic aromatic hydrocarbons (PAHs) have been developed as organic semiconductors and chiral recognizers. However, the direct synthesis of enantioenriched PAH atropisomers without any heteroatom is challenging. In 2020, the Shibata group also reported an investigation on the enantioselective synthesis of polycyclic aromatic hydrocarbons **68** through regioselective C–C bond cleavage and a consecutive cyclization reaction of biphenylenes **67** (Scheme 17).[68] Notably, phenylene tethers bearing two biphenylene units and alkyne

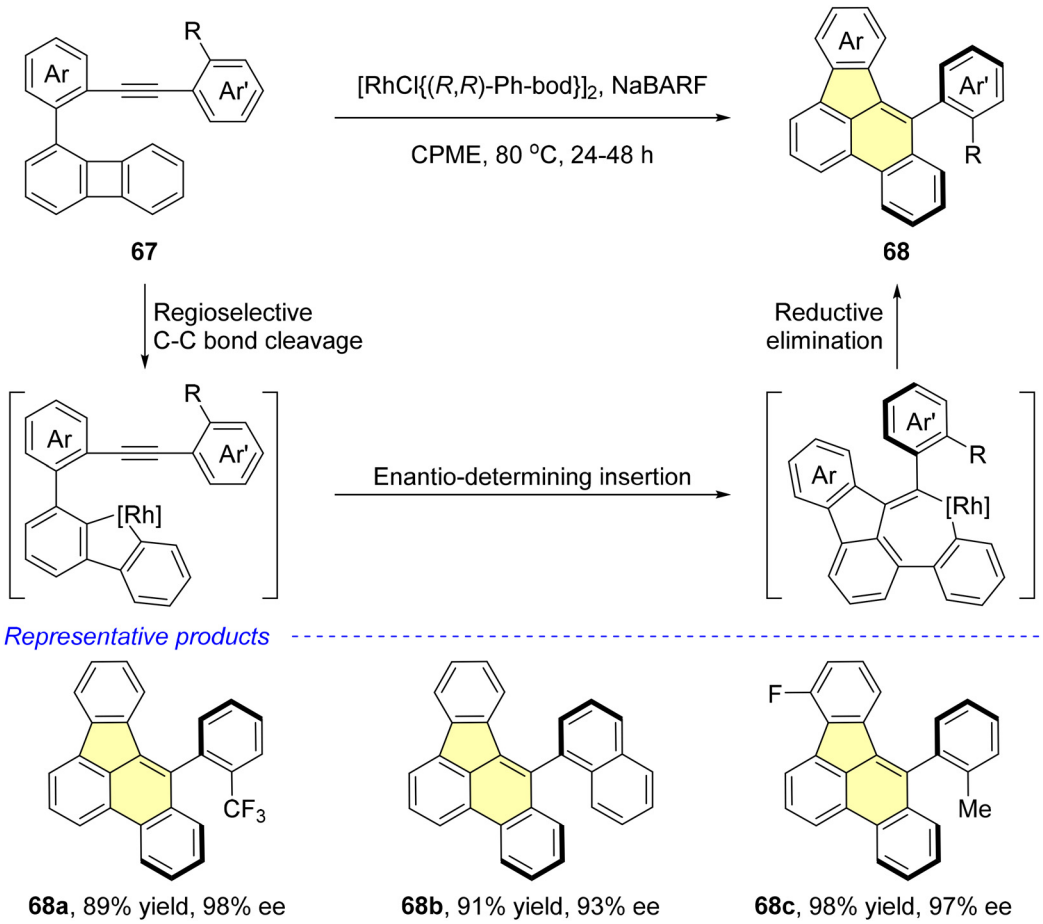


Scheme 15 Rh-catalyzed pathway to construct challenging C–B axial chirality.



Scheme 16 Synthesis of axially chiral 1,4-teraryls.

groups proved to be appropriate substrates for this type of conversion. Additionally, the resulting pyrene-substituted products displayed prominent photophysical characteristics. This elegant work drew significant attention from chemists as a valuable complement to the C–C bond functionalization of axially chiral polyaromatic rings.

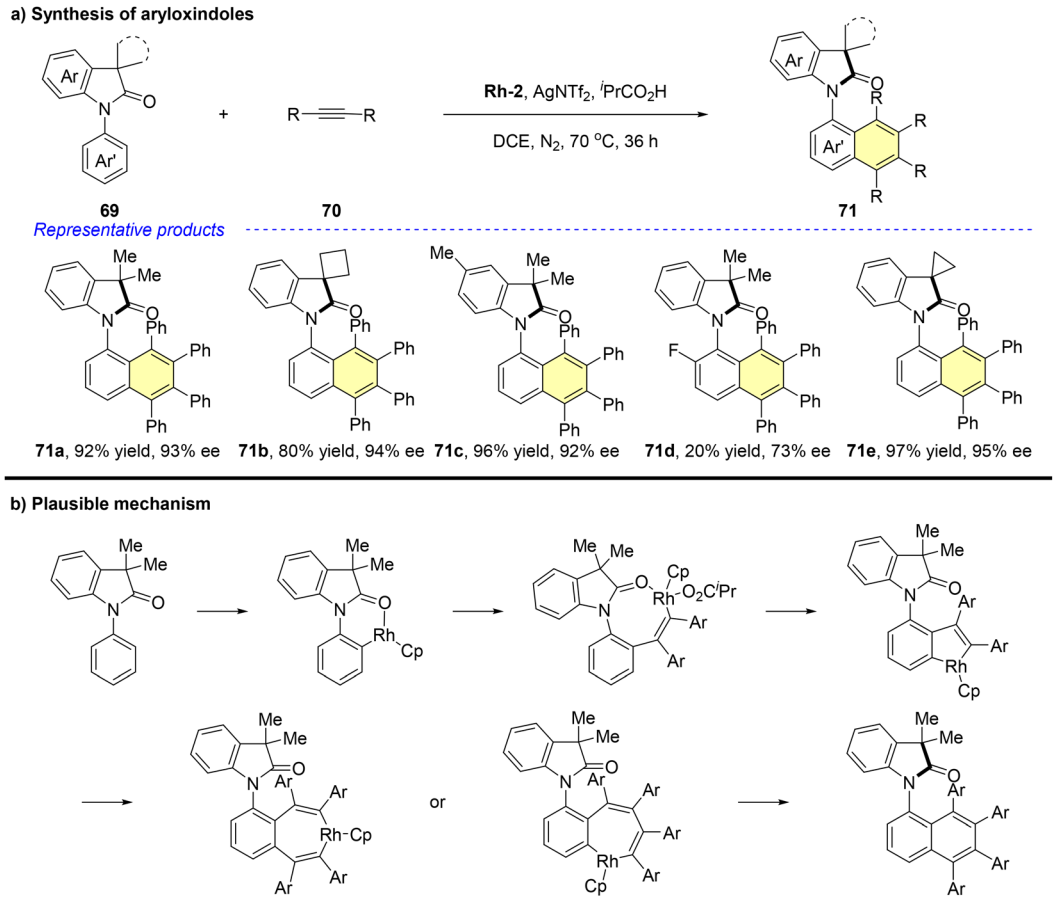


Scheme 17 Synthesis of axially chiral polycyclic aromatic hydrocarbons.

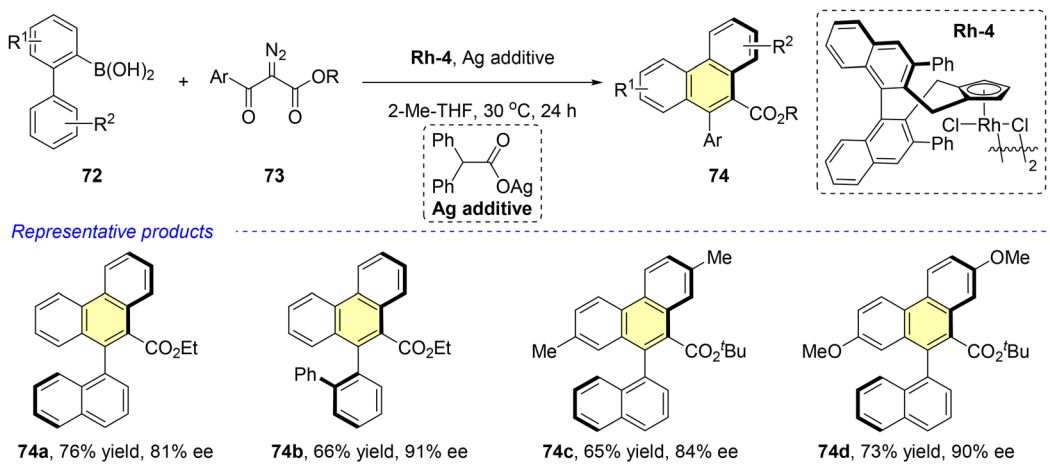
Despite the academic accomplishments in Satoh–Miura-type reaction, asymmetric construction of C–N axial chirality with directing groups had not yet been reported through a dual C–H activation approach. In 2019, Wang and colleagues devised a highly efficient rhodium-catalyzed strategy for the enantioselective construction of *N*-aryloxindoles **71** through the Satoh–Miura type reaction involving *N*-aryloxindoles **69** and alkynes **70** (Scheme 18).[69] Unlike previous studies on Satoh–Miura cross-coupling reactions, this approach has shown notable results with enantioselective dual C–H activation, resulting in the generation of C–N axially chiral products in good yields with excellent enantioselectivity. The process began with the generation of a six-membered rhodacyclic species *via* coordination and C–H bond cleavage of *N*-phenyloxindole by rhodium salt and isobutyric acid. This species then underwent the insertion of alkyne, followed by a second C–H bond activation and another alkyne insertion, forming a seven-membered rhodacyclic species. Subsequently, the reductive elimination of this intermediate yielded the target axially chiral aryloxindole product. Remarkably, this protocol reached the full transformation with excellent atropoisomeric selectivity by activating dual C–H bonds during the aromatization process.

To settle the restriction of atroposelective annulation systems containing intermediates with indistinguishable bonds, which would induce stereodivergence, novel divergent–convergent chiral induction modes should be developed to achieve a highly efficient effect on chiral control, while retaining the desired chiral elements. Shortly thereafter, in 2022, the Li group established an efficient enantioselective intermolecular [4 + 2] cycloaddition of biphenyl-2-boronic acids **72** with α-diazo β-ketoesters **73**, employing a chiral rhodium catalyst (Scheme 19).[70] This method produced a series of asymmetric biaryl frameworks **74** with a stereogenic C–C axis. Notably, this reaction system introduced chirality in a stereodivergent–convergent manner, which was different from traditional point-to-axial chiral induction or linear chirality transfer methods. Remarkably, this approach enabled scalable production without loss of enantioselectivity, providing a practical route to the synthesis of axially chiral phenanthrenes.

Utilization of transition-metal-catalyzed azide–alkyne cycloaddition *via* an enantioselective fashion, leading to the formation of a five-membered biaryl axially chiral molecule, is extremely appealing and challenging. In the same year, Guo *et al.* developed an advanced enantioselective azide–alkyne cycloaddition method to access chiral 1,2,3-triazoles **77** featur-

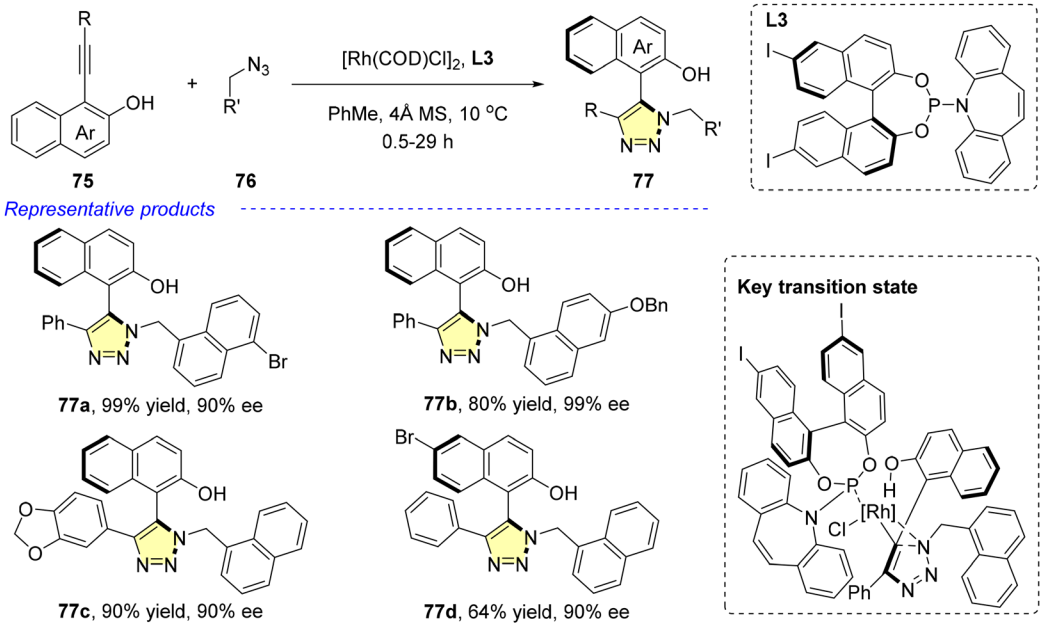


Scheme 18 Rhodium-induced dual C–H functionalization to access *N*-phenyloxindoles.



Scheme 19 Rhodium-induced dual C–H functionalization to access phenanthrenes.

ing a C–C axis, where the challenging construction of five-membered atropisomers was achieved in an atom-efficient manner (Scheme 20).[71] To understand the mechanism and enantioselective process, the authors performed control experiments and DFT calculations, which showed that enantioselectivity was governed by steric repulsion. Regarding regioselectivity, the hydroxy group in the naphthalene ring could interact with the rhodium catalyst through coordination and facilitate the generation of a hydrogen bond between the chlorine atom in $[Rh(COD)Cl]_2$ and the hydroxyl H-atom, thereby lowering the rotational barrier of the transition state. This novel approach held great potential for broad application in



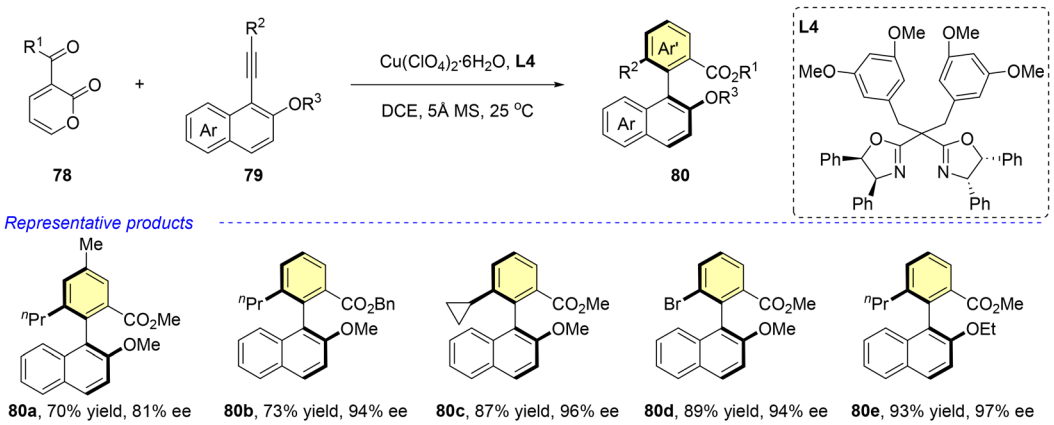
Scheme 20 Rh-catalyzed atroposelective construction of triazoles.

the synthesis of axially chiral five-membered atropisomers and enantioselective catalysis.

3. Copper catalysis

Recently, the application of copper catalysts to facilitate asymmetric C–H functionalization has opened new routes for the synthesis of axially chiral biaryls.[72,73] In 2021, Cai, Yang and colleagues introduced the first example of a catalytic system involving $Cu(ClO_4)_2{\cdot}6H_2O$ and a 3,5-dimethoxybenzyl-derived BOX ligand, enabling the Cu(II)-catalyzed Diels–Alder/retro-Diels–Alder transformation between 2-pyrones **78** and alkynes **79** (Scheme 21).[74] This approach facilitated the efficient and enantioselective construction of diverse biaryl esters **80** with a C–C axis. Based on DFT calculations, the proposed pathway's transition structure, where the alkyne underwent sequential C–C triple bond breakage and dearomatization to form a dihedral angle of 149° with pyrone, showed a more favorable free energy compared to the minor pathway by 1.0 kcal mol^{-1}, exerting an effect on the enantioselectivity determination. It was anticipated that this protocol would become a versatile and straightforward approach for stereoselective arene construction.

Oxazole atropisomers, acting as quintessential frameworks in pharmaceutically relevant molecules owing to their functional versatility, are of great scientific significance and practical value for the precise preparation. As a continuation of the ongoing research into sequential ring-opening and cross-coupling processes induced by copper, in 2022, Zhu and co-workers developed a prominent Cu(I)-catalyzed asymmetric transformation.[75] This method successfully produced atroposelective



Scheme 21 Construction of biaryl esters through Cu-catalyzed cascade reaction.

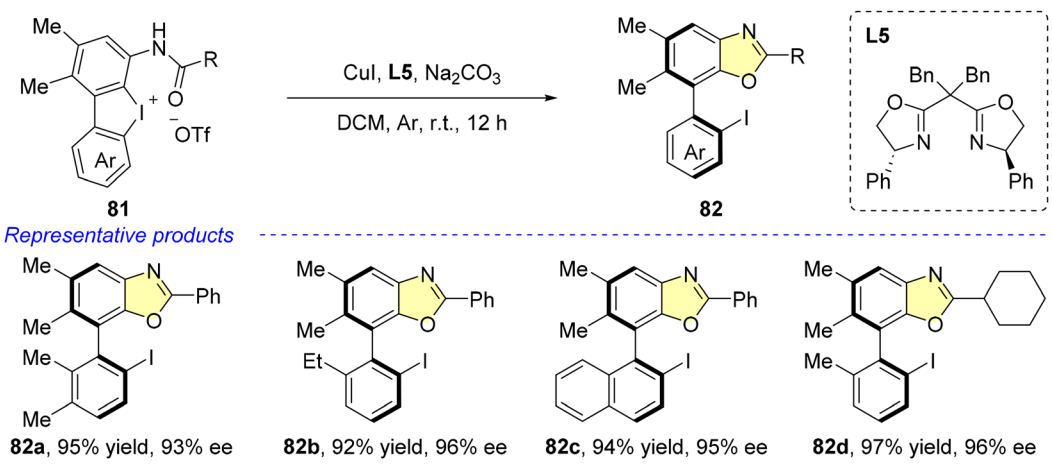
oxazole 2-iodobiaryls **82** through intramolecular annulation of cyclic diaryliodoniums **81** (Scheme 22). It was important to highlight that the aryl iodide products obtained can serve as effective chiral catalysts for subsequent oxidative transformations. This protocol introduced a new type of atroposelective oxazole biaryls and marked the first asymmetric synthesis of such skeletons.

Chemically reactive yne-allylic esters have enabled diverse synthetic pathways, such as asymmetric substitution and cyclization reactions. However, their application in axially chiral scaffold synthesis remains rarely explored. Given that the asymmetric formation of atroposelective aryl-pyrroles bearing 1,2-diaxes maintained a great challenge owing to the *ortho*-steric hindrance of aryl substituents, the Xu group developed the Cu(I)/Pybox catalysis for the asymmetric [4 + 1] cycloaddition aiming for their construction.[76] Through this strategy, the authors successfully obtained C–C or C–N axially chiral aryl pyrroles by altering the C-4 position of Me-Pybox ligands (Scheme 23a and b). This method also proved to be feasible for the construction of diaxially chiral aryl pyrroles (Scheme 23c). Mechanistic investigation indicated that the reaction involved remote amination, followed by a cascade of cyclization and aromatization procedures. Notably, this annulation strategy provided a viable access to heterobiaryl atropisomers, which showed promising performance as functionalized organocatalysts and chiral ligands.

