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Recent advances in the construction of axially chiral arylpyrroles

Yang-Bo Chen[1], Ye-Nan Yang[1], Xuan-Zhu Huo[1], Long-Wu Ye[1,2] & Bo Zhou[1*]

[1]*Key Laboratory of Chemical Biology of Fujian Province, State Key Laboratory of Physical Chemistry of Solid Surfaces, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, China;*
[2]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

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Catalytic enantioselective preparation of axially chiral molecules has gained considerable interest over the past decades, due to their numerous applications in bioactive molecules, natural products, pharmaceuticals, materials, ligands, and catalysts. Compared with the well-established synthetic approaches for six-membered axially chiral skeletons, methodologies directed towards five-membered axially chiral compounds are relatively rare. Among these, axially chiral arylpyrroles are especially important structural motifs with wide utility, and the atroposelective synthesis of them is highly desirable. In recent years, novel strategies have been developed based on transition-metal catalysis and organocatalysis. This review summarizes the recent achievements in atroposelective preparation of arylpyrroles, by emphasizing the synthetic methods for each axially chiral framework, reaction mechanisms, and applications.

axial chirality, pyrrole atropisomers, transition-metal catalysis, organocatalysis

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1 Introduction

Axial chirality, one of the most important properties of organic molecules [1–8], ubiquitously exists in bioactive molecules, natural products, pharmaceuticals and materials, such as vancomycin, michellamine A, mastigophorene, marinopyrrole, steganacin, and eupolyphagin [9–16]. On the other hand, axially chiral compounds are frequently found in chiral ligands and catalysts, such as BINOL, BINAP, SEGPHOS, and chiral phosphoric acids (CPAs), which demonstrate remarkable efficiency in asymmetric synthesis (Figure 1) [17–20]. During the past decades, numerous synthetic strategies have been established for the atroposelective synthesis of axially chiral biaryls, especially for 6-membered biaryl skeletons. Efficient enantioselective transformations, including *de novo* synthesis of arenes [21–23], desymmetrization and kinetic resolution of biaryls [24–34], central to axial chirality transfer [35,36], cross-coupling and Michael addition reactions [37–41], as well as ring-opening reactions [42,43], were developed to construct axially chiral biaryls. In contrast, methodologies for the construction of 5-membered biaryls were less explored [44–47], because of the decreased rotational barrier and configurational stability arising from the increased distance between two aryl substituents (Figure 2) [48].

Pyrrole moiety is among the fundamental building blocks in organic synthesis [49–52], which appears frequently in natural products and pharmaceuticals [53–55]. Among these, axially chiral arylpyrroles are unique structural motifs with important biological applications (Figure 3) [56–58]. For instance, rhazinilam is an important family of natural products with unique venom for the mitotic spindle with high *in vitro* cytotoxic activity [59], and marinopyrrole shows potent antibiotic activity against methicillin-resistant *Sta-*

*Corresponding author (email: zhoubo@xmu.edu.cn)

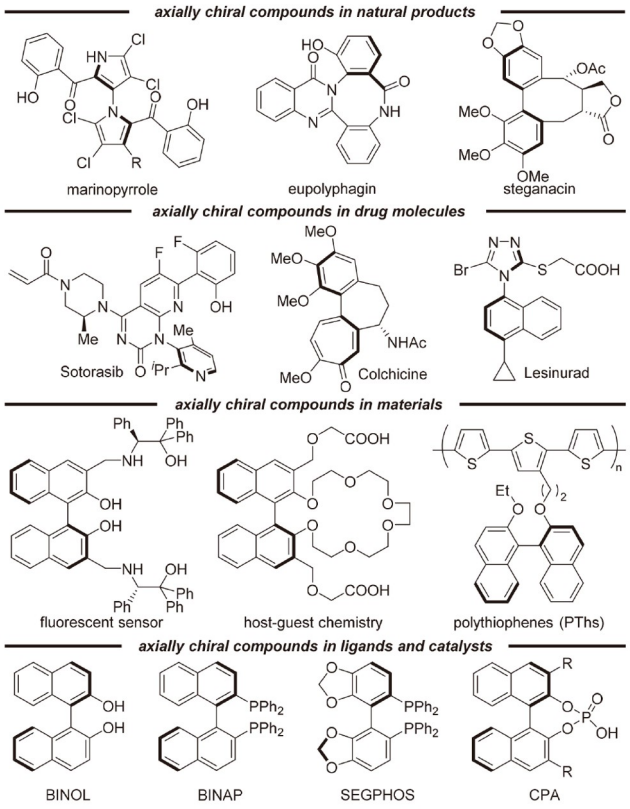


Figure 1 Axially chiral compounds in natural products, drug molecules, materials, ligands, and catalysts.

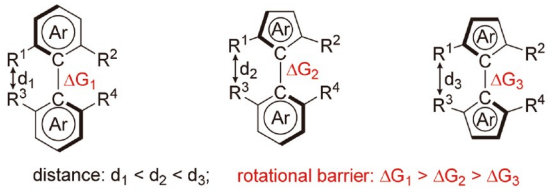


Figure 2 Comparison of the rotational barriers of different biaryls bearing C–C axis (color online).

phylococcus aureus [60]. In recent years, considerable efforts have been devoted to the assembly of optically pure arylpyrroles. Elegant transition metal catalyzed and organocatalytic methods were developed based on different precursors, including *de novo* synthesis of pyrroles, kinetic resolution of racemic arylpyrroles, and desymmetrization of prochiral arylpyrroles (Figure 4).

This review intends to provide a systematic summary of the latest trends and developments for the preparation of axially chiral arylpyrroles by presenting their product diversity, selectivity, and mechanistic rationale. The content is organized based on different reaction categories directed towards axial chirality. In each section, reactions are then displayed according to the different types of catalysts. We believe this review will provide a quick entry to this rapidly expanding area and will promote the further developments in chiral heterocycle synthesis and axial chirality chemistry.