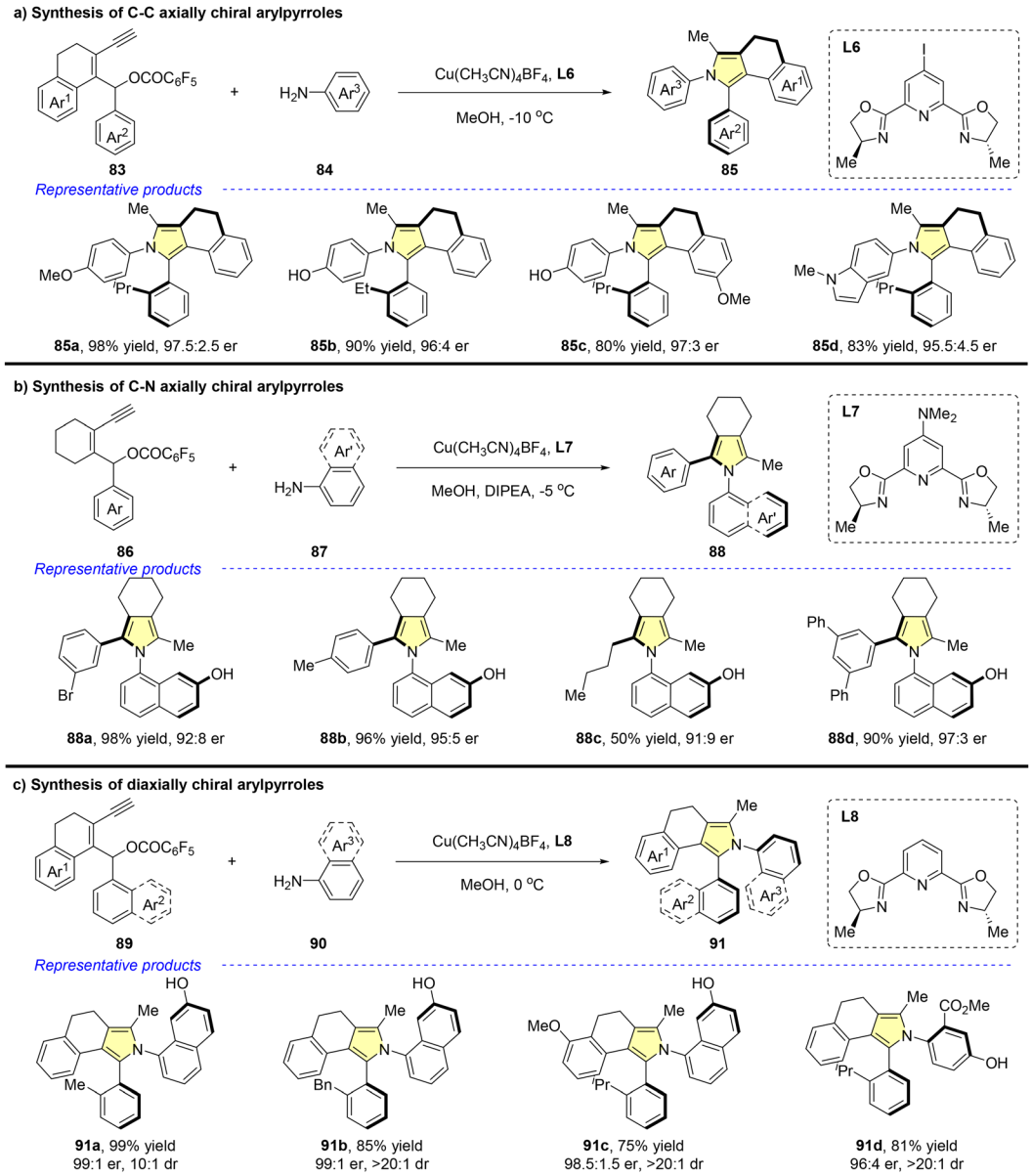
Direct formation of the steric-hindered C–N bonds represents the traditional induction of axial chirality, while harsh reaction conditions greatly diminished the reaction compatibility. Considering these restrictions, intramolecular adjacent cross-coupling emerges as a flexible approach. In 2019, Gu and co-workers developed an ingenious intramolecular Ullmann-type amination approach for the synthesis of atropisomeric anilides, assisted by a new Cu/*N*,*N*′-(cyclohexane-1,2-diyl)dipicolinamide catalyst system (Scheme 24).[77] A series of phenanthridin-6(5*H*)-one-based C–N atropisomers were obtained with outstanding enantioselectivities owing to the steric repulsion between the *ortho*-substituent in anilines and the upward amide moiety. In 2022, He and Yi reported a highly innovative atroposelective strategy *via* copper-catalyzed dearomatization and cycloisomerization to construct axially chiral arylquinolizones, which was enhanced by Brønsted acid.[78] Additionally, analysis of linear free energy relationships suggested that both steric and electronic effects played a role in enantioselectivity. This mechanistic paradigm omitted the requirement of pre-functionalized substrates and showed good functional group tolerance, demonstrating it particularly applicable for the late-stage derivatization of structurally diverse arylquinolizones.

2-Aryl pyrroles could also exhibit remarkable axial chirality owing to the steric hindrance of *ortho*-substituents on the aromatic cores. An innovative study was carried out by the groups of Carretero and Adrio to realize the atropisomerism in naphthylpyrroles.[79] Their system, using a copper catalyst and a chiral Fesulphos ligand, enabled the asymmetric transformation of naphthyl iminoesters **94** and alkenes **95** (Scheme 25). The stereogenic C–C axis was generated through the asymmetric induction of a 1,3-dipolar synthon and subsequent dehydrogenative aromatization, which facilitated the transfer from central to axial chirality. Additionally, appropriate *N*-alkylating agents and low reaction temperatures were essential for good results. This protocol offers a practical alternative to central-to-axial chirality conversion strategies, enhancing methods for assembling arylpyrroles with excellent atroposelectivity and broadening the toolkit for asymmetric synthesis. Collectively, this protocol demonstrated the potential of Cu^{I}/Fesulphos system to merge precise asymmetric conversions with sustainable catalysis and to encourage continued development in earth-abundant metal-promoted atroposelective catalysis.

However, as varied substitutions were introduced and chiral elements continued to increase, the challenge of achieving good enantioselectivity has become an increasingly outstanding issue. In particular, for biaryl atropisomers with minimally different substitutions, precisely controlling enantioselectivity was extremely significant. Encouraged by the achievements



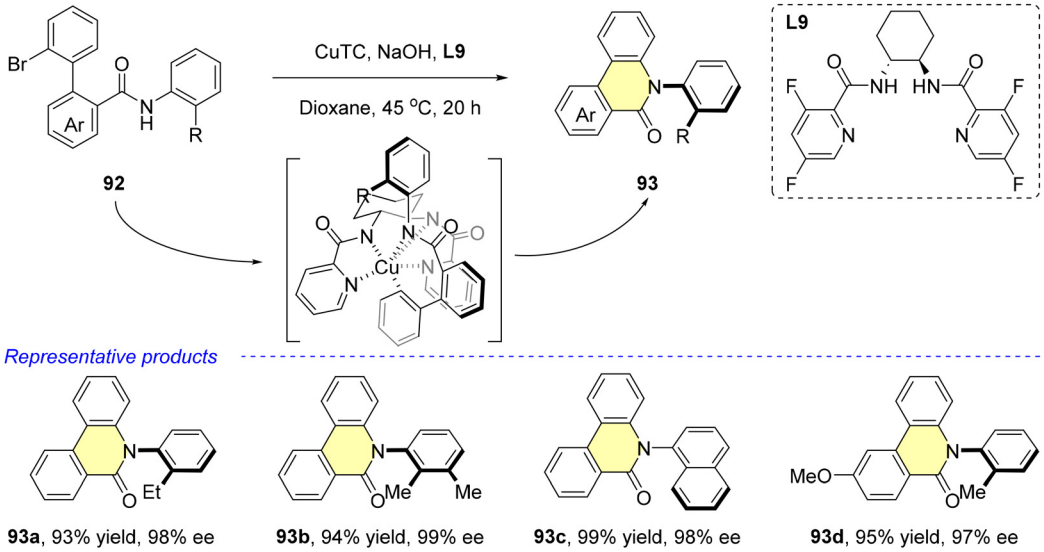
Scheme 22 Construction of oxazole biaryls through Cu-catalyzed cascade reaction.



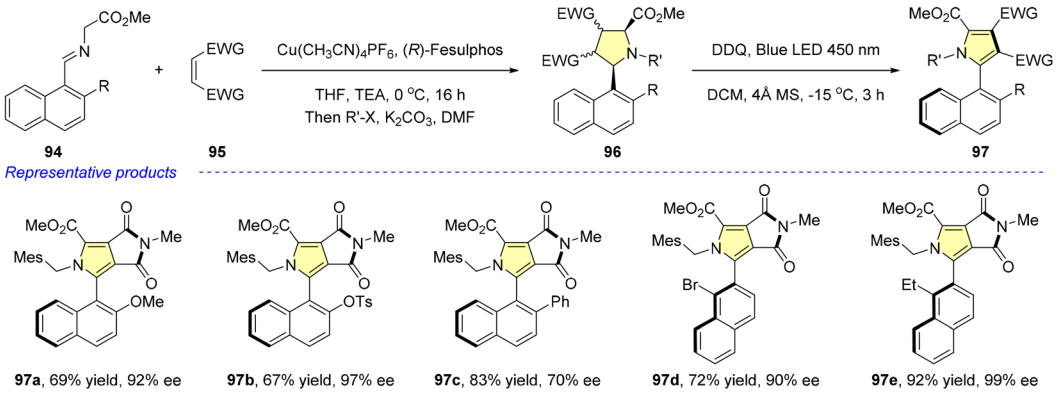
Scheme 23 Atroposelective synthesis of arylpyrroles *via* Cu/Pybox-catalyzed annulation.

mentioned above, Xu and his team developed the central-to-axial chirality transfer approach in 2025 for the enantioselective construction of pyrrole-fused atropisomers.[80] In this work, the initial cyclization occurred between yne-allylic esters **98** and *N*-aminoheterocycles **99** in isopropanol, yielding centrally chiral pyrrolidine-bearing intermediates (Scheme 26). The subsequent step, an oxidative aromatization process, converted the central chirality into axial chirality. Through this sequential two-step one-pot process, a broad range of atroposelective *N*,*N*′-indolepyrrole scaffolds **100** were furnished with high enantiocontrol. The presence of bulky *ortho*-substituted groups on *N*-aminoindole substrates significantly influenced the reaction's enantioselectivity. Various conversions concerning the ester functional group of the products, such as reduction, hydrolysis and nucleophilic addition, highlighted the practical value of this methodology.

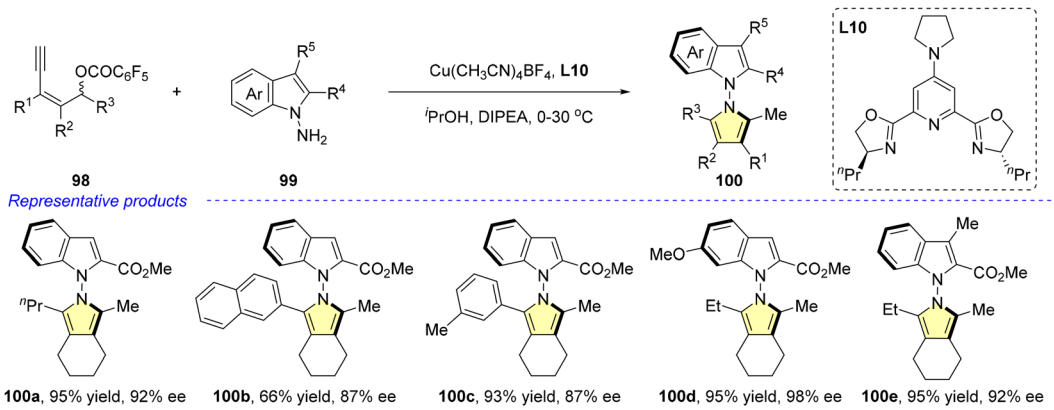
Axially chiral seven-membered bridged biaryl amines serve as basic building blocks for various bioactive substances. However, their conventional synthesis methods generally depend on chiral substrates from chiral pools or chiral auxiliaries, and would involve complicated procedures. Therefore, the development of a straightforward catalytic enantioselective approach, offering modular access to such structural units, remains a desirable goal. Moreover, the preparation of axially chiral amide-bridged biaryls *via* intramolecular cycloaddition was also investigated by Hornillos and co-workers.[81] Starting with 2′-vinyl-biaryl-2-imines **101**, the *in situ*-generated [Cu/(Ph-BPE)] catalyzed an asymmetric cascade hydrocupration reac-



Scheme 24 Synthesis of atropisomeric anilides through adjacent C–N coupling.

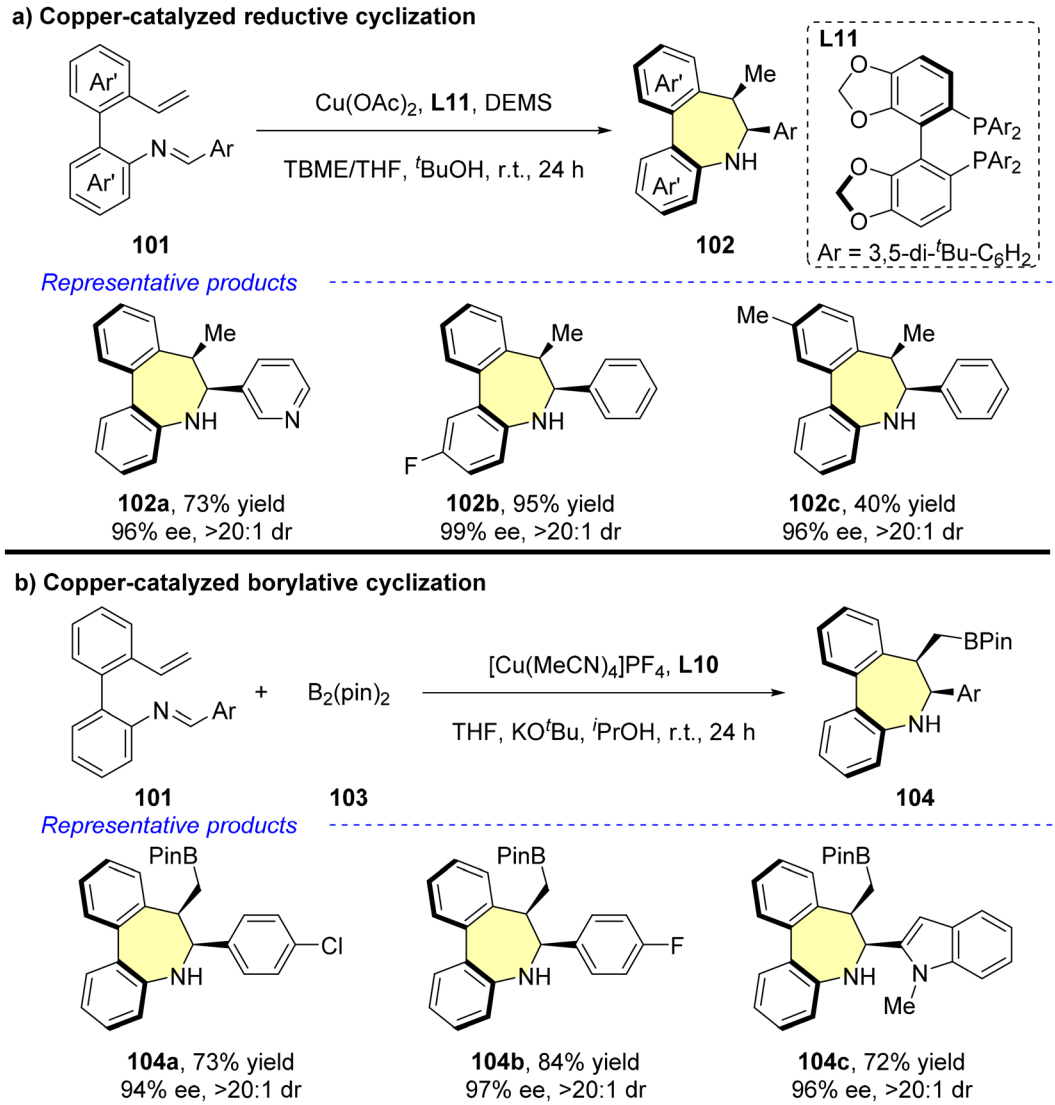


Scheme 25 Cu-catalyzed synthesis of C–C axially chiral naphthylpyrroles.



Scheme 26 Cu-catalyzed synthesis of N–N axially chiral indolepyrroles.

tion that initially produced arylcopper species (Scheme 27a). Subsequently, the *cis*-selective cyclization of arylcopper yielded an amine-bridged complex, with the regeneration of C-centered chirality. Ultimately, $Cu(OAc)_2$ was released from the amine-bridged complex to form the atroposelective intermediate, which was then transformed into the dibenzo[*b*,*d*]

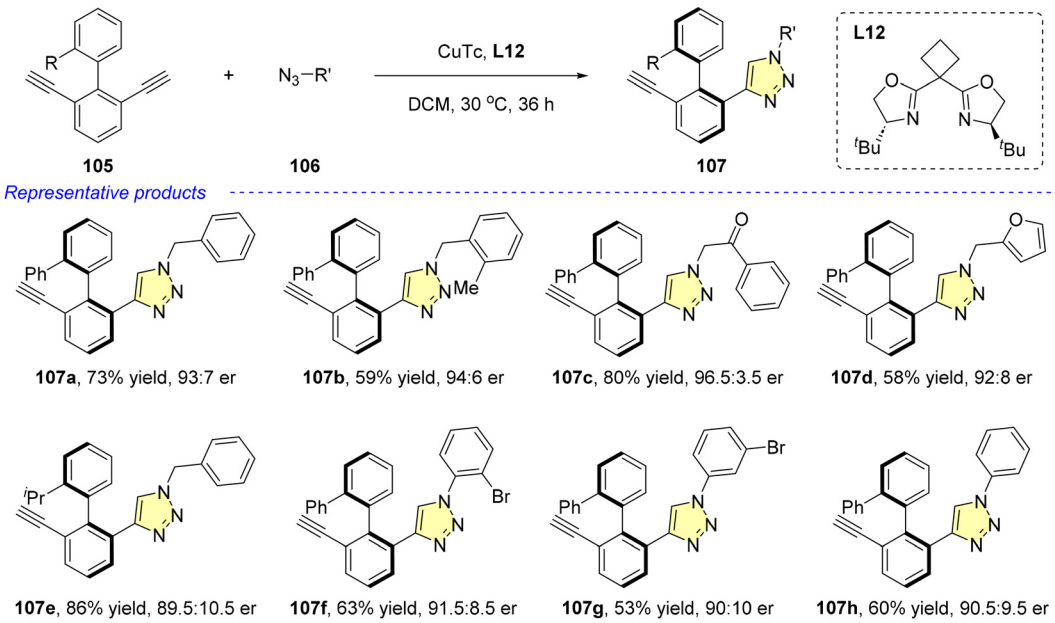


Scheme 27 Copper-catalyzed annulation to access amide-bridged biaryls.

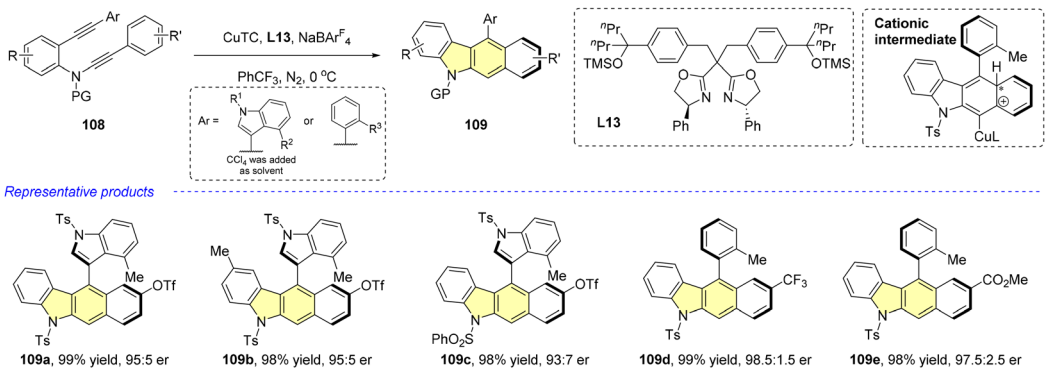
azepine product with the aid of a silane reagent. Additionally, the researchers expanded the range of functional reagents from diethoxymethylsilane to bis(pinacolato)diboron, allowing the formation of various boronic ester derivatives **102** with excellent catalytic activity (Scheme 27b).

Afterwards, in 2025, Lin, Liu, and colleagues successfully developed the asymmetric azide–alkyne cycloaddition of dialkynyl diaryls **105** and azides **106** for the preparation of triazole-decorated atropisomeric biaryls **107** (Scheme 28).[82] In this transformation, commercially available CuTc was employed as the catalyst. Various modifications around the alkyne module of the products, such as reduction, halogenation, click reaction and Sonogashira coupling reaction, highlighted the practical usefulness of this method. This work showed that the azide–alkyne reaction was a promising approach for the atroposelective synthesis of triazole-fused biaryls. The dual function of Cu(I)/BOX catalyst as both redox and chiral control elements underscored the strategy combination of this catalytic system, forming the bridge between chiral catalysis with click chemistry through an earth-abundant metal catalyst.

The dehydro-Diels–Alder (DDA) reaction provides an alternative approach for the atroposelective preparation of atropopure C–C axially chiral molecules. In 2024, the Zhou group achieved the synthesis of optically active carbazoles *via* a Cu-catalyzed asymmetric DDA reaction (Scheme 29).[83] A proposed stereoinduction model speculated that the enantioselectivity resulted from the generation of a cationic intermediate *via* a Friedel–Crafts-type cyclization. This elegant work on non-noble-metal-catalyzed DDA reaction drew widespread attention from chemists for providing a new access to axially chiral carbazoles. Building on this progress, Chen *et al.* disclosed a vinyl cation-involved enantioselective intramolecular diyne cyclization of *N*-propargyl ynamides for the synthesis of axially chiral



Scheme 28 Copper-catalyzed preparation of triazole-decorated atropisomeric biaryls.

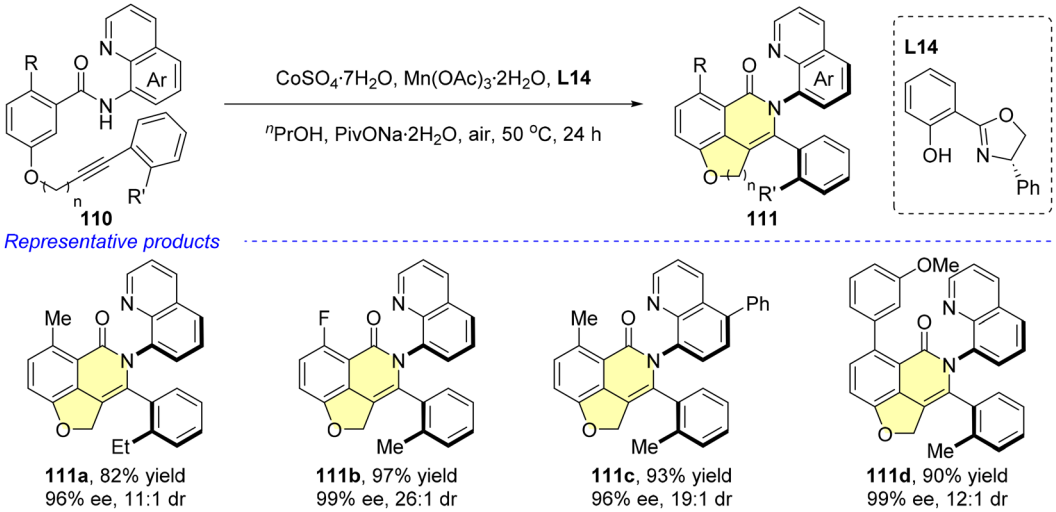


Scheme 29 Synthesis of atropisomeric carbazoles through dehydro-Diels–Alder reaction.

arylpyrroles bearing a C–N atropisomeric axis.[84] This work not only expanded the synthetic application of ynamides in axial chirality chemistry but also established a significant paradigm for devising new vinyl cation transformations.