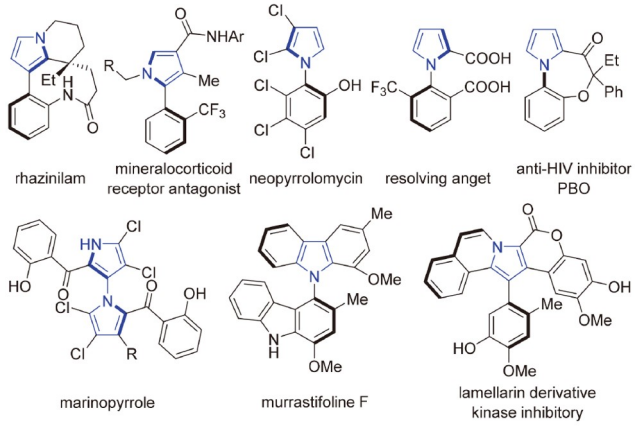


Figure 3 Axially chiral arylpyrroles in natural products, bioactive molecules, and pharmaceuticals (color online).

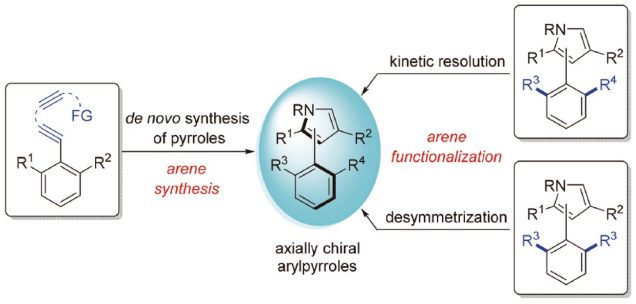
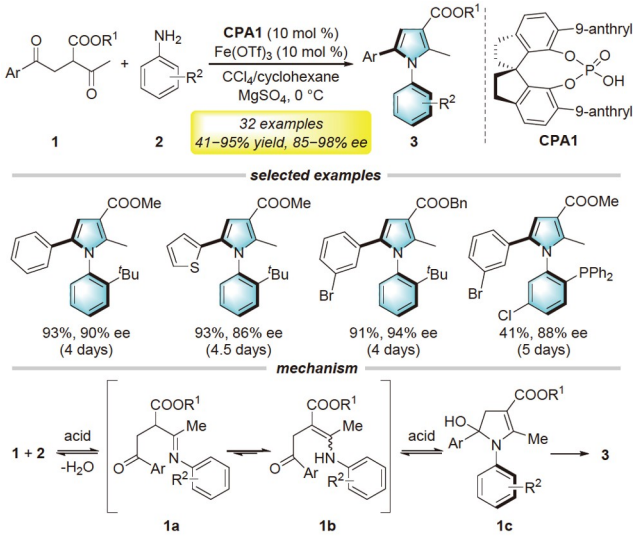


Figure 4 Synthetic strategies for the construction of axially chiral arylpyrroles (color online).

2 *De novo* synthesis of pyrroles

De novo synthesis of pyrroles is a straightforward pathway for the enantioselective preparation of axially chiral arylpyrroles, which has received increasing attention due to the high bond-forming efficiency and atom economy involved in this method. Divergent catalytic systems, especially organocatalytic approaches, have been discovered to prepare arylpyrrole frameworks from simple starting materials through atroposelective cyclization reactions.

Paal-Knorr reaction is one of the most common protocols for the synthesis of pyrroles [61,62], which becomes a potential pathway for the enantioselective assembly of arylpyrroles. However, the asymmetric versions were rarely explored. In 2017, Tan and co-workers [63] reported the first asymmetric Paal-Knorr reaction to construct arylpyrrole atropisomers bearing C–N axis. As shown in Scheme 1, the reaction of 1,4-diketones **1** and anilines **2** under the promotion of chiral phosphoric acid (CPA) catalyst delivered various axially chiral arylpyrroles **3** in good yields (up to 95% yield) with good to excellent enantioselectivities (up to 98% ee). In particular, the phosphine-tethered aniline also reacted smoothly to give the axially chiral phosphine product in 41%

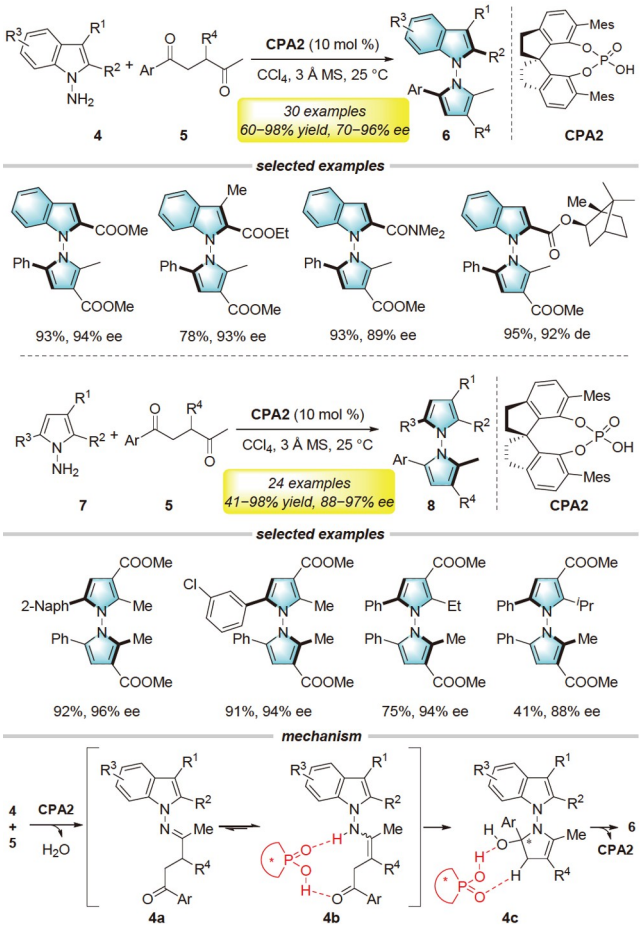


Scheme 1 Atroposelective synthesis of arylpyrroles bearing chiral C–N axis *via* Paal-Knorr reaction (color online).

yield with 88% ee. The plausible mechanism was proposed based on control experiments. The reaction starts with the condensation of ketone **1** with aniline **2**, followed by imine-enamine isomerization to give the enamine intermediate **1b**. Then an acid-catalyzed dehydrative cyclization takes place to produce the desired product **3**, which is considered as the enantio-determining step. Notably, the ester group on 1,4-diketones **1** was found to be essential for the stereoinduction.

By employing the CPA catalyzed Paal-Knorr reaction between *N*-aminoindoles **4** and 1,4-diketones **5**, Shi and co-workers [64] recently disclosed another approach for the formation of N–N axially chiral indolyl pyrroles **6** (Scheme 2). In addition, the switch of *N*-aminoindoles to *N*-aminopyrroles enabled the atroposelective synthesis of N–N axially chiral bispyrroles **8** in good to excellent yields with high enantioselectivities. This transformation represents the first atroposelective construction of N–N axially chiral arylpyrrole scaffolds. Importantly, the synthesized N–N axially chiral arylpyrroles could be transformed into chiral organocatalysts, which were utilized in asymmetric catalysis. Similar with Tan's work [63], the reaction undergoes a typical Paal-Knorr mechanism. Furthermore, the origin of enantioselectivity could be attributed to the hydrogen-bonding effects between CPA catalyst and enamine intermediate **4b** in the dehydrative cyclization process. Preliminary biological studies indicated that these axially chiral arylpyrroles demonstrate potential bioactivities.

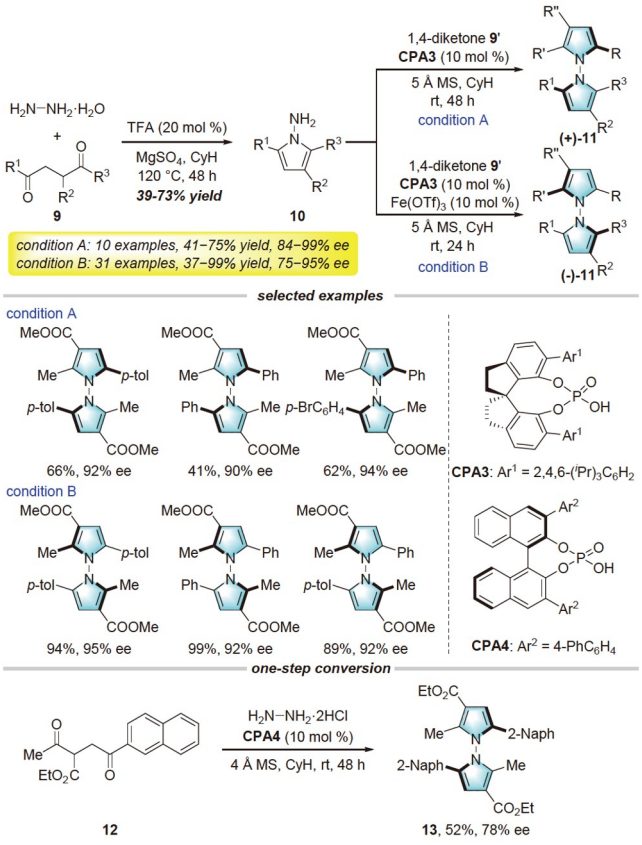
Simultaneously, Zhao and co-workers [65] reported a CPA catalyzed asymmetric double Paal-Knorr reaction, for the atroposelective synthesis of axially chiral bispyrroles **11** (Scheme 3). Starting from simple hydrazine and 1,4-diketones **9**, a wide range of C_2- and C_1-symmetric 1,1′-bipyrroles could be obtained in generally good yields with good to excellent enantioselectivities. It is worth noting that



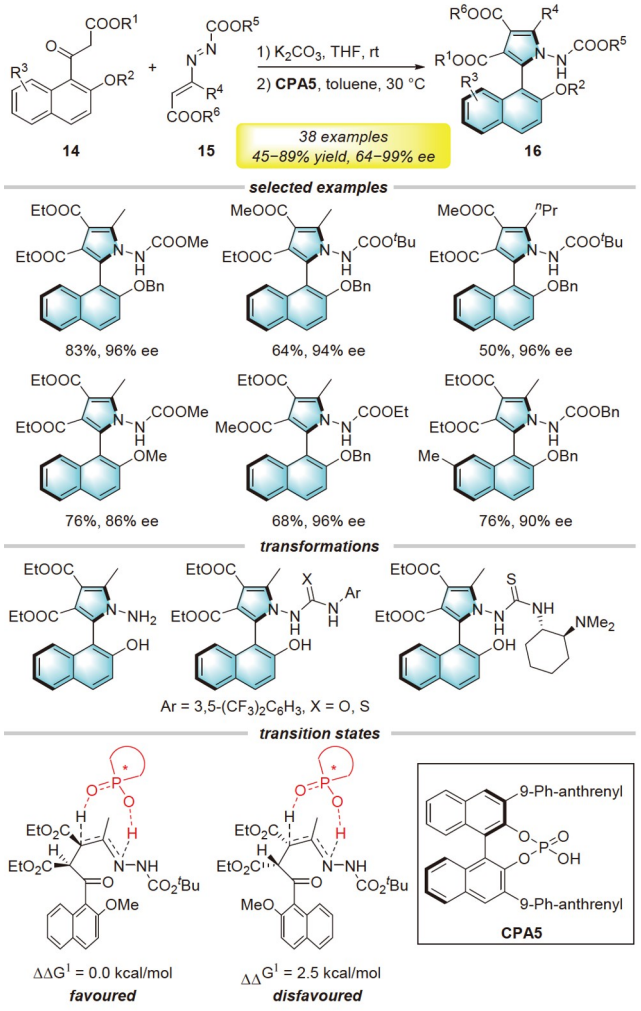
Scheme 2 Atroposelective synthesis of arylpyrroles bearing chiral N–N axis *via* Paal-Knorr reaction (color online).

the enantiodivergent bispyrrole synthesis could be realized by cooperative catalysis of Lewis acid and CPA catalysts. The detailed mechanism for the intriguing $Fe(OTf)_3$-induced enantiodivergence is still unclear. The attempt to achieve the one-step conversion of hydrazine HCl salt and 1,4-diketone **12** to the axially chiral bispyrrole **13** was also successful, although decreased enantioselectivity was observed (52% yield, 78% ee). This methodology provides an efficient pathway for the construction of axially chiral arylpyrroles from readily available hydrazine and 1,4-diones.