4. Cobalt catalysis

Cobalt catalysts, especially high-valent Co(III) complexes, have grabbed much attention owing to their unique reactivity and cost-effectiveness.[85–89] In the approaches to enantioselective C–H bond activation reactions, these species have enabled the development of promising approaches with favorable outcomes.[90–94] While the transition-metal-catalyzed construction of atropisomers bearing a single axis (*e.g.*, C–C, C–N, C–O, C–B, or N–N) has been extensively studied, the enantioselective synthesis of compounds possessing multiple axes, especially vicinal diaxes, remains underdeveloped. The *in situ*-formed high-valent cobalt catalyst using air as the oxidant, as demonstrated by Grigorjeva and Daugulis, represented an environmentally friendly and highly versatile strategy.[95] Based on this method, Wang *et al.* established an unprecedented cobalt-catalyzed asymmetric C–H annulation for the construction of heterocyclic atropisomers with two stereogenic axes.[96] After developing a straightforward approach to access well-designed benzamides **110** as starting materials, they subjected the benzamides to the $Co(OAc)_2$/Salox activation system, followed by intramolecular annulation to produce atropisomers **111** bearing adjacent C–N and C–C axes (Scheme 30). DFT studies suggested that the rotational energy of the C–N axis was significantly influenced by the sterically hindered *ortho*-substituents, which ruled out the possibility of cooperative rotation of the axes. Furthermore, the atroposelective products bearing a conjugated aromatic moiety exhibited optical absorption

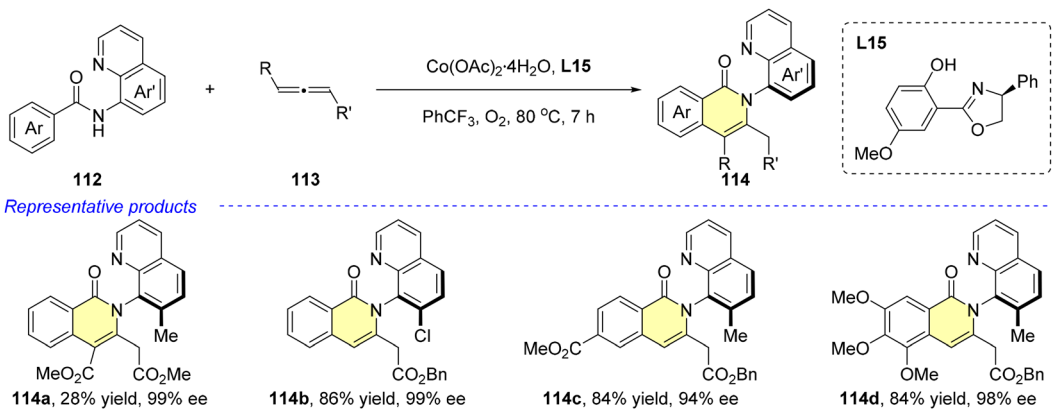


Scheme 30 Cobalt/Salox-catalyzed synthesis of heterocyclic atropisomers *via* C–H annulation.

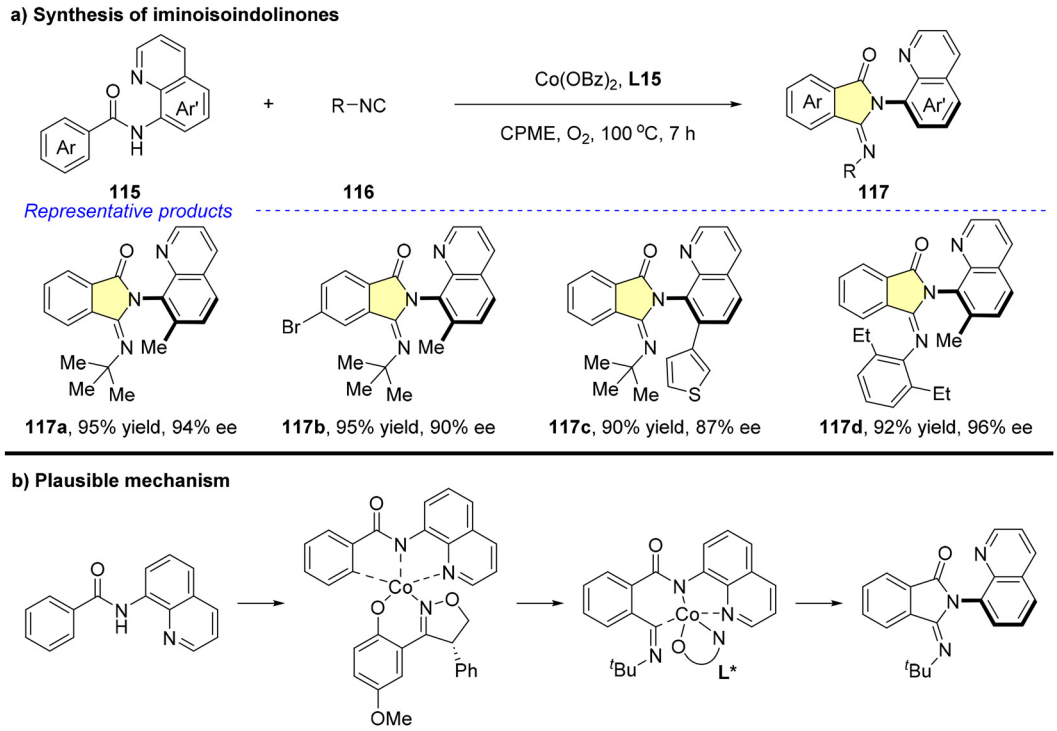
characteristics, making them potential candidates for CPL utilization.

Besides vicinal diaxes, the synthesis of atropisomers featuring remote distinct C–N axes was also investigated. In Shi's subsequent studies, in 2025, the substrate scope was extended to amide-substituted indoles to access diaxially chiral pyridoindolones bearing both six-five and six-six C–N axes, using a chiral salicyloxazoline ligand.[97] A proposed catalytic pathway suggested that the stereo configurations of both axes were formed through a C–H cyclometalation process. Moreover, they pointed out that the fascinating fluorescence properties of the products demonstrated their potential as optoelectronic materials. Subsequently, the Niu group expanded the utilization of cobalt/Salox catalysis to build heterobiaryl isoquinolinones through asymmetric C–H functionalization.[98] The critical factor enabling the success of this annulation conversion lay in the employment of an eco-friendly oxygen atmosphere for the oxidation of cobalt salt(II). This protocol facilitated the facile fabrication of isoquinolinones **114** from readily available benzamides **112** and allenes **113**, with excellent enantiopurity (Scheme 31). The authors proposed that this transformation strategy proceeded through four pivotal procedures: C–H activation, migratory insertion, reductive elimination and 1,3-H shift. Impressively, asymmetric electrocatalysis also facilitated the efficient annulation of these two starting materials, eliminating the need for high temperatures. This work demonstrated excellent atomic efficiency, mild conditions and good functional group tolerance, providing a promising route to access heterobiaryl isoquinolinone frameworks.

With the success of the C–H activation/annulation approach for preparing atroposelective isoquinolinones, the authors envisioned that the strategy could be employed to construct axially chiral five-membered N-heterocycles, which are characterized by lower configurational stability and a decreased rotational energy barrier.[99] The Niu group achieved the synthesis of C–N atropisomers **117** based on a five-membered heterobiaryl skeleton through the formal C–H functionalization of benzamides **115** with bifunctional isoni-



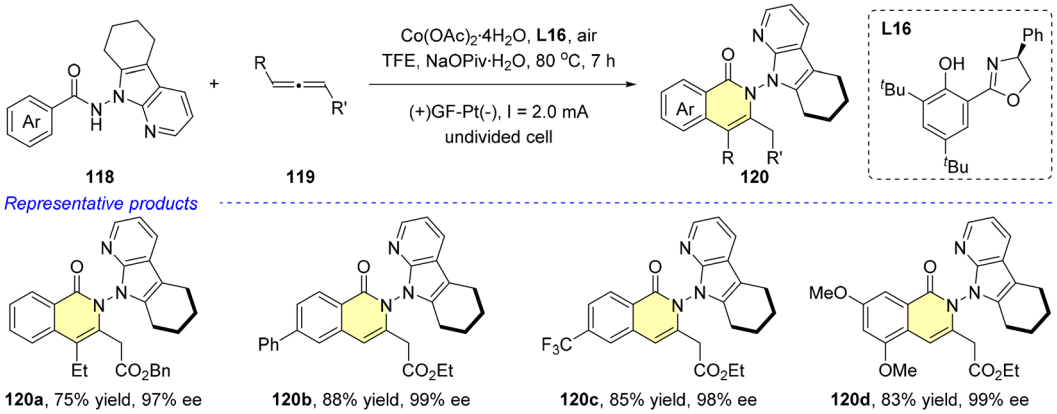
Scheme 31 Preparation of heterobiaryl isoquinolinones *via* Co-catalyzed cyclization.



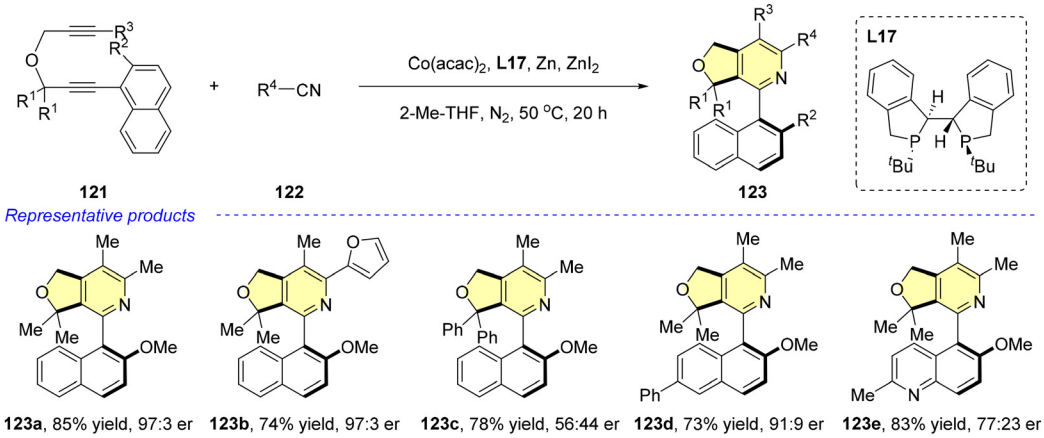
Scheme 32 Preparation of iminoisoindolinones *via* Co-catalyzed cyclization.

triles **116** (Scheme 32).[100] Moreover, the versatility of this protocol was demonstrated by additional derivatizations, leading to the formation of phosphonylated and Sonogashira coupling products with good retention of enantiopurities, respectively. This strategy circumvented the step-intensive conditions of conversional approaches, providing an efficient route to deliver iminoisoindolinones with potential biological activity.

Electrochemical synthesis, widely appreciated for its highly efficient utilization and sustainable development, has revolutionized the atroposelective preparation of function-modified molecules. By utilizing the electrocatalyzed excitation of the cobalt catalyst, various transformations including C–H functionalization, cross-coupling reactions and radical annulation could proceed under mild conditions. Then, in 2024, the same group explored an unprecedented cobalt-electrocatalyzed [4 + 2] cyclization approach for the stereoselective construction of functionalized isoquinolinones with N–N axes.[101] After developing a straightforward avenue towards benzamides **118** as starting materials, they subjected **118** to C–H activation, followed by annulation with allenes **119** (Scheme 33). The cobalt/Salox catalytic complex in an undivided cell was screened as the optimal condition to achieve good results. Furthermore, a gram-scale experiment and diverse derivatizations around the ester moiety of the products, involving acidification and diazotization, highlighted the synthetic practicality of this methodology. Interestingly, this asymmetric electrochemical process



Scheme 33 Preparation of axially chiral azaindoles *via* Co-catalyzed cyclization.

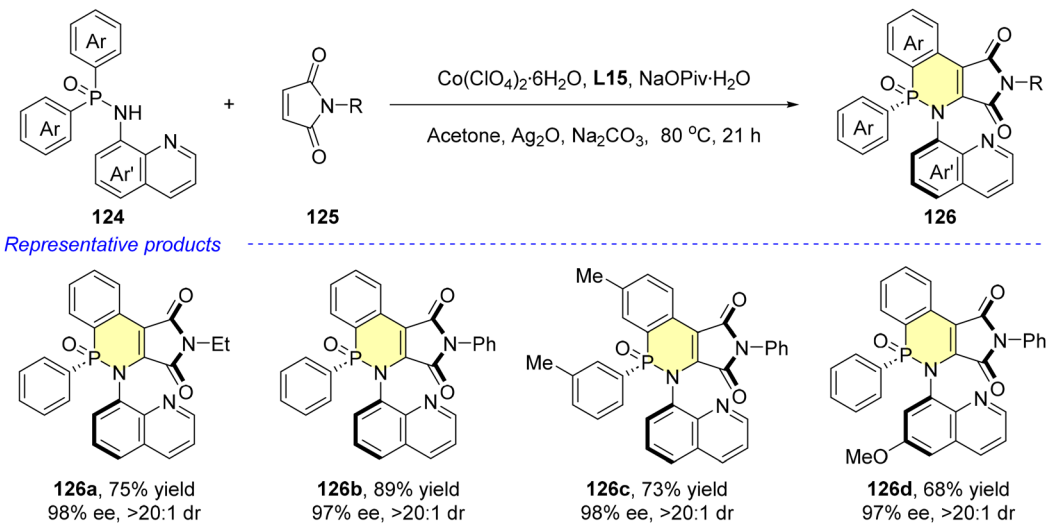


Scheme 34 [2 + 2 + 2] cycloaddition to access atroposelective arylpyridines.

was highly temperature-dependent, and excellent enantioselective control over the N–N axis could be observed through thermal regulation, resulting in the formation of a single isomer with high enantioselectivity, as confirmed by X-ray analysis.

Given that atroposelective construction of densely functionalized arylpyridines was still in its early stages, Huang and co-workers investigated the Co(II)/Phos catalysis for their asymmetric [2 + 2 + 2] cycloaddition aimed at this synthesis (Scheme 34).[102] The preparation of polyfunctionalized atropoisomeric arylpyridines showed great difficulties owing to the challenges in governing atropostability in the presence of harsh conditions. This approach effectively facilitated the Co(acac)$_2$-catalyzed asymmetric intramolecular annulation of easily available diynes. Afterward, nitrile coordinated to the system to form a cationic Co(III) intermediate. Nitrile migratory insertion and subsequent reductive elimination then produced the final arylpyridine product in an atom-efficient manner. DFT calculations suggested the intercalative mode of the cyano moiety dominated regiocontrol. Notably, this reaction was also applicable to access bispyridine compounds and *N*-oxide derivatives, expanding its utility in atroposelective catalysis. This work enabled the challenging acetonitrile insertion reactions with excellent regioselectivity and stereoselectivity, while good functional group tolerance minimized unexpected reactions and side effects. A similar study was developed by Hapke and co-workers to achieve chiral biaryl frameworks bearing five-membered rings.[103] Such features were exceptionally favourable for assembling sophisticated heterocyclic scaffolds.

Although previously mentioned strategies enabled the asymmetric synthesis of biaryl atropisomers, some diversity limitations remained when compared to those with multiple stereogenic elements. To address this, the group of Miao and Xu developed a cobalt/salicyloxazoline catalyst complex to promote the simultaneous incorporation of P-stereogenic centers with C–N axial chirality, expanding the category of atropisomers and filling a gap in the realm (Scheme 35).[104]



Scheme 35 Construction of P-stereogenic phosphinamides *via* cyclization and amination.

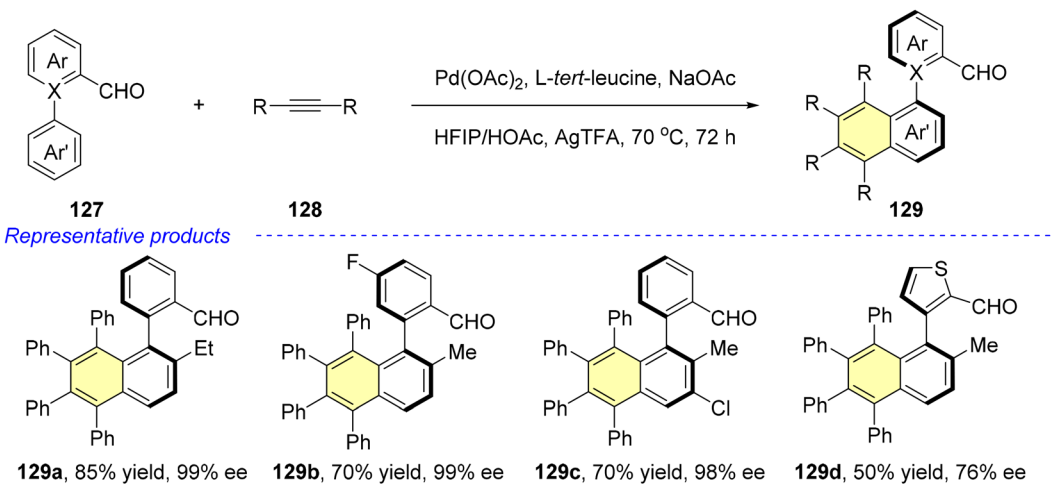
Investigations showed that the reaction involved atroposelective C–H activation, followed by stepwise N–H annulation, assisted by phosphinamide as a directing group. The mechanism was illuminated through density functional theory calculations, along with a kinetic isotope experiment. These achievements demonstrated the sustained evolution of the cobalt/salicyloxazoline catalytic system as a versatile tool in asymmetric catalysis, providing promising routes for a broad range of axial chiral compounds.

5. Palladium catalysis

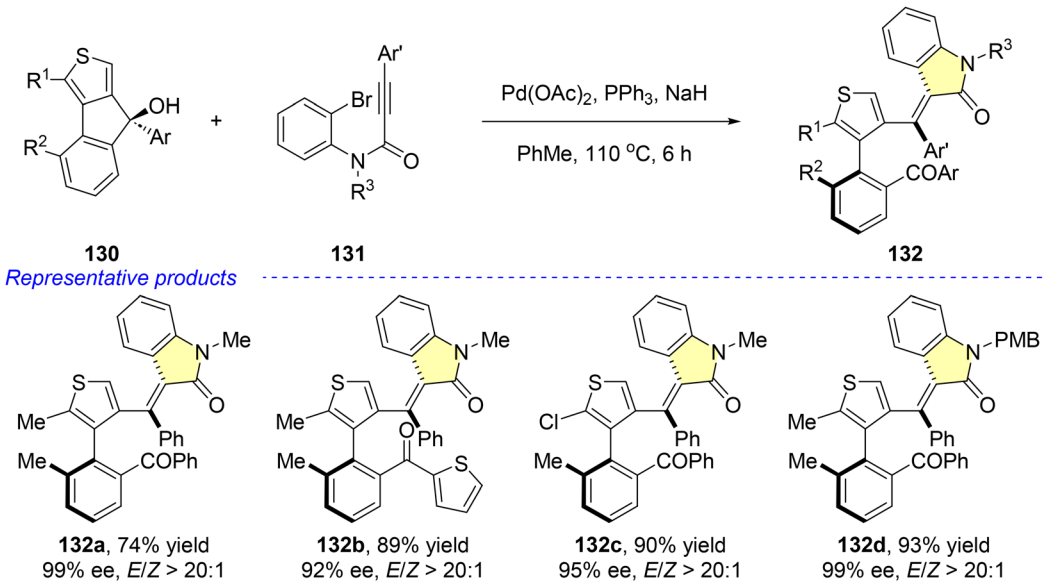
Palladium catalysts play a key role in atropisomeric synthesis, offering advantages like higher efficiency, superior selectivity, and milder reaction conditions, aligning with green chemistry principles.[105–107] The development of a cost-effective and earth-abundant palladium catalyst for preparing atropisomeric compounds represents a significant and rapidly expanding trend. In 2021, Zhang and co-workers discovered an unprecedented palladium-catalyzed enantioselective twofold C–H cyclization of biaryl aldehydes **127** with readily available alkynes **128**, leading to the assembly of axially chiral biaryl aldehydes **129** (Scheme 36).[108] This innovative strategy showcased outstanding features such as broad substrate scope, high efficiency and diverse late-stage modifications. Mechanistic studies suggested that the L-*tert*-leucine ligand not only promoted the reversible Schiff's base reaction throughout the entire procedure, but also helped the *in situ* coordination with palladium to form the active palladacycle species. Thus, this palladium-mediated twofold C–H annulative methodology provided a green and versatile platform for the efficient assembly of atropisomeric aldehyde architectures.

Despite significant progress that was achieved in the synergistic collaboration of palladium catalysis and point-to-axial chirality transfer, the enantioselective synthesis of diversely functionalized styrene atropisomers remains challenging. In the following year, the Gu group successfully introduced a cascade cyclization/ring-opening strategy.[109] This reaction featured a highly stereospecific point-to-axial chirality transfer procedure for the synthesis of atropisomeric thiophenes **132**, showing outstanding enantio- and stereoselectivity (up to 99% ee and $Z/E > 20:1$) (Scheme 37). Notably, these molecules had both a vinyl–aryl axis and an aryl–aryl axis. The process began with the oxidative addition of (2-bromophenyl)propiolamide to Pd(0) species, forming an aryl-stabilized palladium-cycle intermediate, which underwent Heck-type cyclization to form a vinylpalladium intermediate. Subsequently, a ligand exchange with 8*H*-indeno[1,2-*c*]thiophen-8-ol sodium took place, followed by β-carbon elimination and reductive elimination, yielding the target atropisomeric thiophene product. The single-crystal structure of **132a** indicated that both chiral axes were formed and fixed in a rigid frame during the key C–H metalation process. The strong π–π interaction of indolin-2-one group with benzoyl ring likely facilitated the observed outstanding diastereocontrol.