Apart from Paal-Knorr reaction, the asymmetric Attanasi reaction has also been explored for the preparation of pyrryl atropisomers. In 2022, Mei and co-workers [66] reported a CPA catalyzed Attanasi reaction between 1,3-dicarbonyl compounds **14** and azoalkenes **15**, affording a wide range of 1-(1-aminopyrrol-2-yl)naphthalen-2-ols (NPNOLs) **16** in mostly good yields with excellent ee (Scheme 4). Benefiting from the unique properties of NPNOLs, these axially chiral arylpyrroles could be easily transformed into various frameworks, which are potentially applicable for the development of chiral ligands and catalysts. The authors also carried out density functional theory (DFT) calculations to probe the



Scheme 3 Atroposelective synthesis of bispyrroles bearing chiral N–N axis *via* Paal-Knorr reaction (color online).

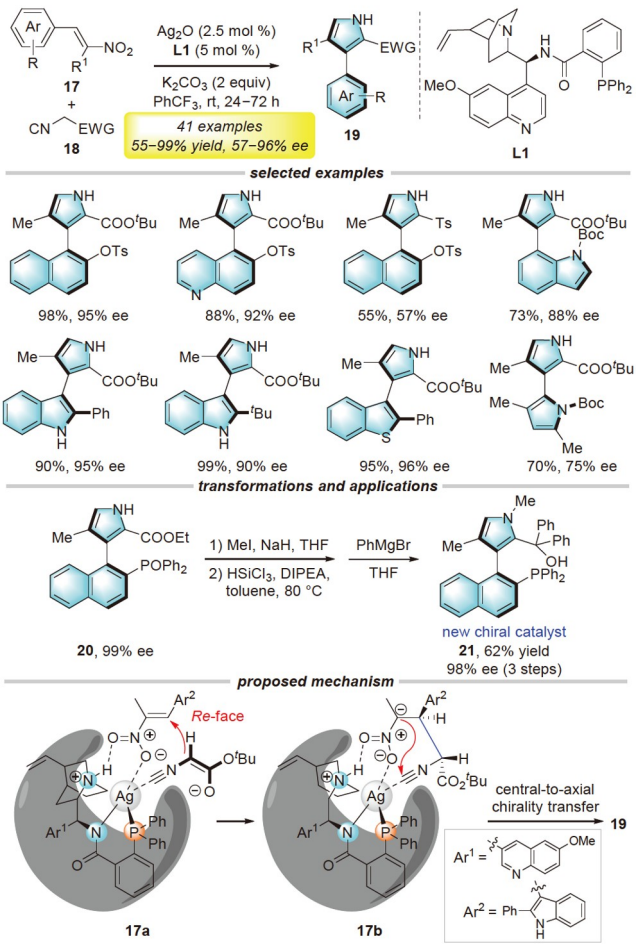


Scheme 4 Atroposelective synthesis of arylpyrroles bearing chiral C–C axis *via* Attanasi reaction (color online).

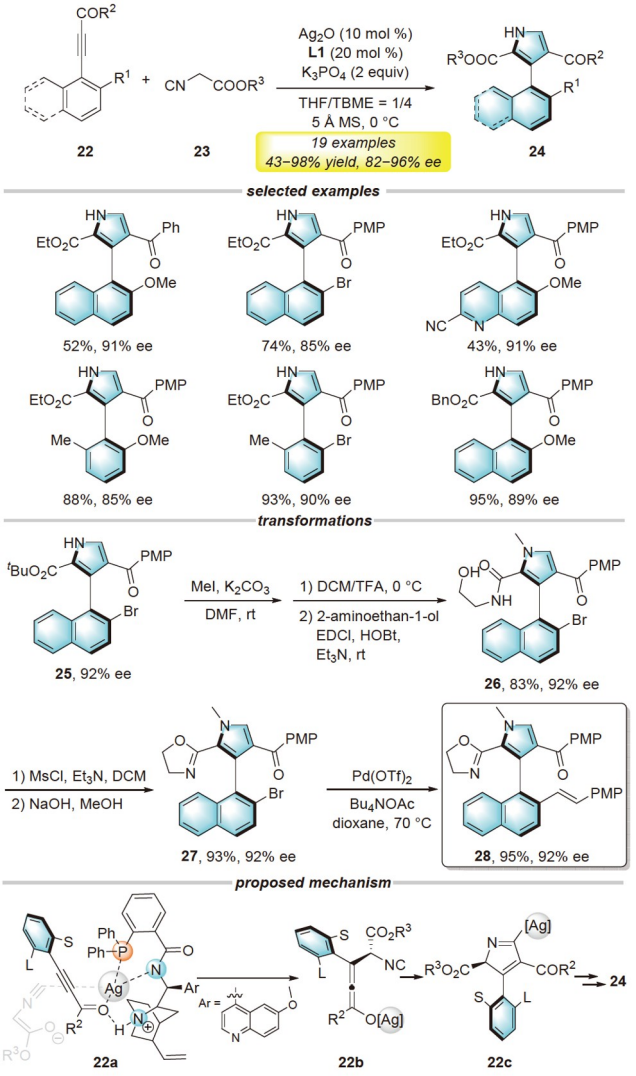
reaction mechanism. After the formation of hydrazonic intermediates from the base-mediated 1,4-addition of 1,3-dicarbonyl compound **14** to azoalkene **15**, hydrazine-enamine isomerization and CPA-assisted dehydrative cyclization occurs to form desired product **16**. The origin of enantioselectivity in the cyclization step could be explained by the difference in free energies for CPA-bonded transition states (2.5 kcal/mol), which resulted from steric repulsion. These CPA catalyzed approaches provide a versatile entry to axially chiral arylpyrroles.