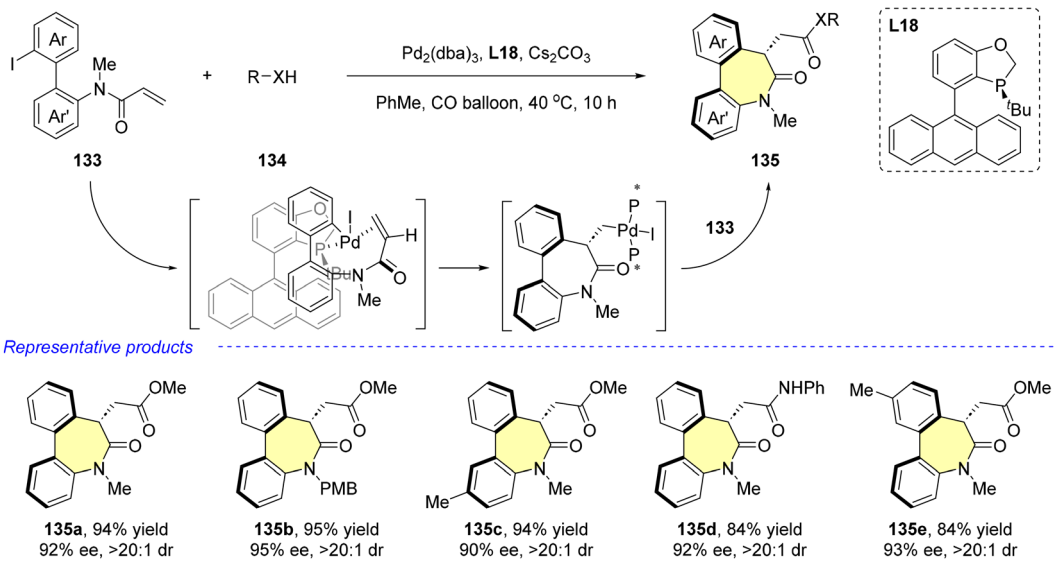
While enantioselective cascade Heck/carbonylation approaches for preparing five- and six-membered rings have been widely realized, the efficient enantioselective access to seven-membered rings has been less explored because of the competing pathways between carbonylation of arylpalladium and alkene insertion.[110,111] To settle this problem, Zhu and Luo proposed that less-hindered terminal alkenes might facilitate 7-*exo*-*dig* cyclocarbopalladation, reducing competition from alkene insertion. In this work, the authors extended the atroposelective C–H arylation from 5- and 6-membered bridged biaryls to 7-membered dibenzo[*b*,*d*]azepin-6-ones **135** (Scheme 38).[112] The processes involving oxidative addition, migratory insertion, CO insertion and reductive elimination were successively achieved utilizing palladium/phosphane catalysis. Moreover, this method enabled the functionalization of marketed drugs like riluzole and estroneto to yield the ligated derivatives, highlighting its outstanding compatibility with diverse functional groups. This work successfully circum-



Scheme 36 Palladium catalysis of intermolecular annulation to access aldehydes.



Scheme 37 Palladium catalysis of intermolecular annulation to access thiophenes.

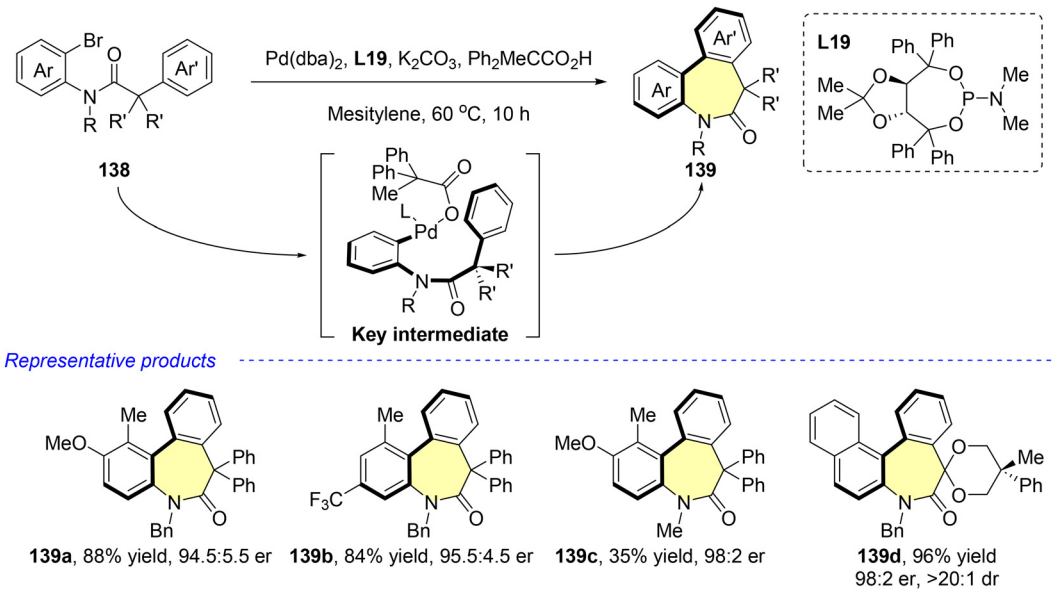


Scheme 38 Pd(II)-catalyzed preparation of dibenzo[*b*,*d*]azepin-6-ones.

vented the limitations including competing carbonylation and β-H elimination, providing a modular approach for the streamlined construction of valuable atropisomeric seven-membered architectures.

Over the past decades, axially chiral dibenzazepinones have emerged as privileged scaffolds with appealing biological properties. Effective enantioselective preparation of atroposelective dibenzazepinones has remained elusive until 2018, when Cramer and co-workers reported a palladium(0)-catalyzed asymmetric C–H arylation of achiral amides (Scheme 39). Taddol-decorated phosphoramidite ligand proved crucial to achieve promising selectivity, and various axially chiral dibenzazepinones were furnished in up to 96% yield and 98 : 2 er.[113] DFT computations revealed that C–H activation by metal dicarbene complexes emerged as an enantiodetermining process, in which the palladacycle species was involved in discriminating between enantiotopic faces of the phenyl moiety to set the chiral axis. This strategy thus represented an efficient and practical control of enantio-atroposelectivity, whilst simultaneously constructing a chiral axis, seems more challenging.

In comparison with C–C atropisomeric molecules, C–N atropisomers possess more rotational degrees of freedom and greater conformational flexibility, leading to the increased difficulty in achieving excellent enantiocontrol.[114] This challenge has motivated Zhou and colleagues to explore an alternative Pd(II)/TFP catalytic system for synthesizing atropisomeri-

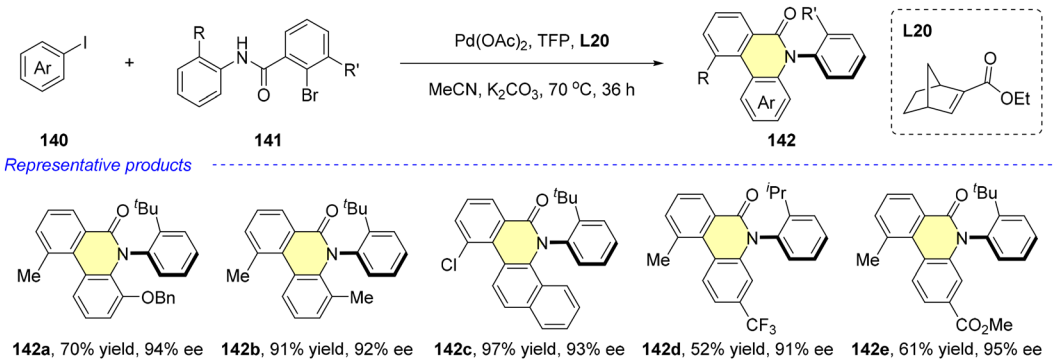


Scheme 39 Atropo-enantioselective C–H arylation to access dibenzazepinones.

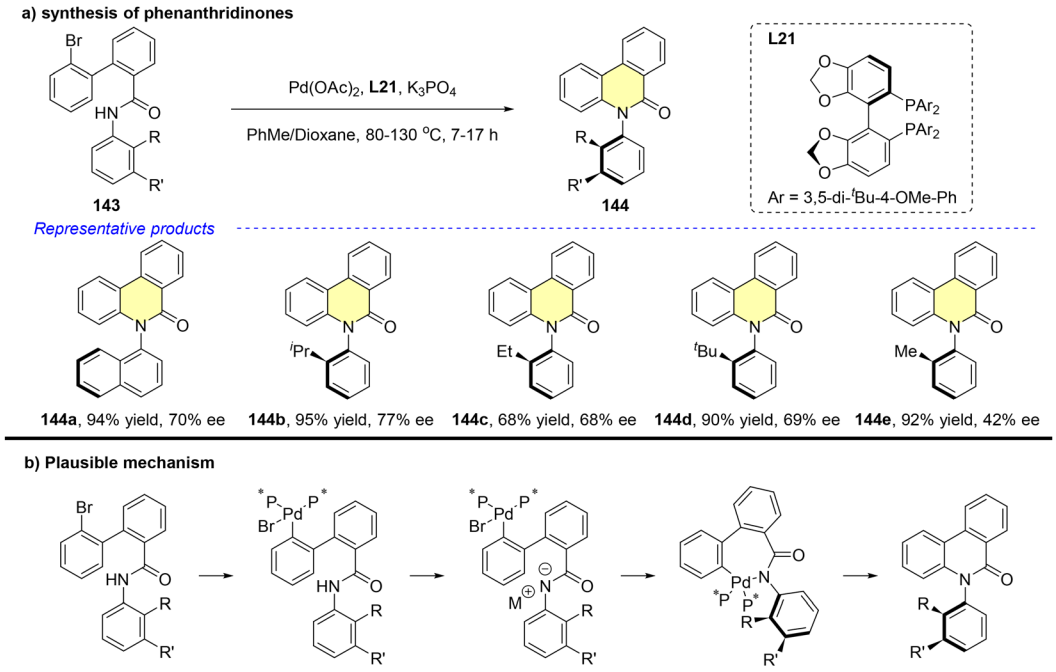
cally enriched phenanthridinones with a C–N axis.[115] Their method enabled the enantioselective cycloaddition of structurally diverse aryl iodides **140** and *N*-arylbenzamides **141** for accessing various phenanthridinone-decorated C–N atropisomers **142** (Scheme 40). Notably, the reaction proceeded through a unique axial-to-axial chirality conversion process. Additionally, introducing a larger steric hindrance of the substituent placed *ortho* to an aniline group contributed to a more stable configuration. DFT studies of free-energy changes highlighted the crucial role of C–C reductive elimination process in influencing the reaction rate. The product diversity, reaction efficiency and mild conditions made this reaction a highly valuable foundation for building enantiopure C–N axial chirality.

Selectively intramolecular Buchwald–Hartwig amination within NH-anilide moiety enabled the atroposelective synthesis of phenanthridin-6-one derivatives that were difficult to prepare through traditional methods. An innovative atroposelective synthesis of phenanthridinones was also reported by Kitagawa and co-workers in 2016.[116] In this elegant work, the authors judiciously employed a chiral ligand, (*R*)-DTBM-SEGPHOS, in the Buchwald–Hartwig amination (Scheme 41). This allowed the efficient palladium-catalyzed intramolecular annulation reaction of easily accessible biphenylamides starting materials. In 2017, the group of Gu realized a dynamic kinetic asymmetric transformation for palladium-catalyzed asymmetric C–H functionalization, delivering axially chiral indole-based frameworks with high efficiency.[117]

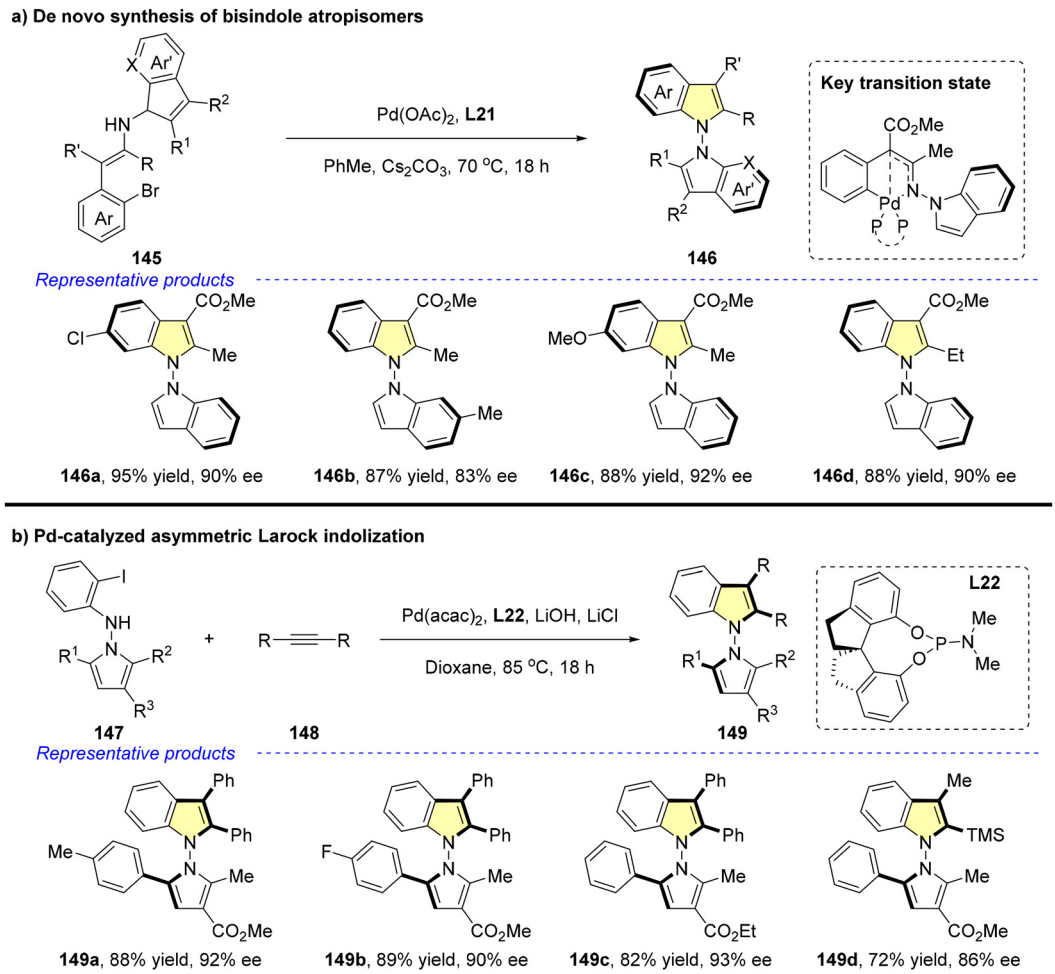
Indole-based axially chiral compounds constitute a privileged class of heteroaromatic platforms in various naturally occurring products, such as schischkiniin and dixiamycin. Building on this, in 2022, Liu and Li elegantly developed a Pd-catalyzed strategy for the *de novo* construction of atropisomerically enriched N–N chiral indoles using commercially available DTBM-SEGPHOS as a chiral ligand (Scheme 42a).[118] As a result, structurally diverse indole–carbazole, indole–pyrrole, and non-biaryl–indole frameworks were conveniently accessed with excellent enantioselectivity. Furthermore, DFT calculations elucidated that the steric repulsion between the ligand



Scheme 40 Intermolecular asymmetric synthesis of phenanthridinones.



Scheme 41 Intramolecular asymmetric synthesis of phenanthridinones.



Scheme 42 Synthesis of N–N axially chiral indoles *via* condensation/*N*-arylation.

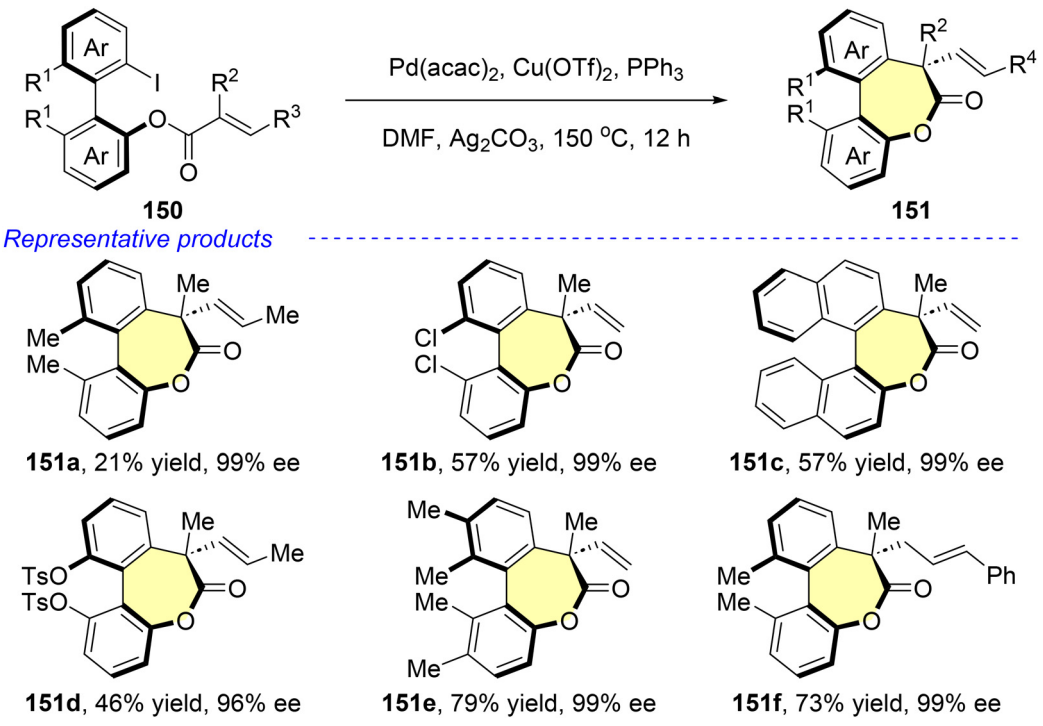
and the indole moiety controlled the enantioselectivity in the rearrangement step. This strategy afforded advantages in the avoidance of employing a strongly coordinating directing group through the intramolecular transformation of a small substituent into "large" groups. In a more recent endeavor, Li, Huang, and Yu achieved the synthesis of N–N chiral indoles using the Pd/SPINOL-catalyzed asymmetric Larock strategy (Scheme 42b).[119] They also proposed a plausible transition state and revealed that the origin of the enantioselectivity might be determined by the migratory insertion process. Importantly, the versatility in the obtained N–N indole atropisomers enabled various post-coupling synthetic elaborations, delivering structurally more complex indole frameworks.

Compared to arylpyrrole frameworks, the enantioselective preparation of bridged biaryl atropisomers is more difficult because of their more complex architectures.[120–123] In 2019, an unprecedented Pd-catalyzed atroposelective Heck-type cycloaddition reaction was established by Xue and Gu.[124] The intramolecular transformation of acyoxylated biaryls **150**, aided by a commercially available $Pd(acac)_2/Cu(OTf)_2/PPh_3$ catalytic system, produced various bridged lactone atropisomers **151** with high enantioselectivity (up to 99% ee) (Scheme 43). However, an extremely high temperature was required to invert the configuration of the carbon–carbon double bond, improving the conversion efficiency. The dual-metal synergistic catalysis improved the reaction efficiency and diastereoselectivity, while the catalysts retained activity over ring-opening/acylation/cyclization processes, affording a facile and efficient platform for constructing lactone-bridged biaryl skeletons.

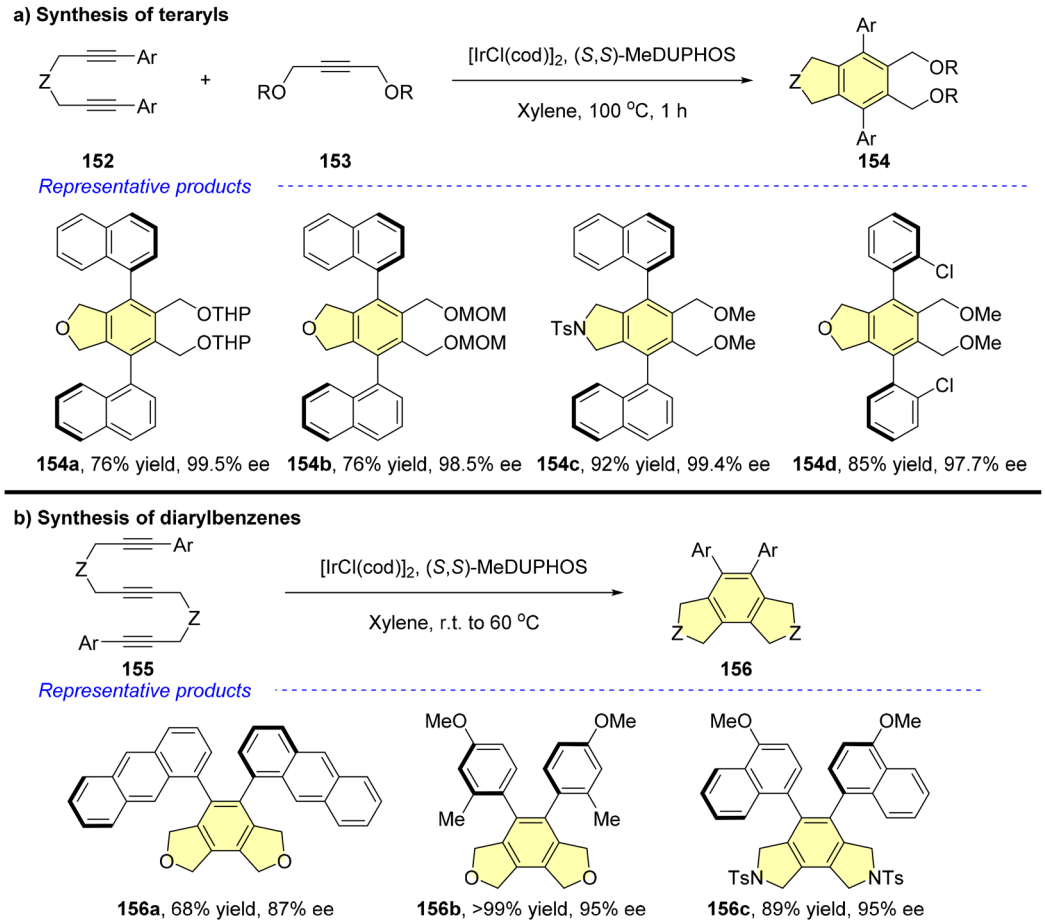
6. Miscellaneous

Several other types of transition metals have been reported for the atropisomeric synthesis of biaryls and heterobiaryls. The first significant work was by Shibata and co-workers, in which the diastereoselective cycloaddition of diverse α,ω-diynes **152** and protected 2-butyne-1,4-diols **153** was achieved by iridium catalysis (Scheme 44a).[125] In the presence of the optimal conditions with $[IrCl(cod)]_2$ as the iridium catalyst of choice, MeDUPHOS as the ligand and xylene as the solvent, extremely high atroposelectivity (up to 99.8% ee) was achieved for the axially chiral teraryls **154**, with broad functional group tolerance. Impressively, an unsymmetrical diyne and methyl-protected 2-butyne-1,4-diol were well-compatible with this protocol. Its high efficiency and straightforward operation afforded a concise access to achieve axially chiral teraryls possessing C_2 symmetry. Inspired by this work, the catalytic system was further applied by the Shibata group for an asymmetric intramolecular cyclotrimerization reaction of oxo/aza-bridged triynes **155**.[126] As illustrated in Scheme 44b, a wide-ranging substrate scope and relatively mild conditions demonstrated that the method could serve as an outstanding platform for the preparation of axially chiral *ortho*-diarylbenzene derivatives **156**.

Besides rhodium catalysts, a new catalytic system for the atroposelective cycloaddition of alkynes was rarely explored but highly desired. Since these seminal investigations, chloro(1,5-cyclooctadiene)iridium(I) dimer has been extensively applied in the asymmetric cyclotrimerization of substrates bearing diverse alkynyl moieties. In 2023, Li and co-workers



Scheme 43 Palladium-catalyzed intramolecular annulation to access lactone-bridged biaryls.

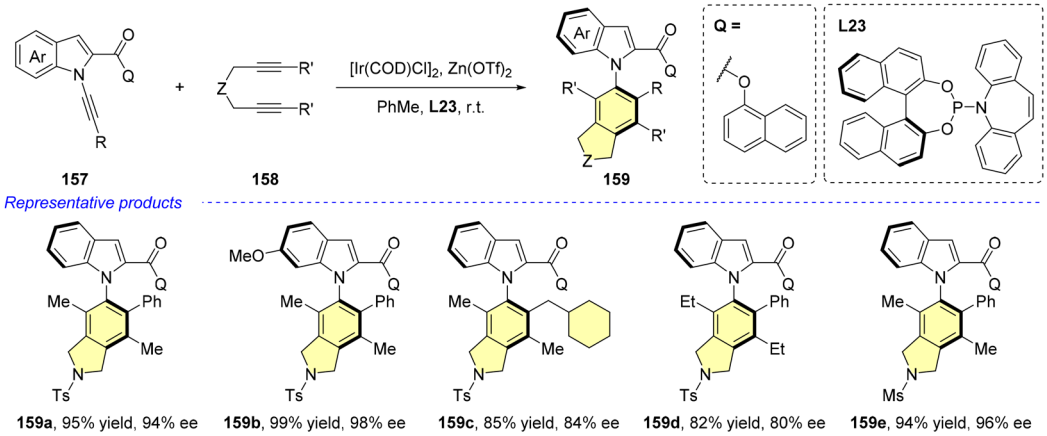


Scheme 44 Iridium-catalysis of enantioselective cyclotrimerization reaction.

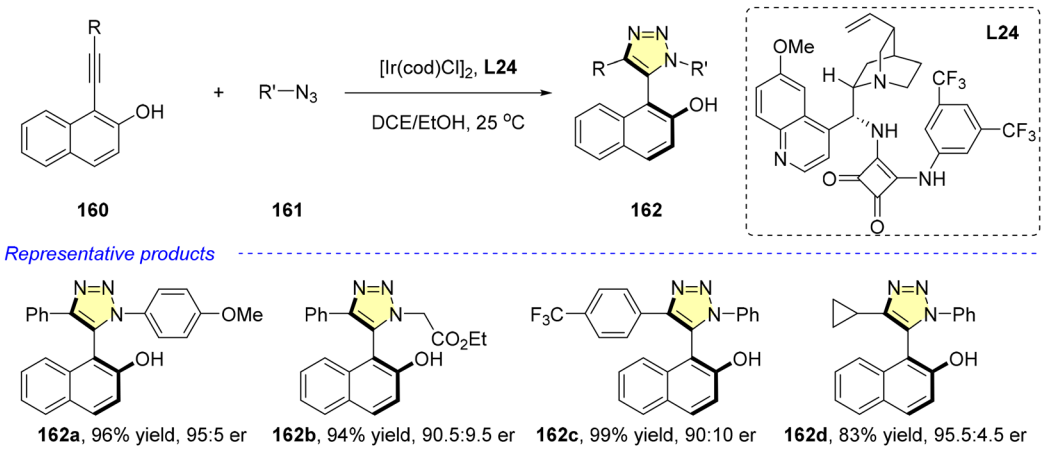
reported a reliable atroposelective alkynylative [2 + 2 + 2] annulation of ynamines **157** and 1,6-diynes **158** using $[IrCl(cod)]_2$/$Zn(OTf)_2$ as the synergistic catalysts, resulting in a library of functionalized axially chiral indole atropisomers **159** with good optical purity (80–98% ee) (Scheme 45).[127] Of note, computational studies indicated that zinc trifluoromethanesulfonate could dramatically enhance reaction efficiency by reducing the energy barrier of migratory insertion pathway. Furthermore, this strategy featured applicability to a gram-scale reaction as well as late-stage derivatization, offering a versatile modular platform for the construction of value-added C–N atropisomers.

Triazoles have emerged as valuable connecting junctions that serve as important pharmacophores. Atropo-enantioselective azide–alkyne cycloaddition enabled the targeted construction of axially chiral aryltriazoles that are difficult to obtain *via* traditional click reactions. An unprecedented example of an Ir/squaramide-catalyzed cooperative catalysis was achieved by Xu and co-workers in 2022, by an atroposelective azide–alkyne cycloaddition between internal alkynes and azides (Scheme 46).[128] Using a newly developed quinidine–squaramide-fused iridium complex, they delivered a wide variety of axially chiral aryltriazoles with high enantioselectivity (up to 98 : 2 er). Alkynes with varied electron properties and both aliphatic and aromatic azides were compatible. This protocol showed scalability and robustness, as demonstrated by gram-scale reactions and versatile late-stage derivatization. Mechanistically, alkynes initially coordinated with the catalyst to form the vinylidene *ortho*-quinone methide, which then underwent an enantioselective cycloaddition to afford a chiral triazole product. This breakthrough enabled straightforward aryltriazole synthesis that could not be achieved by classical click reactions.

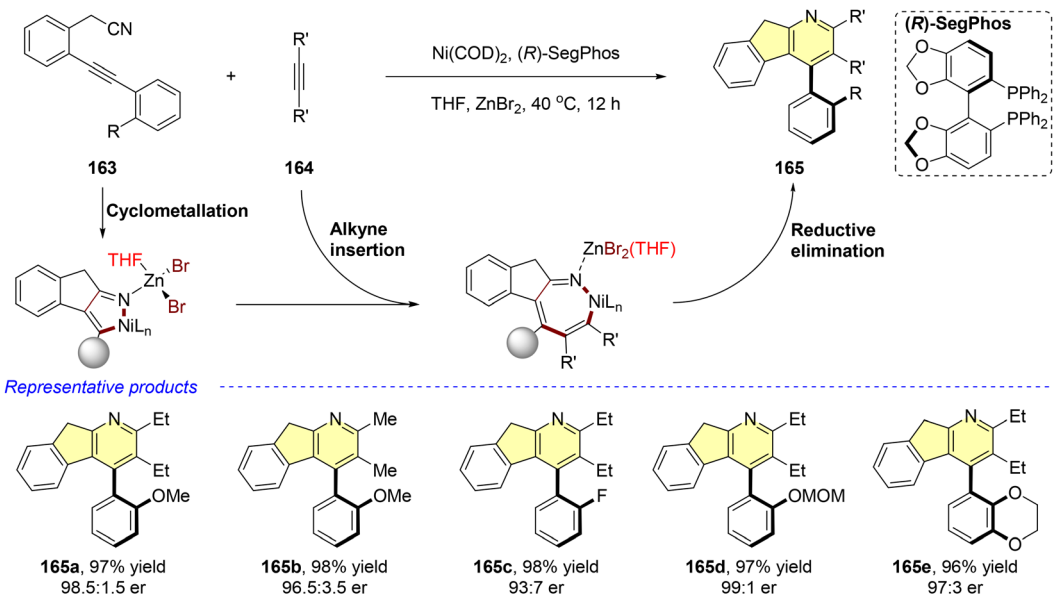
In addition to the iridium-catalyzed atroposelective synthesis mentioned earlier, there are other transition metals used for preparing atropisomers through annulation strategies. For instance, in 2023, Liu and co-workers locked a flexible C–C bond of (*o*-alkynyl)benzyl nitrile substrates to create a unique C4-chiral axis in pyridine derivatives by employing a nickel catalyst (Scheme 47).[129] By leveraging the bulkiness of the aza-fluorene moiety and the chiral cavity in the aza-nickelpentadine complex, even small steric *ortho*-substituents like a fluorine atom or alkoxy groups helped stabilize the biaryl atropisomers. Experimental and computational studies showed hetero-oxidative cyclometallation as a stereodetermining step, where the nickel center complexed with the ligand to provide a rigid C_2-symmetric environment. Featuring mild reaction para-



Scheme 45 Ir/Zn dual catalysis of asymmetric cyclotrimerization.



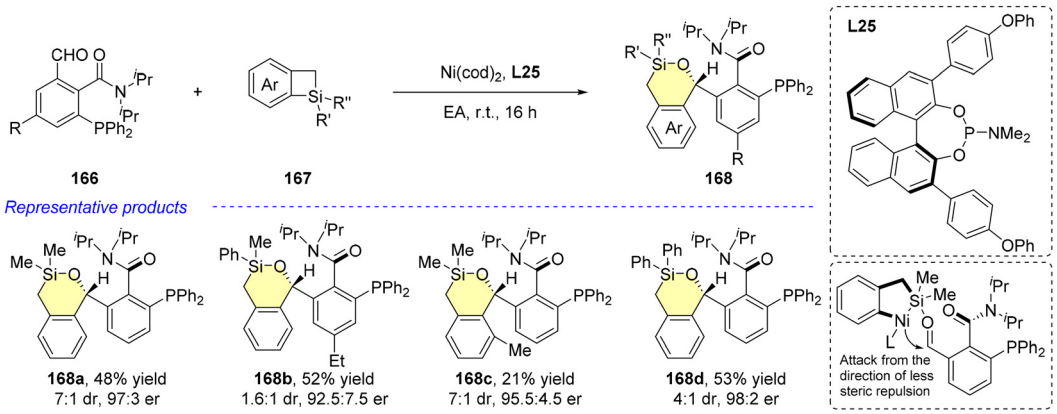
Scheme 46 Atropo-enantioselective synthesis of aryltriazoles *via* azide–alkyne cycloaddition.



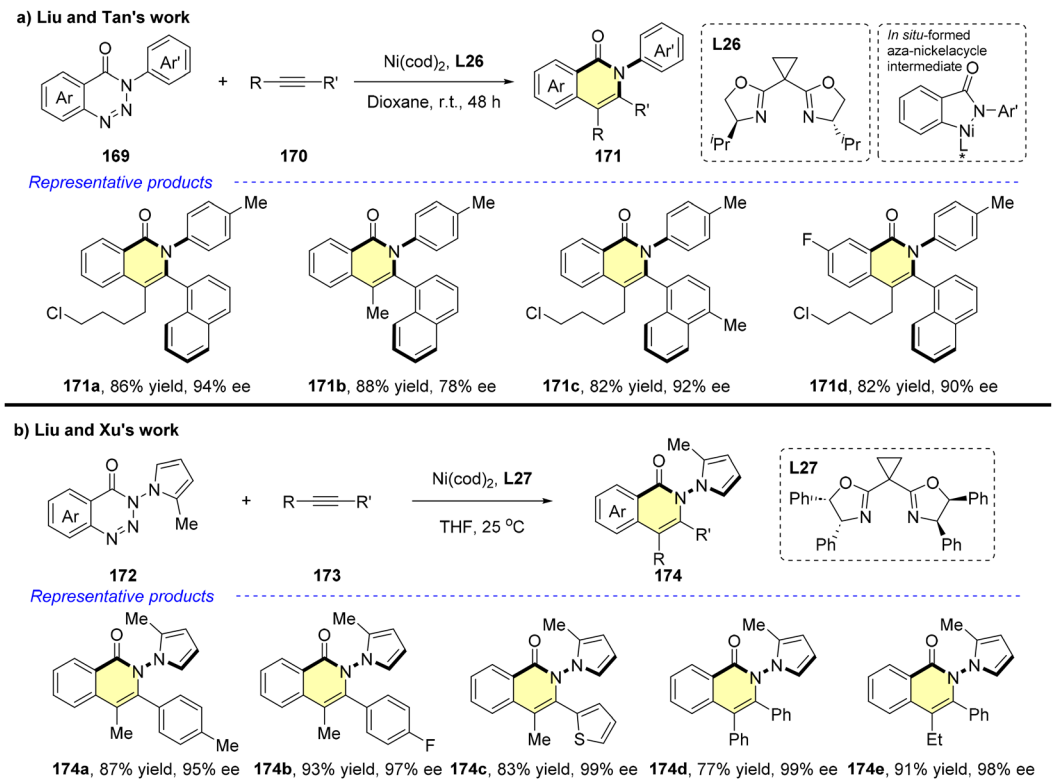
Scheme 47 Synthesis of azafluorenes *via* Ni-catalyzed [2 + 2 + 2] cycloaddition.

meters, practical operational simplicity and a non-noble-metal catalyst, this method provided a convenient approach to pharmacologically relevant azafluorenes.

Although numerous methodologies have been developed for non-biaryl atropisomer synthesis, the atropisomeric construction of non-biaryl amides has been less explored. Very recently, Xu and colleagues reported a highly enantio- and regioselective chiral nickel/phosphoramidite-catalyzed ring expansion silacycloaddition of benzosilacyclobutenes and aromatic aldehydes to synthesize a novel series of amide-derived atropisomers (Scheme 48).[130] The authors modeled the geometric configuration of intermediates and identified transition states using DFT calculations to understand the origin of the stereogenic center. The results showed that the process involved sequential oxidative addition, migratory insertion, and reductive elimination. Additionally, the studies indicated that high enantioselectivity was mainly resolved by the orientation difference of the nickelacycle intermediate relative to the aldehyde moiety during the key migratory insertion step. This reaction produced a new class of multistereogenic phosphines and marked the first atroposelective synthesis of such scaffolds.

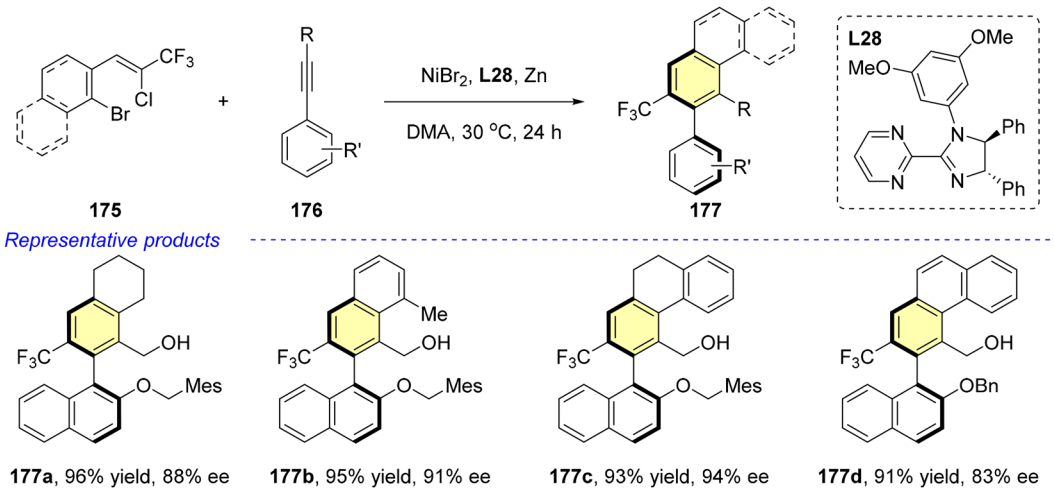


Scheme 48 Ni-catalyzed selective synthesis of multistereogenic phosphines.

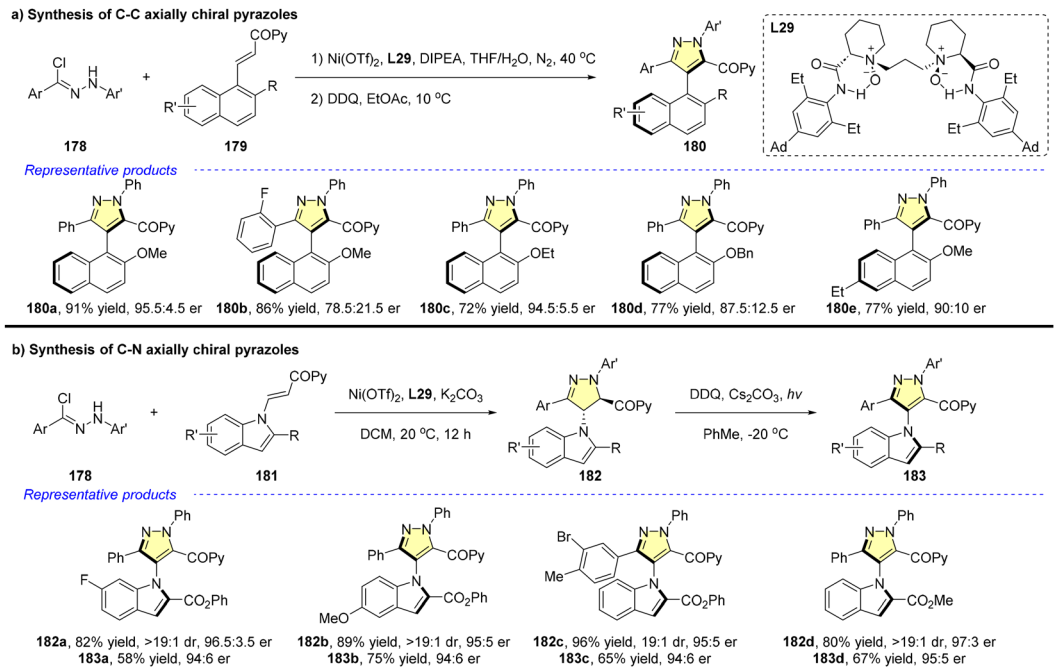


Scheme 49 Ni-catalyzed denitrogenative synthesis of isoquinolones.

Although most transition metals exhibited catalytic activity, the rates of denitrogenative transannulation highly depended on the intrinsic properties of the metals. Nickel catalysts showed good catalytic efficiency owing to their distinctive electronegativity and atomic radius. An unprecedented example of a nickel-catalyzed atroposelective denitrogenative reaction was achieved by Liu and Tan's group in 2015 through an asymmetric transannulation of benzotriazin-4(3*H*)-ones **169** with internal alkynes **170** (Scheme 49a).[131] Using a newly designed cyclopropylidene-linked ligand, various axially chiral isoquinolones **171** were produced with high enantioselectivity (up to 98% ee). DFT calculations confirmed that the steric interaction between the isopropyl moiety of the catalyst and the naphthyl group of the alkyne facilitated restricted rotation around a C–C bond, resulting in a stable atropisomer whose configuration was assigned as *aR* by X-ray diffraction analysis. Notably, the products showed significant cytotoxic effects on several human cancer cell lines, highlighting the practical value of this protocol. Subsequently, the group of Liu and Xu developed a similar method for the catalytic atroposelective denitrogenative transannulation of benzotriazones **172** with internal alkynes **173**, producing axially chiral isoquinolone-based frameworks **174** with good regio- and enantioselectivity under mild conditions (Scheme 49b).[132] The significance of



Scheme 50 Nickel-catalyzed atroposelective reductive annulation.