In addition to the above chiral Brønsted acid catalyzed reactions, transition-metal catalysis and other organocatalysis have also been successfully developed for the atroposelective synthesis of arylpyrroles. In 2019, Chen and co-workers [67] discovered an asymmetric Barton-Zard reaction under the Ag_2O/quinine-derived aminophosphine catalytic system (Scheme 5). The reaction of α-substituted nitroolefins **17** and α-isocyano substrates **18** led to a range of 3-arylpyrroles **19** bearing chiral C–C axis. Various α-substituted nitroolefins **17** containing different arenes, including naphthalene, quinoline, indole, pyrrole, and benzothiophene reacted well to give desired products in generally good yields with good enantioselectivities. The synthesized axially chiral phosphine oxide could undergo methylation, reduction, and nucleophilic addition to afford a new organocatalyst **21**. This catalyst has been applied to the formal (4+2) cycloaddition of electron-deficient alkene and 2,2′-dienone to afford a chiral spiro-oxindole product in moderate yield with good enantioselectivity. In their proposed mechanism, the enantioselective Michael addition takes place preferentially from the *Re*-face due to the enantiocontrol of chiral sliver complex. Then the central-to-axial chirality transfer is responsible for the generation of axially chiral product **19**.

After switching nitroolefins to electron-deficient alkynes, Zhu and co-workers [68] reported another heteroannulation sequence for the assembly of axially chiral 3-arylpyrroles. As depicted in Scheme 6, the reaction of α-aryl-α,β-alkynicketones **22** with α-isocyanoacetates **23** in the presence of chiral silver catalyst delivered chiral 3-arylpyrroles **24** in moderate to good yields with generally good enantioselectivities. To show the utility of the reaction, some transformations of the obtained axially chiral skeleton were carried out. After derivatizations based on the bromide and ester



Scheme 5 Atroposelective synthesis of 3-arylpyrroles bearing chiral C–C axis *via* Barton-Zard reaction (color online).



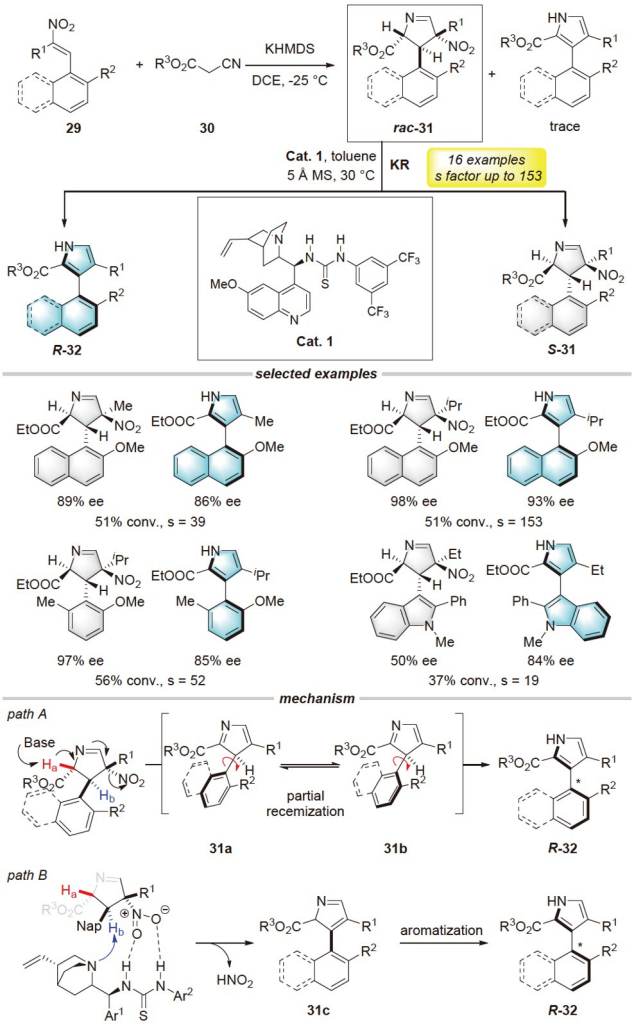
Scheme 6 Atroposelective synthesis of 3-arylpyrroles bearing chiral C–C axis *via* heteroannulation (color online)

moieties on the product, a chiral olefin-oxazole derivative **28** was synthesized in six steps, which may be useful in asymmetric catalysis [69]. Notably, no erosion of enantioselectivity was observed in these transformations. Similar with Chen's work [67], the coordination between phosphine ligand **L1**, sliver catalyst, and substrate provides a suitable chiral environment for the enantioinduction.

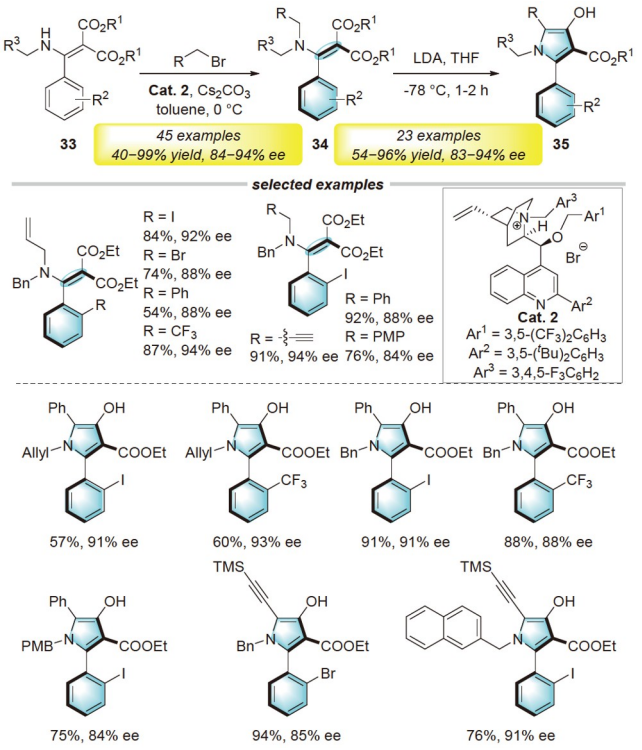
Besides, Zhu and co-workers [70] disclosed a stepwise protocol for the atroposelective construction of arylpyrroles *via* the Barton-Zard reaction. As illustrated in Scheme 7, they synthesized racemic 3,4-dihydro-2*H*-pyrroles **31** in high diastereoselectivity through the KHMDS promoted Barton-Zard reaction under low temperature. Subsequently, the obtained racemic Barton-Zard intermediates **31** were treated with quinine-derived thiourea **Cat. 1**, delivering the desired axially chiral arylpyrroles ***R*-32** with enantioenriched 3,4-dihydro-2*H*-pyrroles ***S*-31** *via* kinetic resolution. The enantioselective aromatization demonstrated high selectivity, and the highest selectivity factor (*s* factor) is 153.