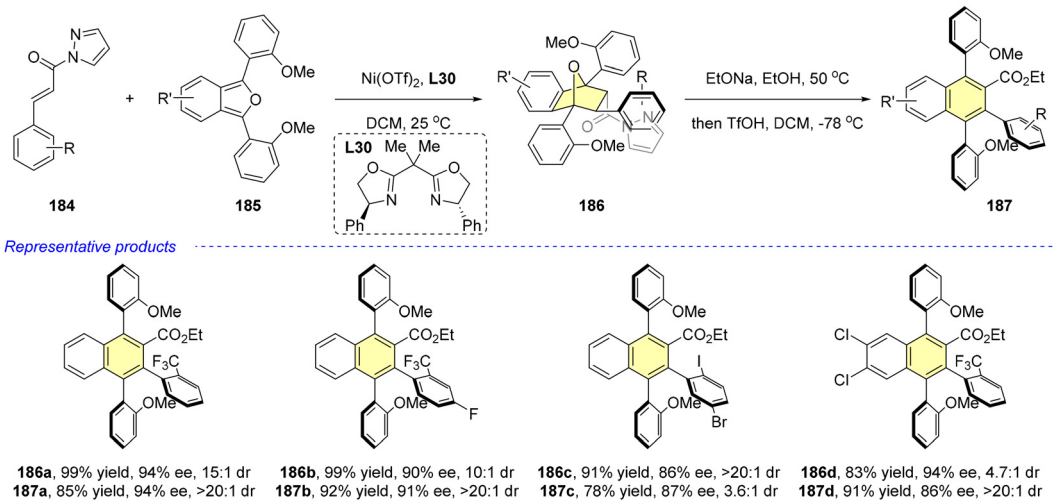
Scheme 51 Atropo-enantioselective synthesis of pyrazole-based heterobiaryls.

this strategy was confirmed by its effectiveness on a larger scale and its versatility for synthetic derivatizations. This modular protocol was particularly valuable for preparing isoquinolone-functionalized systems, with significant implications for drug discovery.

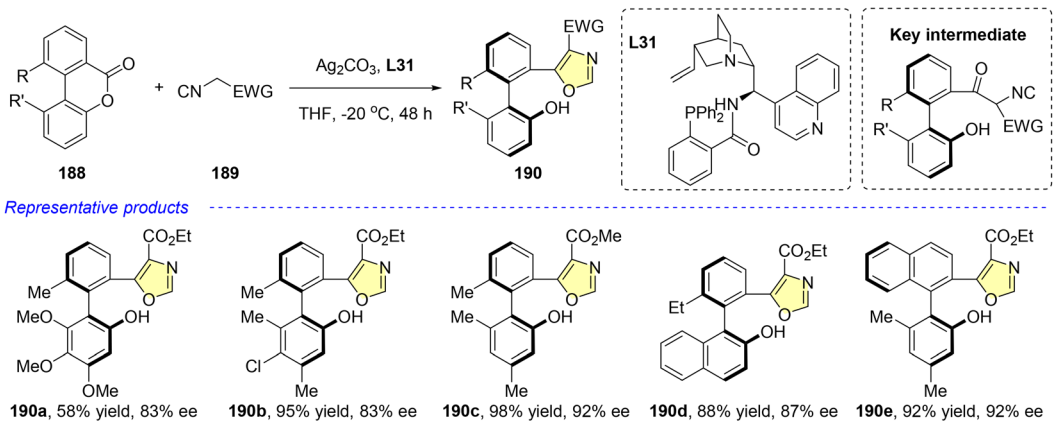
The merger of atroposelective synthesis and reductive cross-coupling was a fascinating theme to form enantioenriched biaryls *via* nickel catalysis. The atroposelective reductive strategies were developed by Wang and co-workers through a formal [4 + 2] annulation of α-naphthylalkynes and biselectrophiles (Scheme 50).[133] This method was used to create a variety of axially chiral bifunctional organocatalysts or bidentate ligands, showcasing the practical usefulness of this approach. Mechanistic studies showed that the *in situ*-generated Ni(0) activated the alkyne by coordination and positioned it close to the aryl bromide moiety, enabling a unique oxidative-addition mode. The following reaction sequence, including another oxidative addition, migratory insertion and reductive elimination, yielded the final biaryl product.

Atroposelective cycloaddition of dipole precursors was extended to other species, such as hydrazonoyl chlorides. The Feng group developed a nickel-catalyzed asymmetric [3 + 2] 1,3-dipolar annulation/oxidation of hydrazonoyl chlorides and naphthyl-derived enones (Scheme 51).[134] This central-to-axial chirality transfer technique enabled the generation of a broad spectrum of C–C axially chiral pyrazole-decorated heterobiaryls with exceptional yield rates and impressive enantioselectivities. To demonstrate the practical efficiency, a range of additional transformations and scale-up experiments were conducted. It was noteworthy that indole-derived substrates were still compatible, creating matching C–N axially chiral pyrazoles while maintaining enantioselectivity. Distinguished by mild reaction parameters and excellent atom economy, this strategy afforded a versatile entry toward biologically relevant five-membered heteroaryls.

Compared with the fruitful results of constructing axially chiral scaffolds with a single stereogenic axis, there are few reports on the stereoselective synthesis of atropisomers with

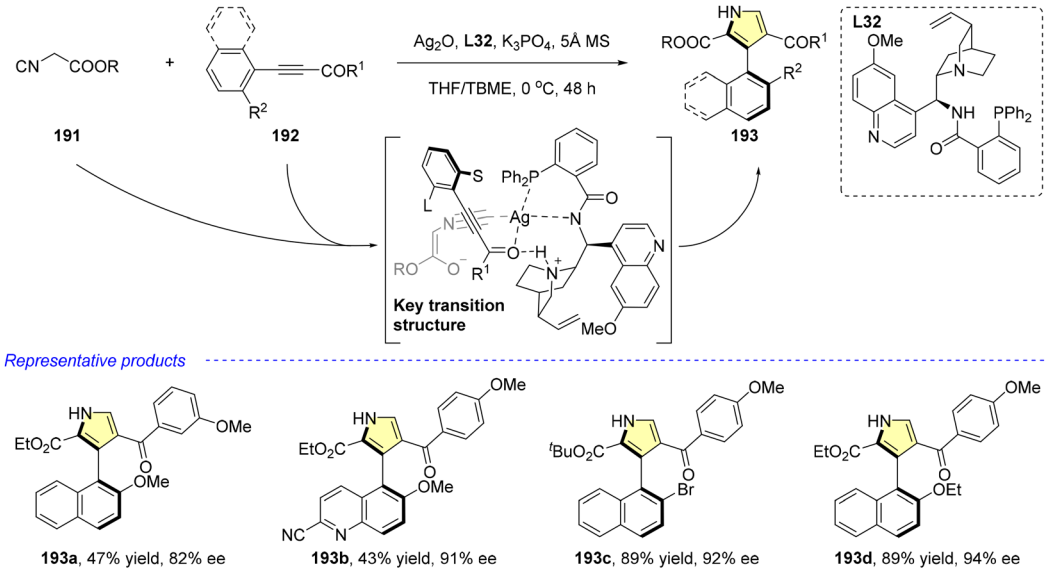


Scheme 52 Enantioselective synthesis of tri-axis naphthalenes.

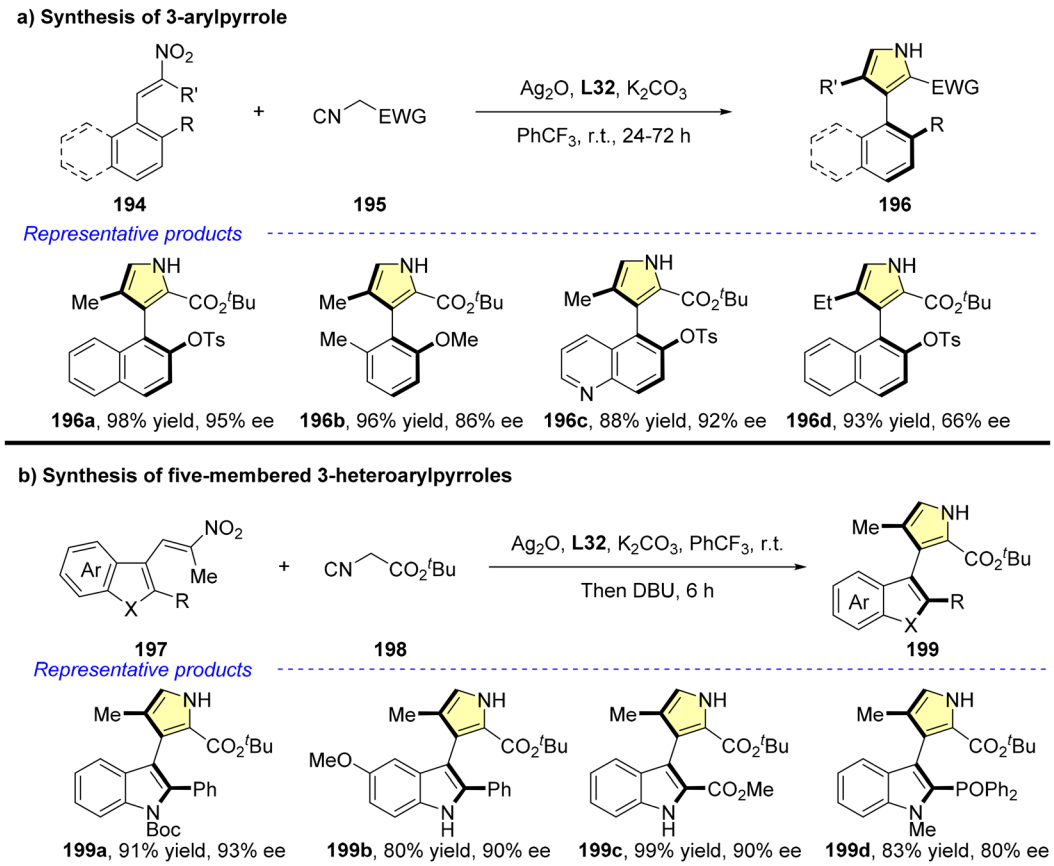


Scheme 53 Ag-catalyzed atropo-enantioselective annulation with isocyanides.

multiple stereogenic axes. Tri-axis naphthalenes, serving as quintessential frameworks in atropisomeric chemistry due to their combined structural stability and functional versatility, exhibit significant scientific value in their precise synthesis. Very recently, the Cai group developed an asymmetric cascade reaction between isobenzofurans **185** and *N*-acyl pyrazoles **184**



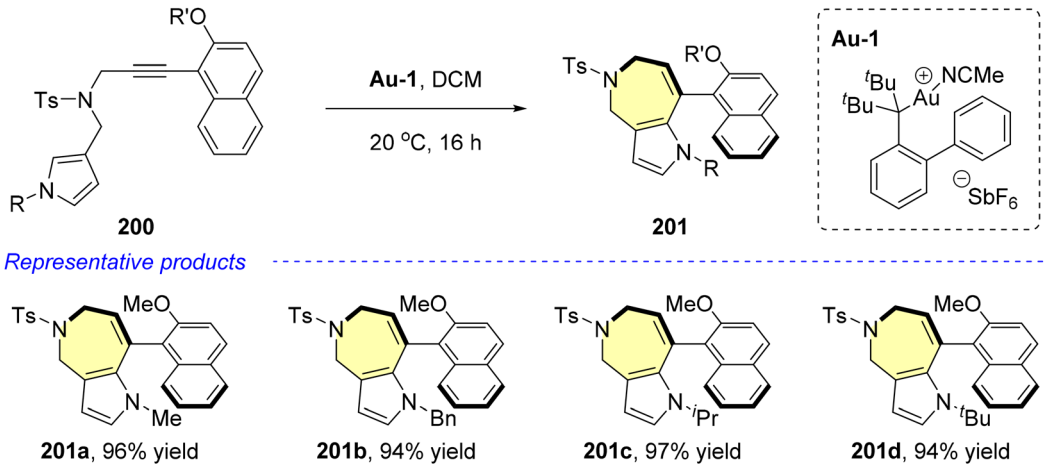
Scheme 54 Atropenantioselective synthesis of enantioenriched 3-arylpyrroles.



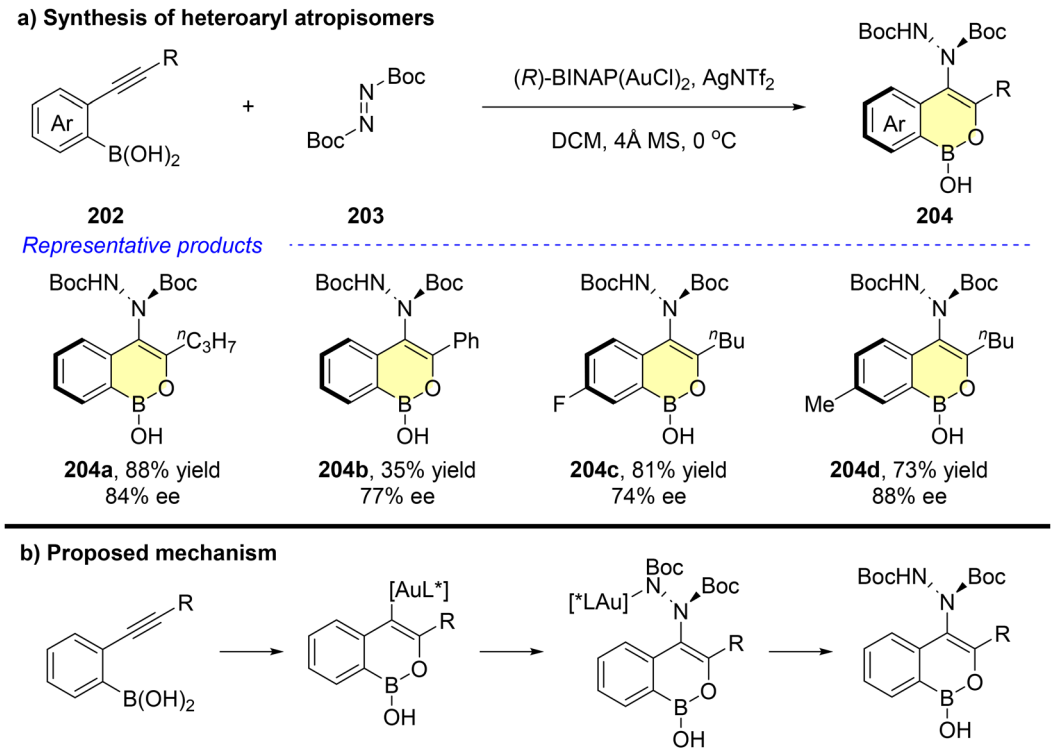
Scheme 55 Ag-mediated stereoselective cycloaddition to access pyrrole atropisomers.

by employing nickel catalysis (Scheme 52).[135] Initially, 7-oxabicyclo[2.2.1]hept-5-*en*-2-yl cycloadducts **186** were achieved *via* normal-electron-demand Diels–Alder reactions, followed by the dehydrative aromatization process to provide axially chiral polysubstituted naphthalenes **187** with three stereogenic axes. Control experiments indicated that the pyrazole group on the dienophile was crucial for achieving high reactivity and enantioselectivity. Moreover, the atropisomeric tri-axis naphthalene products could be readily attached with two pyrene chromophores, which showed green luminescence and could be efficiently applied as chiroptical organic materials, underscoring the applicability of this method.

Isocyanides have proven to be a group of ubiquitous building blocks in transition metal-catalyzed asymmetric annulation, used for building functional heterocycles with diverse π-systems.[136] Under a silver-based catalytic system, lactones could be attacked by isocyanides to oxazoles rather than the acetal process. In 2021, Liao and colleagues first demonstrated the dynamic kinetic resolution of readily available lactones **188** and isocyanides **189** through a silver-catalyzed [3 + 2] cyclization,



Scheme 56 Au-catalyzed hydroalkenylation of pyrrole-propargylamines.



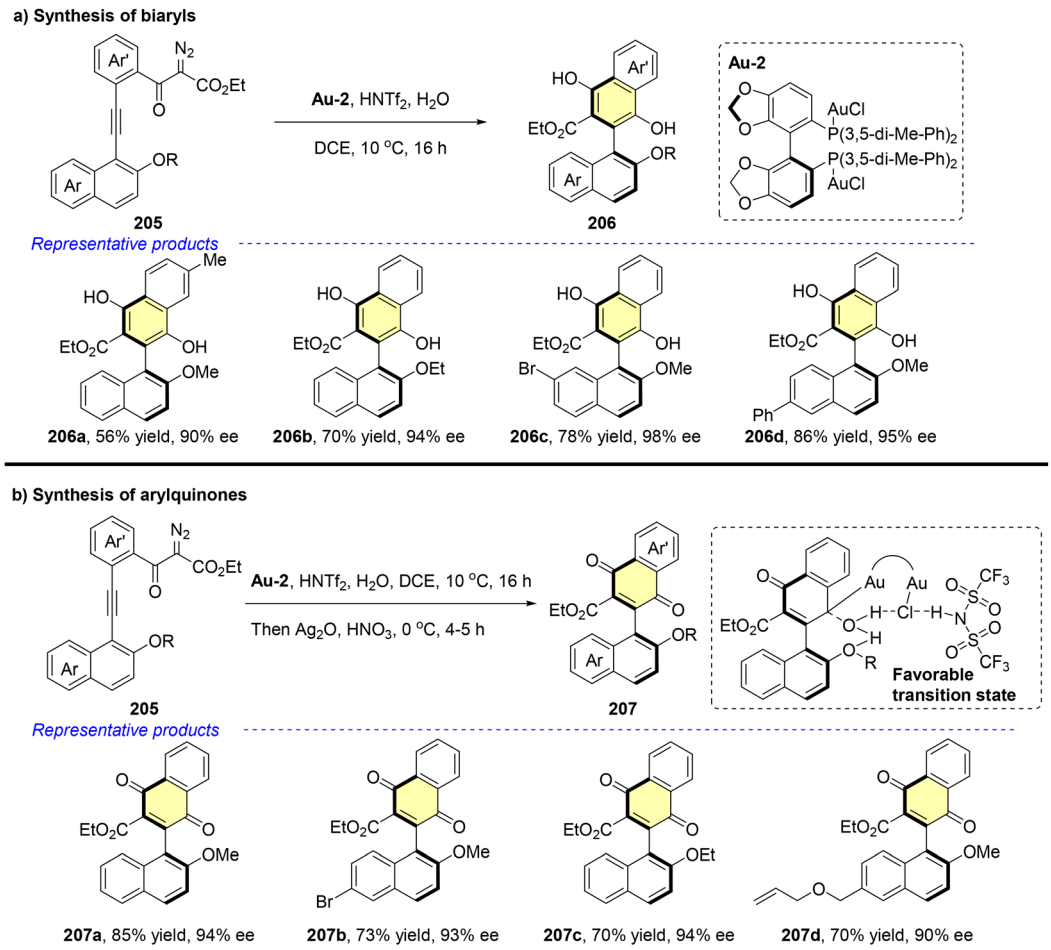
Scheme 57 Au-catalyzed cycloisomerization/amination of boronic acids with diazenes.

employing an alkaloid-derived phosphine ligand (Scheme 53).[137] In addition, thermal racemization studies showed that higher temperatures contributed to achieving highly atroposelective dynamic kinetic resolution. Mechanistically, the process involved ring-opening of the lactone *via* nucleophilic attack by activated isocyanide, followed by a rapid annulation pathway to form the oxazole product. This approach provided a solution to the stereochemical leakage caused by *in situ*-formed lactol.

Despite extensive research on arylpyrrole preparation, there remain abundant opportunities for development in constructing axially chiral arylpyrroles using metal–oxide catalysis. In 2018, Zhu and colleagues pioneered the silver-catalyzed asymmetric oxidative synthesis of enantioenriched 3-arylpyrroles *via* the annulation of α-isocyanoacetates with α-aryl–α,β-alkynic ketones (Scheme 54).[138] Mechanistic studies implicated that the hydrogen-bonding interaction between the ketone oxygen and protonated quinuclidine helped orient the reactants in the catalytic pocket, thereby directly influencing the stereochemical outcome of the key transition species by stabilizing the preferred transition state. This atropenantioselective heteroannulation approach provided a robust synthesis platform for the scale-up synthesis of 3-arylpyrrole-functionalized pharmaceuticals.

Apart from alkynyl ketones, α-isocyanoacetates could also serve as versatile feedstocks in pyrrole synthesis. Around the same period, Chen and Du also reported a strategy that employed an Ag-mediated atropenantioselective Barton–Zard reaction to access pyrrole atropisomers *via* central-to-axial chirality transfer (Scheme 55a and b).[139] In the presence of a cinchona-derived phosphine ligand, the stereoselective formal cycloaddition reaction achieved perfect axial chirality control and excellent functional group compatibility. Moreover, the authors proposed that N–H···O═N hydrogen bonding generated the transition mode, followed by Michael addition from the *Re*-face and annulation to yield the chiral cycloadduct. This method provided an alternative and reliable route to the privileged pyrrole skeletons in a highly atom-economical manner.

Afterwards, the use of gold catalysts to facilitate atroposelective transformations has opened new opportunities for asymmetric annulations. In 2022, Voituriez, Gandon and colleagues utilized an Au(I)-catalyzed asymmetric hydroarylation reaction of *N*-tethered pyrrole-furylpropargyls **200** to achieve atroposelective annulation (Scheme 56).[140] The catalyst [Au(JohnPhos)(CH_3CN)]SbF_6 was identified as the optimal choice for this transformation, yielding a library of axially chiral tetrahydro-



Scheme 58 Gold/$HNTf_2$-cocatalyzed annulation of diazo-alkynes.

pyrrolo[3,2-*c*]azepine derivatives **201** with high efficiency. With regard to the reaction mechanism, the pyrrole moiety was first attacked by the Au(I) catalyst-alkyne complex, followed by protodeauration to form a spiro species. Then, 7-*endo-dig* cyclization and proto-demetallation occurred to provide the desired 7-membered product and regenerated the catalyst. Notably, the *N*-protecting group proved to play a crucial role in maintaining a stable configuration by increasing steric congestion. The authors further incorporated the (*R*)-DM-BINAP ligand to address the asymmetric aspect of this protocol, substantially improving the enantiomeric ratio. The approach operated under mild and simple reaction conditions, showing broad substrate tolerance and demonstrating a straightforward synthetic entry to the azepine scaffold class.