According to the experimental observations, the authors proposed two different reaction pathways for the atroposelective aromatization step (Scheme 7). In path A, the reaction begins with the deprotonation of 3,4-dihydro-2*H*-pyrrole **31**, and subsequent elimination of NO_2 affords the aromatization product ***R*-32**. However, the rotation of the C(sp^3)–C(sp^2) bond of 3*H*-pyrrole intermediate **31a** is unavoidable under specific conditions, leading to the partial racemization of product. Alternatively, the mechanism involving a bifunctional catalysis was proposed in path B. The hydrogen bonding between thiourea and the nitro group would shorten the distance between the tertiary amine and C–H_b bonds. Therefore, a formal *syn*-elimination of HNO_2 takes place and affords the axially chiral 2*H*-pyrrole intermediate **31c**. Finally, the desired product ***R*-32** could be generated *via* aromatization. Although high enantioselectivities obtained in most examples, the stepwise procedure limited further applications of this method.

In 2019, another type of stepwise protocol was achieved by



Scheme 7 Atroposelective synthesis of 3-arylpyrroles bearing chiral C–C axis *via* kinetic resolution (color online).

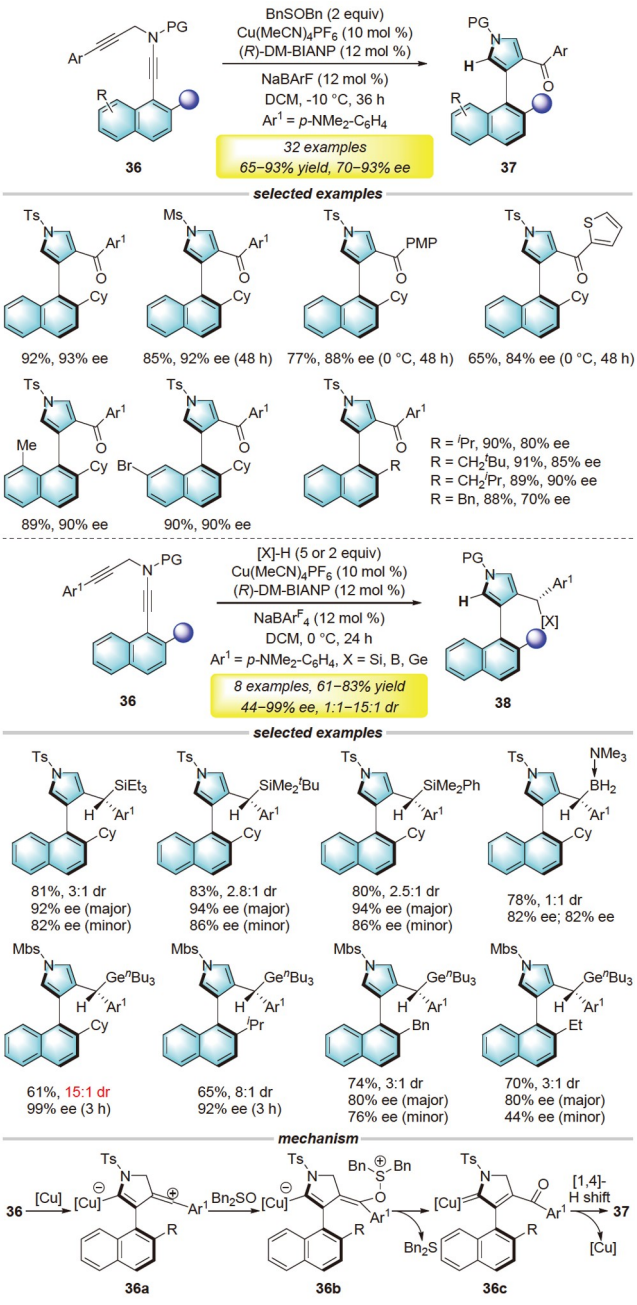


Scheme 8 Atroposelective synthesis of 2-arylpyrroles bearing chiral C–C axis *via* chirality transfer (color online).

Tan and co-workers [71] to synthesize arylpyrrole frameworks. As shown in Scheme 8, *N*-alkylation of multi-substituted enamines **33** was conducted in the presence of cinchonine-derived organocatalyst **Cat. 2** to give axially chiral alkenes **34** in moderate to good yields with good to excellent enantioselectivities. Further LDA-promoted cyclization of alkenes **34** furnished the desired chiral 2-arylpyrroles **35** in 54%–96% yields and 83%–94% ee. Notably, the enantiopurity could be well maintained under strong basic condition in the cyclization step. The reaction has a broad substrate scope, and various alkylation reagents, including allyl bromide, benzyl bromide, propargyl bromide, and their derivatives, can be well tolerated in this reaction. This strategy provides a versatile approach towards two different axially chiral skeletons.

During the past several years, Ye and co-workers [72] developed a facile diyne cyclization strategy *via* vinyl cation intermediates, enabling the synthesis of divergent chiral pyrroles through the remote control of enantioselectivity [73–79]. On the basis of their previous findings, the same group successfully discovered a copper-catalyzed atroposelective diyne cyclization/oxidation and X–H insertion sequence by introducing bulky naphthyl groups onto diynes [80]. As shown in Scheme 9, the reaction of diynes **36** in the presence of $Cu(MeCN)_4PF_6$/(*R*)-DM-BINAP catalyst and oxidant (BnSOBn) afforded axially chiral naphthylpyrroles **37** in moderate to excellent yields with moderate to excellent enantioselectivities. Alternatively, a series of X–H insertion reactions could also be achieved by employing this atroposelective diyne cyclization strategy. The diyne cyclization/X–H insertion cascade demonstrated broad substrate scope for hydrosilanes, trimethylamine-borane adduct and hydrogermane. It should be pointed out that, the diastereoselectivity of product **38** could be greatly improved by increasing the radius of inserted atom.