Given the expanding demand for core structures in atropisomers (*e.g.*, biaryl and non-biaryl atropisomers), the development of novel types of heteroaryl atropisomers was highly critical. Inspired by work on gold-catalyzed enantioselective cascade transformations, the Gong group reported an asymmetric cycloisomerization–amination of diazenes **203** and 2-(alkynyl)phenyl boronic acids **202** in 2014 (Scheme 57).[141] A bidentate phosphine-based digold catalyst (*R*)-BINAP$(AuCl)_2$ proved to be crucial for achieving good enantioselectivity, and a library of hydrazide atropisomers **204** with up to 91% ee was produced. Notably, this research provided an alternative approach to access axially chiral heteroaryls through the tandem formation of new C–O and C–N bonds. This breakthrough enabled the efficient synthesis of a new class of atropisomers.

Afterwards, the groups of Li and Tang realized a gold/$HNTf_2$-catalyzed asymmetric diazo-alkyne cyclization for the synthesis of axially chiral biaryls (Scheme 58).[142] Building on this, they subsequently added Ag_2O and HNO_3 as oxidizing agents to achieve the one-pot preparation of axially chiral arylquinones through cascade sequential carbocyclization, addition and oxidation of diazo-alkynes. Notably, a series of functional groups at different positions on aromatic rings were well compatible with this enantioselective catalytic system. A pivotal element was the employment of a chlorine-containing gold catalyst, which dominated the enantioselectivity *via* a strong Cl–H bond, as demonstrated by control experiments and DFT calculations. They overcome the restrictions of the linear coordination of Au(I) complexes by adding Brønsted acid as a proton-shuttle cocatalyst. More impressively, the utility of this protocol was extended to the asymmetric synthesis of seven-membered-ring atropisomers with both C–C axial and C-central chirality.

7. Conclusion and perspective

The ability of transition metal-catalyzed annulation reactions to construct atropisomeric biaryls and heterobiaryls has advanced rapidly due to increasing interest in axially chiral compounds and the rapid development of chiral organocatalysts and ligands. In this context, we summarize the development of transition metal-catalyzed annulation reactions, focusing specifically on the various mechanistic pathways that govern axial chirality formation. Compared to classical synthetic methods, these approaches benefit from mild reaction conditions and simple procedures, which enable excellent stereochemical control of axial chirality. A broad range of mono- and biaxially chiral compounds can be produced in a step- and atom-efficient manner.

Despite numerous synthetic advances so far, the transition metal-catalyzed atroposelective annulation strategy remains in its infancy. Too many concerns currently focus on designing and preparing atropisomers with C–N and C–C axes. However, there is a great need to develop effective atropisomeric C–B, C–S, and C–O bond-forming reactions. Precious metals like rhodium, palladium, iridium, aurum, and silver have been mostly used so far. Yet, cost-effective transition metals from green and earth-abundant materials, such as copper, cobalt, nickel, and iron, are highly worth exploring. Combining enantioselective C–H bond activation with photocatalysis or electrocatalysis may offer advantageous and environmentally-friendly ways to achieve axially chiral molecules. Using advanced technologies, including high-throughput automated synthesis and continuous-flow chemistry, could improve efficiency and scale up production.

Considering the constantly increasing significance of atropisomeric biaryls and heterobiaryls, it is quite necessary to explore practical and green catalytic reaction systems to address current limitations and enlarge the repertoire of such intriguing frameworks. It is our hope that this context will inspire ongoing efforts in this thriving field, leading to the rapid development of more practical and innovative asymmetric strategies in the future.

Conflicts of interest

There are no conflicts to declare.

Data availability

Data sharing may not be applicable to this article as no new data were created or analyzed in this study.

Acknowledgements

We would like to acknowledge the funders Health Commission of Sichuan Province Medical Science and Technology Program (grant no. 202401AS070096) and Chengdu Medical Research Project (grant no. 2025290).

References

1 E. Kumarasamy, R. Raghunathan, M. P. Sibi and J. Sivaguru, Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations, *Chem. Rev.*, 2015, **115**, 11239–11300.
2 G. H. Christie and J. Kenner, LXXI.—The molecular configurations of polynuclear aromatic compounds. Part

I. The resolution of γ-6 : 6′-dinitro- and 4 : 6 : 4′ : 6′-tetranitro-diphenic acids into optically active components, *J. Chem. Soc., Trans.*, 1922, **121**, 614–620.

3 S. Fayez, J. Li, D. Feineis, L. Aké Assi, M. Kaiser, R. Brun, M. A. Anany, H. Wajant and G. Bringmann, A Near-Complete Series of Four Atropisomeric Jozimine A2-Type Naphthylisoquinoline Dimers with Antiplasmodial and Cytotoxic Activities and Related Alkaloids from Ancistrocladus abbreviatus, *J. Nat. Prod.*, 2019, **82**, 3033–3046.

4 Y. Xiao, J. Yang, L. Zou, P. Wu, W. Li, Y. Yan, Y. Li, S. Li, H. Song, W. Zhong and Y. Qin, Synthesis of 10,10′-bis(trifluoromethyl) marinopyrrole A derivatives and evaluation of their antiviral activities in vitro, *Eur. J. Med. Chem.*, 2022, **238**, 114436.

5 S. T. Toenjes and J. L. Gustafson, Atropisomerism in medicinal chemistry: challenges and opportunities, *Future Med. Chem.*, 2018, **10**, 409–422.

6 I. B. Abubakar, I. Malami, Y. Yahaya and S. M. Sule, A review on the ethnomedicinal uses, phytochemistry and pharmacology of Alpinia officinarum Hance, *J. Ethnopharmacol.*, 2018, **224**, 45–62.

7 Z. Li, W. Ma, L. Gu, J. Xie, K. Yang and S. Lin, Recent developments in the utilization of pyridones as privileged scaffolds in drug discovery, *Expert Opin. Drug Discovery*, 2025, **20**, 873–889.

8 U. Mukherjee, J. A. Shah and M.-Y. Ngai, Visible light-driven excited-state copper-BINAP catalysis for accessing diverse chemical reactions, *Chem. Catal.*, 2024, **4**, 101184.

9 A. Mustafai, R. Farooqi, A. G. Woldegiorgis and X. Lin, Emerging progress in chiral phosphoric acid-catalyzed asymmetric synthesis of unnatural α-amino acids, *Catal. Sci. Technol.*, 2025, **15**, 3465–3486.

10 Y.-C. Zhang, F. Jiang and F. Shi, Organocatalytic Asymmetric Synthesis of Indole-Based Chiral Heterocycles: Strategies, Reactions, and Outreach, *Acc. Chem. Res.*, 2020, **53**, 425–446.

11 S.-J. Liu, X. Wang, J.-X. Yang, X.-S. Ao, S.-F. Ni, Y.-C. Zhang and F. Shi, Atroposelective construction of axially chiral alkenylindole-fused nine-membered rings via catalytic asymmetric formal (4 + 5) cycloaddition, *Nat. Commun.*, 2025, **16**, 6605.

12 H.-L. Liu, Q. Peng, Y.-D. Wu, D. Chen, X.-L. Hou, M. Sabat and L. Pu, Highly Enantioselective Recognition of Structurally Diverse α-Hydroxycarboxylic Acids using a Fluorescent Sensor, *Angew. Chem., Int. Ed.*, 2010, **49**, 602–606.

13 L. Pu, Enantioselective Fluorescent Sensors: A Tale of BINOL, *Acc. Chem. Res.*, 2012, **45**, 150–163.

14 Y.-B. Chen, Y.-N. Yang, X.-Z. Huo, L.-W. Ye and B. Zhou, Recent advances in the construction of axially chiral arylpyrroles, *Sci. China:Chem.*, 2023, **66**, 2480–2491.

15 H. Zhu, L. Cheng, J. Wang, Z. Han, J. Sun and H. Huang, Catalytic atroposelective electrophilic amination of diaryl anilines and diaryl phenols for the synthesis of axially chiral diaryl compounds, *Org. Chem. Front.*, 2024, **11**, 6672–6677.

16 C. Gao, T. Ren, Y. Liu, X. Meng, J. Liu, Z. Song, J. Hu, Y. Yang, W.-X. Zhang and H. Zhang, Enantioselective construction of planar, axially and central chiral ferrocenyl phosphines via a Pd-catalyzed domino reaction and diastereoselective phosphination, *Org. Chem. Front.*, 2024, **11**, 5908–5913.

17 Q. Huang, Y. Li, C. Yang, W. Wu, J. Hai and X. Li, Atroposelective synthesis of N–N axially chiral pyrrolyl (aza)-quinolinone by de novo ring formation, *Org. Chem. Front.*, 2024, **11**, 726–734.

18 Q.-Y. Zhang, H.-Y. Wang, S. Wang, J. Ma and H.-M. Guo, Kinetic resolution of heterobiaryl N-oxides by asymmetric C–H olefination: an expeditious access to (R)-QUINAP, *Org. Chem. Front.*, 2023, **10**, 5210–5215.

19 G. Wang, G. Yuan, C. Wei, Y. Zhang, H. Zhu, W. Yang, D. Shi, X. Zhang and Z. Fu, Carbene-Catalyzed Asymmetric Ring-Opening Reaction of Biaryl Lactams to Access Axially Chiral Biaryls, *Chin. J. Chem.*, 2024, **42**, 1734–1740.

20 G. Wang, J. Huang, J. Zhang and Z. Fu, Catalytically atroposelective ring-opening of configurationally labile compounds to access axially chiral biaryls, *Org. Chem. Front.*, 2022, **9**, 4507–4521.

21 P. Loxq, E. Manoury, R. Poli, E. Deydier and A. Labande, Synthesis of axially chiral biaryl compounds by asymmetric catalytic reactions with transition metals, *Coord. Chem. Rev.*, 2016, **308**, 131–190.

22 W. Luo, Y. Zhang, M. Ming and L. Zhang, Recent advances in the catalytic asymmetric construction of axially chiral azole-based frameworks, *Org. Chem. Front.*, 2024, **11**, 6819–6849.

23 Z. Wang, L. Meng, X. Liu, L. Zhang, Z. Yu and G. Wu, Recent progress toward developing axial chirality bioactive compounds, *Eur. J. Med. Chem.*, 2022, **243**, 114700.

24 N. Tajuddeen and G. Bringmann, N,C-Coupled naphthylisoquinoline alkaloids: a versatile new class of axially chiral natural products, *Nat. Prod. Rep.*, 2021, **38**, 2154–2186.

25 L. Cai, J. Chen, Y. Zhu, G. Yang and S. Gu, Recent Advances in Catalytic Atroposelective Synthesis of Seven- and Eight-Membered Rings with Inherent Chirality, *Adv. Synth. Catal.*, 2025, **367**, e70020.

26 Y. Luo, S. Luo and Q. Zhu, Inherently Chiral Seven- and Eight-Membered Rings: Enantioselective Synthesis and Applications, *J. Org. Chem.*, 2025, **90**, 5307–5322.

27 N. Brodt and J. Niemeyer, Chiral organophosphates as ligands in asymmetric metal catalysis, *Org. Chem. Front.*, 2023, **10**, 3080–3109.

28 M. Mancinelli, G. Bencivenni, D. Pecorari and A. Mazzanti, Stereochemistry and Recent Applications of Axially Chiral Organic Molecules, *Eur. J. Org. Chem.*, 2020, 4070–4086.

29 Sumit, D. Chandra and U. Sharma, Chiral phosphoric acids: a chiral lobby for enantioselective C–H activation, *Chem. Commun.*, 2023, **59**, 9288–9300.

30 J. Feng, L.-L. Xi, C.-J. Lu and R.-R. Liu, Transition-metal-catalyzed enantioselective C–N cross-coupling, *Chem. Soc. Rev.*, 2024, **53**, 9560–9581.

31 J. K. Cheng, S.-H. Xiang, S. Li, L. Ye and B. Tan, Recent Advances in Catalytic Asymmetric Construction of Atropisomers, *Chem. Rev.*, 2021, **121**, 4805–4902.
32 Q. Zhao, C. Peng, Y.-T. Wang, G. Zhan and B. Han, Recent progress on the construction of axial chirality through transition-metal-catalyzed benzannulation, *Org. Chem. Front.*, 2021, **8**, 2772–2785.
33 A. Gaucherand, E. Yen-Pon, A. Domain, A. Bourhis, J. Rodriguez and D. Bonne, Enantioselective synthesis of molecules with multiple stereogenic elements, *Chem. Soc. Rev.*, 2024, **53**, 11165–11206.
34 K. Feng, C. Yao and H. Xu, Biaxially chiral compounds: research and development of synthesis, *Chem. Commun.*, 2025, **61**, 2217–2234.
35 W.-W. Chen and M.-H. Xu, Recent advances in rhodium-catalyzed asymmetric synthesis of heterocycles, *Org. Biomol. Chem.*, 2017, **15**, 1029–1050.
36 Y. L. Tsang, P. Y. Choy, M. P. Leung, X. He and F. Y. Kwong, Recent advances in rhodium-catalysed cross-dehydrogenative-coupling between two C(sp2)–H bonds, *Org. Chem. Front.*, 2022, **9**, 1992–2012.
37 J.-l. Ma, X.-m. Zhou, J.-l. Chen, J.-x. Shi, H.-c. Cheng, P.-h. Guo and H.-b. Ji, Directing group strategies in rhodium-catalyzed C–H amination, *Org. Biomol. Chem.*, 2022, **20**, 7554–7576.
38 D. Chen, D. Q. Dong, Z. X. Qiu, Y. M. Wang, S. Q. Yan, X. M. Xu and Z. L. Wang, Research Progress of Rhodium (III)–Catalyzed C(sp2)–H Bond Functionalization, *Eur. J. Org. Chem.*, 2025, e202401177.
39 F. E. Paulik and J. F. Roth, Novel catalysts for the low-pressure carbonylation of methanol to acetic acid, *Chem. Commun.*, 1968, 1578.
40 M. Maneesha, T. Aneeja and G. Anilkumar, Advances and prospects in rhodium catalyzed domino reactions, *J. Organomet. Chem.*, 2024, **1008**, 123049.
41 M. Alisha, R. M. Philip and G. Anilkumar, An overview of rhodium-catalysed heck type reactions, *J. Organomet. Chem.*, 2022, **959**, 122207.
42 S. Qiu, X. Gao and S. Zhu, Dirhodium(II)-catalysed cycloisomerization of azaenyne: rapid assembly of centrally and axially chiral isoindazole frameworks, *Chem. Sci.*, 2021, **12**, 13730–13736.
43 X. Zhu, H. Wu, Y. Wang, G. Huang, F. Wang and X. Li, Rhodium-catalyzed annulative approach to N–N axially chiral biaryls via C–H activation and dynamic kinetic transformation, *Chem. Sci.*, 2023, **14**, 8564–8569.
44 Y. Wang, X. Zhu, D. Pan, J. Jing, F. Wang, R. Mi, G. Huang and X. Li, Rhodium-catalyzed enantioselective and diastereodivergent access to diaxially chiral heterocycles, *Nat. Commun.*, 2023, **14**, 4661.
45 P. Wang, Y. Huang, J. Jing, F. Wang and X. Li, Rhodium (III)-Catalyzed Atroposelective Synthesis of C–N Axially Chiral Naphthylamines and Variants via C–H Activation, *Org. Lett.*, 2022, **24**, 2531–2535.
46 P. Hu, L. Kong, F. Wang, X. Zhu and X. Li, Twofold C–H Activation-Based Enantio- and Diastereoselective C–H Arylation Using Diarylacetylenes as Rare Arylating Reagents, *Angew. Chem., Int. Ed.*, 2021, **60**, 20424–20429.
47 F. Wang, J. Jing, Y. Zhao, X. Zhu, X.-P. Zhang, L. Zhao, P. Hu, W.-Q. Deng and X. Li, Rhodium-Catalyzed C–H Activation-Based Construction of Axially and Centrally Chiral Indenes through Two Discrete Insertions, *Angew. Chem., Int. Ed.*, 2021, **60**, 16628–16633.
48 F. Wang, Z. Qi, Y. Zhao, S. Zhai, G. Zheng, R. Mi, Z. Huang, X. Zhu, X. He and X. Li, Rhodium(III)-Catalyzed Atroposelective Synthesis of Biaryls by C–H Activation and Intermolecular Coupling with Sterically Hindered Alkynes, *Angew. Chem., Int. Ed.*, 2020, **59**, 13288–13294.
49 Z.-Y. Xie, C. Tang, L. Li, Z. Zhou, J. Zou and P.-C. Qian, Rhodium-Catalyzed Regioselective [4 + 2] Cycloaddition of Ynamines and 2-(Cyanomethyl)phenylboronates, *Org. Lett.*, 2024, **26**, 6586–6590.
50 X. Zhang, Q. Teng, Y. Ren, B. Wei, C.-H. Tung and Z. Xu, Neighboring group-directed asymmetric [2 + 2 + 2] cycloaddition to access C–N axially chiral indoles, *Org. Chem. Front.*, 2024, **11**, 2857–2863.
51 S. Ogaki, Y. Shibata, K. Noguchi and K. Tanaka, Enantioselective Synthesis of Axially Chiral Hydroxy Carboxylic Acid Derivatives by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition, *J. Org. Chem.*, 2011, **76**, 1926–1929.
52 J. Oppenheimer, R. P. Hsung, R. Figueroa and W. L. Johnson, Stereochemical Control of Both C–C and C–N Axial Chirality in the Synthesis of Chiral N,O-Biaryls, *Org. Lett.*, 2007, **9**, 3969–3972.
53 T. Shibata, H. Nikawa, E. Kadosaka, M. Ito, T. Taniguchi and K. Monde, Enantioselective Synthesis of Axially Chiral 1,8-Diarylnaphthalenes by Rh-Catalyzed [2 + 2 + 2] Cycloaddition and Evaluation of Their Chiroptical Properties, *Org. Lett.*, 2025, **27**, 4524–4528.
54 H. Liu, Z. Qi, Y. Shi, W. Wang, F. Wang, Z.-W. Ding, A.-Q. Jia, G. Huang and X. Li, Catalytic asymmetric intermolecular [4 + 2] annulation of benzocyclobutenones with Alkynes and activated carbonyls via C—C activation, *Nat. Commun.*, 2025, **16**, 5741.
55 M. Augé, A. Feraldi-Xypolia, M. Barbazanges, C. Aubert, L. Fensterbank, V. Gandon, E. Kolodziej and C. Ollivier, Double-Stereodifferentiation in Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition: Chiral Ligand/Chiral Counterion Matched Pair, *Org. Lett.*, 2015, **17**, 3754–3757.
56 K. Kashima, K. Teraoka, H. Uekusa, Y. Shibata and K. Tanaka, Rhodium-Catalyzed Atroposelective [2 + 2 + 2] Cycloaddition of Ortho-Substituted Phenyl Diynes with Nitriles: Effect of Ortho Substituents on Regio- and Enantioselectivity, *Org. Lett.*, 2016, **18**, 2170–2173.
57 C. R. McConnell and S.-Y. Liu, Late-stage functionalization of BN-heterocycles, *Chem. Soc. Rev.*, 2019, **48**, 3436–3453.
58 Z. X. Giustra and S.-Y. Liu, The State of the Art in Azaborine Chemistry: New Synthetic Methods and Applications, *J. Am. Chem. Soc.*, 2018, **140**, 1184–1194.
59 M. Birepinte, F. Robert, S. Pinet, L. Chabaud and M. Pucheault, Non-biaryl atropisomerism at the C–B bond

in sterically hindered aminoarylboranes, *Org. Biomol. Chem.*, 2020, **18**, 3007–3011.
60 J. Yang, J.-W. Zhang, W. Bao, S.-Q. Qiu, S. Li, S.-H. Xiang, J. Song, J. Zhang and B. Tan, Chiral Phosphoric Acid-Catalyzed Remote Control of Axial Chirality at Boron–Carbon Bond, *J. Am. Chem. Soc.*, 2021, **143**, 12924–12929.
61 X. Bao, J. Rodriguez and D. Bonne, Enantioselective Synthesis of Atropisomers with Multiple Stereogenic Axes, *Angew. Chem., Int. Ed.*, 2020, **59**, 12623–12634.
62 Y. L. Li, K. K. Wang and X. L. He, Recent Progress of Electron–Withdrawing–Group–Tethered Arenes Involved Asymmetric Nucleophilic Aromatic Functionalizations, *Adv. Synth. Catal.*, 2022, **364**, 3630–3650.
63 J. Zhang, X. Huo, Y. Liu and C. Zhu, Dynamic kinetic resolution and dynamic kinetic asymmetric transformation of atropisomeric biaryls, *Chem. Catal.*, 2025, **5**, 101329.
64 H. Wang, B. Qiao, J. Zhu, H. Guo, Z. Zhang, K. Yang, S.-J. Li, Y. Lan and Q. Song, Enantio- and regioselective [2 + 2 + 2] cycloaddition of BN-diynes for construction of C-B axial chirality, *Chem*, 2024, **10**, 317–329.
65 Y. Ping, X. Shi, M. Lei and J. Wang, Atroposelective Construction of Carbon–Boron Axial Chirality through Rh-Catalyzed [2 + 2 + 2] Cycloaddition, *ACS Catal.*, 2024, **14**, 5064–5076.
66 X. Zhu, Y. Shi, J. Li, H. Peng, M. Gong, W. Zhou, F. Wang, G. Huang, X. Li and Y. Fang, Rhodium-catalyzed construction of boron-based point and axial chirality via asymmetric annulation of alkynylborons, *Nat. Commun.*, 2025, **16**, 9764.
67 K. Tanaka, T. Suda, K. Noguchi and M. Hirano, Catalytic [2 + 2 + 2] and Thermal [4 + 2] Cycloaddition of 1,2-Bis (arylpropiolyl)benzenes, *J. Org. Chem.*, 2007, **72**, 2243–2246.
68 H. Takano, N. Shiozawa, Y. Imai, K. S. Kanyiva and T. Shibata, Catalytic Enantioselective Synthesis of Axially Chiral Polycyclic Aromatic Hydrocarbons (PAHs) via Regioselective C–C Bond Activation of Biphenylenes, *J. Am. Chem. Soc.*, 2020, **142**, 4714–4722.
69 H. Li, X. Yan, J. Zhang, W. Guo, J. Jiang and J. Wang, Enantioselective Synthesis of C–N Axially Chiral N-Aryloxindoles by Asymmetric Rhodium-Catalyzed Dual C–H Activation, *Angew. Chem., Int. Ed.*, 2019, **58**, 6732–6736.
70 P. Hu, B. Liu, F. Wang, R. Mi, X.-X. Li and X. Li, A Stereodivergent–Convergent Chiral Induction Mode in Atroposelective Access to Biaryls via Rhodium-Catalyzed C–H Bond Activation, *ACS Catal.*, 2022, **12**, 13884–13896.
71 W.-T. Guo, B.-H. Zhu, Y. Chen, J. Yang, P.-C. Qian, C. Deng, L.-W. Ye and L. Li, Enantioselective Rh-Catalyzed Azide-Internal-Alkyne Cycloaddition for the Construction of Axially Chiral 1,2,3-Triazoles, *J. Am. Chem. Soc.*, 2022, **144**, 6981–6991.
72 L.-L. Xi and R.-R. Liu, Enantioselective electrochemical and photochemical synthesis of atropisomers, *Trends Chem.*, 2024, **6**, 556–571.
73 Z.-X. Zhang, T.-Y. Zhai and L.-W. Ye, Synthesis of axially chiral compounds through catalytic asymmetric reactions of alkynes, *Chem. Catal.*, 2021, **1**, 1378–1412.
74 M.-M. Xu, X.-Y. You, Y.-Z. Zhang, Y. Lu, K. Tan, L. Yang and Q. Cai, Enantioselective Synthesis of Axially Chiral Biaryls by Diels–Alder/Retro-Diels–Alder Reaction of 2-Pyrones with Alkynes, *J. Am. Chem. Soc.*, 2021, **143**, 8993–9001.
75 D. Zhu, Y. Sun, H. Peng, H. Li, Y. Yan and H. Kuang, Enantioselective Synthesis of Axially Chiral Oxazole Biaryls by Copper-Catalyzed Oxidation of Cyclic Diaryliodoniums, *Eur. J. Org. Chem.*, 2022, e202101449.
76 C. Yao, D.-R. Li, H.-M. Xiang, S.-J. Li, Y. Lu, Z. Wang, T. Yin, J. Wang, K. Feng, C. Zhu and H. Xu, Copper-catalysed asymmetric annulation of yne-allylic esters with amines to access axially chiral arylpyrroles, *Nat. Commun.*, 2024, **15**, 6848.
77 X. Fan, X. Zhang, C. Li and Z. Gu, Enantioselective Atropisomeric Anilides Synthesis via Cu-Catalyzed Intramolecular Adjacent C–N Coupling, *ACS Catal.*, 2019, **9**, 2286–2291.
78 X.-L. Min, X.-L. Zhang, W. Yi and Y. He, Brønsted acid-enhanced copper-catalyzed atroposelective cycloisomerization to axially chiral arylquinolizones via dearomatization of pyridine, *Nat. Commun.*, 2022, **13**, 373.
79 I. Maclean, E. Gallent, O. Orozco, A. Molina, N. Rodríguez, J. Adrio and J. C. Carretero, Atroposelective Synthesis of Axially Chiral Naphthylpyrroles by a Catalytic Asymmetric 1,3-Dipolar Cycloaddition/Aromatization Sequence, *Org. Lett.*, 2024, **26**, 922–927.
80 Z. Ge, C. Zhu, G. Xu, S.-N. Guan and H. Xu, Remote Copper-Catalyzed Atroposelective Synthesis of N–N Axially Chiral Compounds Bearing Minimally Different Alkyl Groups, *Org. Lett.*, 2025, **27**, 5632–5636.
81 P. Rodríguez-Salamanca, R. Martín-de la Calle, V. Rodríguez, P. Merino, R. Fernández, J. M. Lassaletta and V. Hornillos, Asymmetric synthesis of dibenzo[b,d] azepines by Cu-catalyzed reductive or borylative cyclization, *Chem. Sci.*, 2021, **12**, 15291–15297.
82 M.-D. Li, Y. Tian, R.-X. Liu, B. Liu and T.-Y. Lin, Copper-Catalyzed Desymmetric Alkyne–Azide Cycloaddition to Access Axially Chiral Biaryls, *Eur. J. Org. Chem.*, 2025, e202500041.
83 H.-H. Chen, Y.-B. Chen, J.-Z. Gao, L.-W. Ye and B. Zhou, Copper-Catalyzed Enantioselective Dehydro-Diels–Alder Reaction: Atom-Economical Synthesis of Axially Chiral Carbazoles, *Angew. Chem., Int. Ed.*, 2024, **63**, e202411709.
84 Y.-B. Chen, L.-G. Liu, C.-M. Chen, Y.-X. Liu, B. Zhou, X. Lu, Z. Xu and L.-W. Ye, Construction of Axially Chiral Arylpyrroles via Atroposelective Diyne Cyclization, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303670.
85 B. Kokić, B. Vulović, M. Jović, A. Andrijević, V. Ajdačić and I. M. Opsenica, Strategies for Carbon Electrophile Addition to Carbonyls and Imines by Cobalt Catalysis, *Eur. J. Org. Chem.*, 2023, e202300997.

86 G. Wang, Z. Chen, J. Xie, L. Ding, J. Zhu, W. Wei, Y.-M. Yan, D. Chu and B.-J. Ni, Recent trends and prospects in electrochemical nitrate reduction to ammonia with an emphasis on cobalt catalysts, *Coord. Chem. Rev.*, 2025, **539**, 216751.
87 M. M. Tohidi, B. Paymard, S. R. Vasquez-García and D. Fernández-Quiroz, Recent progress in applications of cobalt catalysts in organic reactions, *Tetrahedron*, 2023, **136**, 133352.
88 N. Bhaduri and A. B. Pawar, Redox-neutral C–H annulation strategies for the synthesis of heterocycles via high-valent Cp*Co(iii) catalysis, *Org. Biomol. Chem.*, 2023, **21**, 3918–3941.
89 A. Khosravi and M.-Y. Ngai, Cobalt-catalyzed alkene hydrohalogenation via hydrogen atom transfer, *Tetrahedron*, 2025, **187**, 134944.
90 T. Yoshino and S. Matsunaga, (Pentamethylcyclopentadienyl)cobalt(III)-Catalyzed C–H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity, *Adv. Synth. Catal.*, 2017, **359**, 1245–1262.
91 P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, 3d Transition Metals for C–H Activation, *Chem. Rev.*, 2019, **119**, 2192–2452.
92 J. Park and J. Son, Cobalt–Catalyzed C(sp2)—O Bond Formation by Directing Group Assisted C—H Activation, *Eur. J. Org. Chem.*, 2022, 18–29.
93 B. Garai, A. Das, D. V. Kumar and B. Sundararaju, Enantioselective C–H bond functionalization under Co (iii)-catalysis, *Chem. Commun.*, 2024, **60**, 3354–3369.
94 T. Yoshino and S. Matsunaga, (Pentamethylcyclopentadienyl)cobalt(III)–Catalyzed C–H Bond Functionalization: From Discovery to Unique Reactivity and Selectivity, *Adv. Synth. Catal.*, 2017, **359**, 1245–1262.
95 L. Grigorjeva and O. Daugulis, Cobalt-Catalyzed, Aminoquinoline-Directed C(sp^2)–H Bond Alkenylation by Alkynes, *Angew. Chem.*, 2014, **126**, 10373–10376.
96 B.-J. Wang, G.-X. Xu, Z.-W. Huang, X. Wu, X. Hong, Q.-J. Yao and B.-F. Shi, Single-Step Synthesis of Atropisomers with Vicinal C—C and C—N Diaxes by Cobalt-Catalyzed Atroposelective C—H Annulation, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208912.
97 P.-F. Qian, Y.-X. Wu, J.-H. Hu, J.-H. Chen, T. Zhou, Q.-J. Yao, Z.-H. Zhang, B.-J. Wang and B.-F. Shi, Atroposelective Synthesis of Pyridoindolones Bearing Two Remote Distinct C–N Axes through Cobalt-Catalyzed Enantioselective C–H Activation, *J. Am. Chem. Soc.*, 2025, **147**, 10791–10802.
98 X. Wang, X.-J. Si, Y. Sun, Z. Wei, M. Xu, D. Yang, L. Shi, M.-P. Song and J.-L. Niu, C–N Axially Chiral Heterobiaryl Isoquinolinone Skeletons Construction via Cobalt-Catalyzed Atroposelective C–H Activation/Annulation, *Org. Lett.*, 2023, **25**, 6240–6245.
99 J. Wei, M. Zhu, B. Zhang, K. Li and X. Zhang, Recent advances in atroposelective synthesis of axially chiral heterobiaryl featuring indole frameworks, *Tetrahedron*, 2023, **149**, 133716.
100 T. Li, L. Shi, X. Zhao, J. Wang, X.-J. Si, D. Yang, M.-P. Song and J.-L. Niu, C–N Axially Chiral Heterobiaryl Skeletons Construction via Cobalt-Catalyzed Atroposelective Annulation, *Org. Lett.*, 2023, **25**, 5191–5196.
101 Y. Sun, T. Yang, Q. Wang, L. Shi, M.-P. Song and J.-L. Niu, Atroposelective N–N Axes Synthesis via Electrochemical Cobalt Catalysis, *Org. Lett.*, 2024, **26**, 5063–5068.
102 Z.-Q. Wang, L.-W. Wei, Z.-Q. Wang, Y.-J. Yang, Y. Zhao, S. Liu and Y. Huang, Modular synthesis of polyfunctionalized axial-chiral 2-arylpyridines via cobalt-catalyzed asymmetric [2 + 2 + 2] cycloaddition of diynes and nitriles, *Chin. Chem. Lett.*, 2026, **37**, 111377.
103 F. Fischer, A. F. Siegle, M. Checinski, C. Fischer, K. Kral, R. Thede, O. Trapp and M. Hapke, Synthesis of Naphthylpyridines from Unsymmetrical Naphthylheptadiynes and the Configurational Stability of the Biaryl Axis, *J. Org. Chem.*, 2016, **81**, 3087–3102.
104 B. Jiang, H. Wang, X. Sun, Y. Qiao, X. Xu and Z. Miao, Cobalt/Salox-Catalyzed Stereoselective C—H Functionalization: Enantioselective Construction of Axially Chiral Cyclic Phosphinamides with P-Stereogenic Center, *Adv. Synth. Catal.*, 2025, **367**, e202500021.
105 Z. Wang, Palladium-catalyzed asymmetric dearomative cyclization in natural product synthesis, *Org. Biomol. Chem.*, 2020, **18**, 4354–4370.
106 B.-B. Zhan, L. Jin and B.-F. Shi, Palladium-catalyzed enantioselective C–H functionalization via C–H palladation, *Trends Chem.*, 2022, **4**, 220–235.
107 S. Horiuchi and K. Umakoshi, Recent advances in pyrazolato-bridged homo- and heterometallic polynuclear platinum and palladium complexes, *Coord. Chem. Rev.*, 2023, **476**, 214924.
108 J. Zhang, Q. Xu, J. Fan, L. Zhou, N. Liu, L. Zhu, J. Wu and M. Xie, Pd(ii)-Catalyzed enantioconvergent twofold C–H annulation to access atropisomeric aldehydes: a platform for diversity-oriented-synthesis, *Org. Chem. Front.*, 2021, **8**, 3404–3412.
109 J. Gu, B. Hong, X. Xue, J. Xi and Z. Gu, Synthesis of Atropisomers with Biaryl and Vinylaryl Chirality via Pd-Catalyzed Point-to-Axial Chirality Transfer Ring-Opening Reaction, *Org. Lett.*, 2022, **24**, 9097–9101.
110 A. N. Reznikov, M. A. Ashatkina and Y. N. Klimochkin, Recent developments in asymmetric Heck type cyclization reactions for constructions of complex molecules, *Org. Biomol. Chem.*, 2021, **19**, 5673–5701.
111 Z. Wang, G. Fei, C. Xue and P. Xie, Recent advances in light-induced carbonylation utilizing carbon monoxide as a carbonyl source: Applications and prospective developments, *Mol. Catal.*, 2025, **574**, 114859.
112 H. Hu, Y. Peng, T. Yu, S. Cheng, S. Luo and Q. Zhu, Palladium-Catalyzed Enantioselective 7-exo-Trig Carbopalladation/Carbonylation: Cascade Reactions To Achieve Atropisomeric Dibenzo[b,d]azepin-6-ones, *Org. Lett.*, 2021, **23**, 3636–3640.

113 C. G. Newton, E. Braconi, J. Kuziola, M. D. Wodrich and N. Cramer, Axially Chiral Dibenzazepinones by a Palladium(0)-Catalyzed Atropo-enantioselective C–H Arylation, *Angew. Chem., Int. Ed.*, 2018, **57**, 11040–11044.
114 Y.-J. Wu, G. Liao and B.-F. Shi, Stereoselective construction of atropisomers featuring a C–N chiral axis, *Green Synth. Catal.*, 2022, **3**, 117–136.
115 Z.-S. Liu, P.-P. Xie, Y. Hua, C. Wu, Y. Ma, J. Chen, H.-G. Cheng, X. Hong and Q. Zhou, An axial-to-axial chirality transfer strategy for atroposelective construction of C–N axial chirality, *Chem*, 2021, **7**, 1917–1932.
116 T. Hirata, I. Takahashi, Y. Suzuki, H. Yoshida, H. Hasegawa and O. Kitagawa, Catalytic Enantioselective Synthesis of N-C Axially Chiral Phenanthridin-6-one Derivatives, *J. Org. Chem.*, 2016, **81**, 318–323.
117 C. He, M. Hou, Z. Zhu and Z. Gu, Enantioselective Synthesis of Indole-Based Biaryl Atropisomers via Palladium-Catalyzed Dynamic Kinetic Intramolecular C–H Cyclization, *ACS Catal.*, 2017, **7**, 5316–5320.
118 P. Zhang, Q. Xu, X.-M. Wang, J. Feng, C.-J. Lu, Y. Li and R.-R. Liu, Enantioselective Synthesis of N–N Bisindole Atropisomers, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212101.
119 J. Wang, D. Pan, F. Wang, S. Yu, G. Huang and X. Li, Pd-catalyzed asymmetric Larock reaction for the atroposelective synthesis of N—N chiral indoles, *Sci. Adv.*, 2024, **10**, eado4489.
120 N. Kotwal, Tamanna and P. ChauhanCatalytic asymmetric synthesis of medium-sized bridged biaryls, *Chem. Commun.*, 2022, **58**, 11031–11044.
121 C. Wu, Y. Jin, X. Zhang, R. Gao and X. Dou, Development of Configurationally Labile Biaryl Reagents for Atropisomer Synthesis, *Eur. J. Org. Chem.*, 2024, e202400402.
122 N. Kotwal and P. Chauhan, Evolution in the asymmetric synthesis of biaryl ethers and related atropisomers, *Chem. Commun.*, 2024, **60**, 6837–6846.
123 N. Kotwal, Tamanna and P. Chauhan, Catalytic asymmetric synthesis of medium-sized bridged biaryls, *Chem. Commun.*, 2022, **58**, 11031–11044.
124 X. Xue and Z. Gu, Synthesis of Bridged Biaryl Atropisomers via Sequential Cu- and Pd-Catalyzed Asymmetric Ring Opening and Cyclization, *Org. Lett.*, 2019, **21**, 3942–3945.
125 T. Shibata, T. Fujimoto, K. Yokota and K. Takagi, Iridium Complex-Catalyzed Highly Enantio- and Diastereoselective [2 + 2 + 2] Cycloaddition for the Synthesis of Axially Chiral Teraryl Compounds, *J. Am. Chem. Soc.*, 2004, **126**, 8382–8383.
126 T. Shibata, K. Tsuchikama and M. Otsuka, Enantioselective intramolecular [2 + 2 + 2] cycloaddition of triynes for the synthesis of atropisomeric chiral ortho-diarylbenzene derivatives, *Tetrahedron:Asymmetry*, 2006, **17**, 614–619.
127 J. Yang, Z.-Y. Xie, Y.-J. Ye, S.-B. Ye, Y.-B. Wang, W.-T. Wang, P.-C. Qian, R.-J. Song, Q. Sun, L.-W. Ye and L. Li, Ir/Zn-cocatalyzed chemo- and atroposelective [2 + 2 + 2] cycloaddition for construction of C—N axially chiral indoles and pyrroles, *Sci. Adv.*, 2023, **9**, eadk1704.
128 X. Zhang, S. Li, W. Yu, Y. Xie, C.-H. Tung and Z. Xu, Asymmetric Azide–Alkyne Cycloaddition with Ir(I)/Squaramide Cooperative Catalysis: Atroposelective Synthesis of Axially Chiral Aryltriazoles, *J. Am. Chem. Soc.*, 2022, **144**, 6200–6207.
129 J.-H. Peng, Y.-Q. Zheng, L.-G. Bai and W.-B. Liu, Chiral discrimination of small substituents in biaryl atropisomer construction: enantioselective synthesis of axially chiral 1-azafluorene via Ni-catalyzed [2 + 2 + 2] cycloaddition, *Sci. China:Chem.*, 2023, **66**, 3148–3153.
130 M.-H. Shen, A.-J. Wen, J.-W. Si, M.-L. Pu, Z. Xu, F. Ye, L. Li and L.-W. Xu, Enantioselective Synthesis of P/Si-Containing Non-Biaryl Atropisomers with Axial and Point Chirality by Ni-Catalyzed Silacycloaddition, *Chin. J. Chem.*, 2026, **44**, 225–233.
131 Z.-J. Fang, S.-C. Zheng, Z. Guo, J.-Y. Guo, B. Tan and X.-Y. Liu, Asymmetric Synthesis of Axially Chiral Isoquinolones: Nickel-Catalyzed Denitrogenative Transannulation, *Angew. Chem., Int. Ed.*, 2015, **54**, 9528–9532.
132 F.-B. Ge, C.-J. Lu, X. Chen, W. Yao, M. An, Y.-K. Jiang, L.-P. Xu and R.-R. Liu, Enantioselective Nickel-Catalyzed Denitrogenative Transannulation En Route to N–N Atropisomers, *Angew. Chem., Int. Ed.*, 2024, **63**, e202400441.
133 Y. Mao, W. Hu and C. Wang, Nickel-Catalyzed Atroposelective Reductive [2 + 4] Annulation toward Synthesis of Axially Chiral Biaryls, *ACS Catal.*, 2024, **14**, 17039–17045.
134 J. He, Z. Yang, L. Lin and X. Feng, Enantioselective synthesis of C–C and C–N axially chiral pyrazole-based heterobiaryls, *Chem. Sci.*, 2025, **16**, 20021–20029.
135 Y.-B. Du, Q.-T. Lu, Y.-S. Cui, K.-W. Wu, Y. Wang, Y.-Z. Zhang, Z. Zhao, J.-L. Hou and Q. Cai, Enantioselective Synthesis of Atropisomeric Tri-Axis Naphthalenes via Diels–Alder Reaction and Dehydrative Aromatization of Isobenzofurans, *Angew. Chem., Int. Ed.*, 2025, **64**, e202421060.
136 M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron and J. Zhu, To each his own: isonitriles for all flavors. Functionalized isocyanides as valuable tools in organic synthesis, *Chem. Soc. Rev.*, 2017, **46**, 1295–1357.
137 L. Qian, L.-F. Tao, W.-T. Wang, E. Jameel, Z.-H. Luo, T. Zhang, Y. Zhao and J.-Y. Liao, Catalytic Atroposelective Dynamic Kinetic Resolution of Biaryl Lactones with Activated Isocyanides, *Org. Lett.*, 2021, **23**, 5086–5091.
138 S.-C. Zheng, Q. Wang and J. Zhu, Catalytic Atropenantioselective Heteroannulation between Isocyanoacetates and Alkynyl Ketones: Synthesis of Enantioenriched Axially Chiral 3-Arylpyrroles, *Angew. Chem., Int. Ed.*, 2019, **58**, 1494–1498.
139 X.-L. He, H.-R. Zhao, X. Song, B. Jiang, W. Du and Y.-C. Chen, Asymmetric Barton–Zard Reaction To Access

3-Pyrrole-Containing Axially Chiral Skeletons, *ACS Catal.*, 2019, **9**, 4374–4381.

140 Q. Gaignard-Gaillard, X. Han, A. Alix, C. Bour, R. Guillot, V. Gandon and A. Voituriez, Atroposelective Synthesis of Tetrahydropyrrolo[3,2-c]azepine Derivatives Through Gold (I)-Catalyzed Hydroarylation, *Adv. Synth. Catal.*, 2022, **364**, 4415–4420.

141 R. Guo, K.-N. Li, B. Liu, H.-J. Zhu, Y.-M. Fan and L.-Z. Gong, Asymmetric synthesis of heteroaryl atropisomers via a gold-catalyzed cycloisomerization–amination cascade reaction, *Chem. Commun.*, 2014, **50**, 5451–5454.

142 Y.-B. Wang, W. Liu, T. Li, Y. Lu, Y.-T. Yu, H.-T. Liu, M. Liu, P. Li, P.-C. Qian, H. Tang, J. Guan, L.-W. Ye and L. Li, Gold/HNTf2-Cocatalyzed Asymmetric Annulation of Diazo-Alkynes: Divergent Construction of Atropisomeric Biaryls and Arylquinones, *J. Am. Chem. Soc.*, 2024, **146**, 33804–33816.