DFT calculations have been conducted to probe the reaction mechanism. After the coordination of Cu(I) complex with diyne **36**, the enantio-determining cyclization takes place quickly to generate axially chiral vinyl cation intermediate **36a**. Then, nucleophilic addition of BnSOBn onto the vinyl cation leads to intermediate **36b**. Finally, S–O bond cleavage and formal [1,4]-H migration occurs to give desired product **37**. Benefit from the high efficiency and convenient enantiocontrol, this diyne cyclization strategy provides a general route to axially chiral skeletons.



Scheme 9 Atroposelective synthesis of 3-arylpyrroles bearing chiral C–C axis *via* diyne cyclization (color online).

3 Desymmetrization and kinetic resolution of arylpyrroles

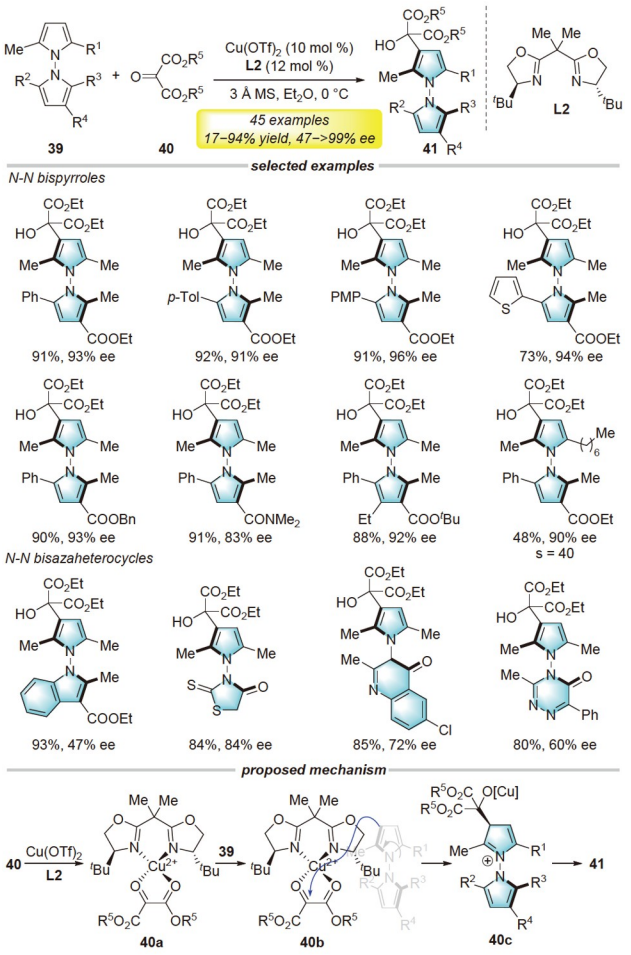
Enantioselective functionalization of prochiral or racemic biaryls through desymmetrization or kinetic resolution of arylpyrroles is another strategy for the construction of axially chiral biaryls. Taking advantage of the nucleophilicity of pyrrole moiety and the easily convertible aryl C–H bond, a series of transition-metal catalyzed and organocatalytic transformations were recently disclosed to achieve the atroposelective synthesis of arylpyrroles.

3.1 Transition-metal catalyzed transformations

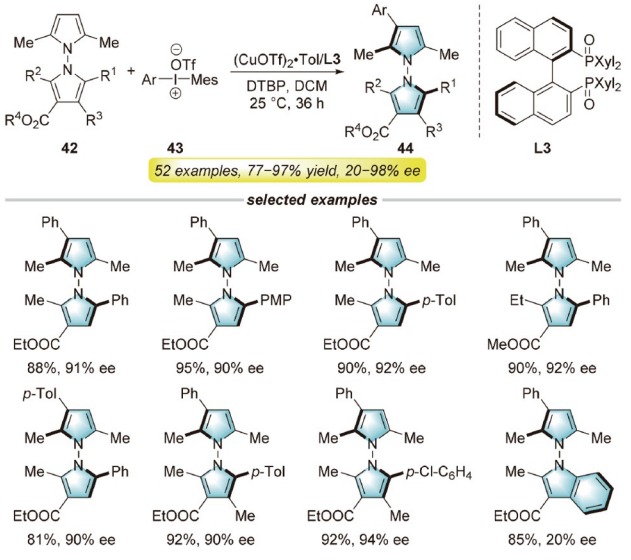
Prochiral bipyrroles are competent nucleophiles in various transition-metal catalyzed reactions, and the enantiocontrol could be obtained by using chiral metal complexes. Recently, Liu and co-workers reported a chiral copper-catalyzed Friedel-Crafts alkylation of prochiral bipyrroles **39** with ketomalonates **40**, enabling the facile synthesis of axially chiral bispyrroles **41** through a desymmetrization manner (Scheme 10) [81]. A range of prochiral bispyrroles, including different substituents on the *para* or *meta* position of the aromatic ring, different types of ester groups and amides, were well tolerated in this reaction. Moreover, racemic bispyrroles with two different substituents on the pyrrole ring could be kinetically resolved with good *s* factors. Furthermore, substrates containing other azaheterocycles, such as indole, 2-thioxo-3λ2-thiazolidin-4-one, pyrimidin-4(3*H*)-one, and 1,2,4-triazin-5(4*H*)-one, worked well to produce the desired axially chiral pyrroles with partially decreased enantioselectivities. The proposed mechanism shows that the copper-BOX complex first coordinates with ketomalonate **40** to form a square-planar Cu(II) complex **40a**, which allows the further enantiocontrol. Then, the nucleophilic attack of pyrrole moiety onto the coordinated ketomalonate species **40a** occurs to generate the carbenium intermediate **40c**. Finally, the desired product **41** is dissociated from intermediate **40c**, with the regeneration of chiral copper catalyst.

Apart from asymmetric alkylation, Liu and co-workers [82] further developed a copper-catalyzed asymmetric arylation of pyrroles to construct axially chiral bispyrroles **44** through desymmetrization process. As shown in Scheme 11, various prochiral bispyrroles **42** and diaryliodonium salts **43** bearing different substituents reacted well in the presence of $(CuOTf)_2 \cdot Tol$ and phosphine bioxide ligand. The reaction demonstrated high enantioselectivity and good scalability. Further investigation into iterative arylations shows the potential utility of the transformation.

By employing the nucleophilicity of pyrroles, Meggers and co-workers [83] reported a unique bis-cyclometalated rhodium-catalyzed C–H alkylation of arylpyrroles (Scheme 12). The reaction of configurationally fluxional *N*-arylpyrroles **45** with *N*-acryloyl-1*H*-pyrazole led to configurationally stable axially chiral *N*-arylpyrroles **46** in generally excellent enantioselectivities through dynamic kinetic resolution. A range of *N*-arylpyrroles with different substituents on aromatic ring reacted smoothly to produce axially chiral pyrroles **46** in moderate to good yields with excellent ee. Phenyl-substituted *N*-acryloyl-1*H*-pyrazole is also a suitable substrate in the reaction, and the desired product was obtained with excellent diastereoselectivity and enantioselectivity. The obtained product could undergo a series of transformations, including nucleophilic substitution, reduction, palladium-catalyzed C–P coupling, and

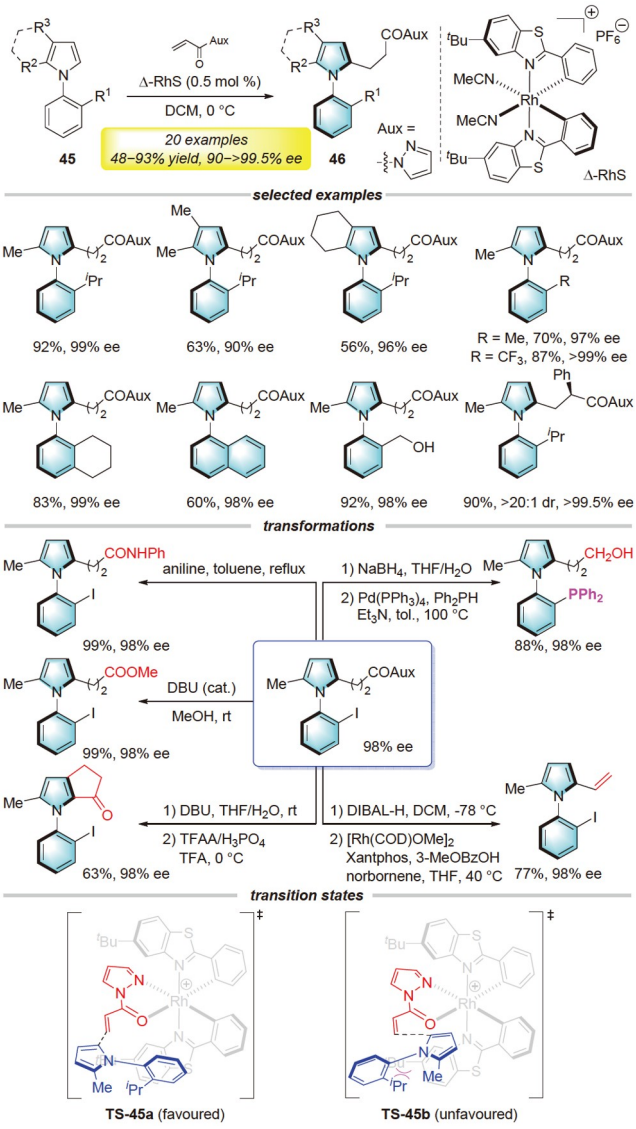


Scheme 10 Atroposelective synthesis of bispyrroles bearing chiral N–N axis *via* Friedel-Crafts alkylation (color online).



Scheme 11 Atroposelective synthesis of bispyrroles bearing chiral N–N axis *via* arylation (color online).

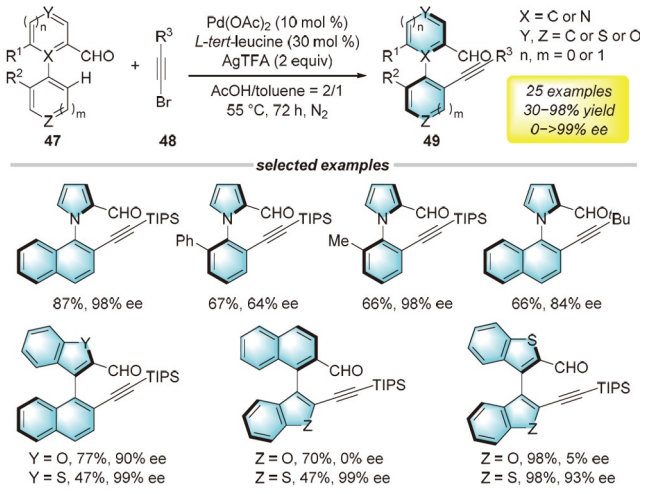
reduction/dehydroformylation. Therefore, the alkylated axially chiral arylpyrroles are important building blocks to-



Scheme 12 Atroposelective synthesis of *N*-arylpyrroles bearing chiral C–N axis *via* alkylation (color online).

wards structurally diverse *N*-arylpyrroles by versatile transformations of acylpyrazole moiety. In their proposed transition states based on DFT calculations, the repulsion between the substituent R^1 on *N*-arylpyrrole and the *tert*-butyl group on chiral ligand is the key for enantiocontrol.

In addition to the above asymmetric nucleophilic addition type of reactions, transition-metal catalyzed C–H functionalization has also been developed as an efficient protocol to access axially chiral arylpyrroles. In 2019, Shi and coworkers [48] achieved a Pd-catalyzed asymmetric C–H alkynylation strategy when an aldehyde moiety was preinstalled to react with transient directing group (TDG). As shown in Scheme 13, racemic biaryls **47** and alkynyl bromides **48** were selected as substrates, and the palladium/L-*tert*-leucine catalyzed dynamic kinetic resolution proceeded well to give alkynylated biaryls **49** in good yields with

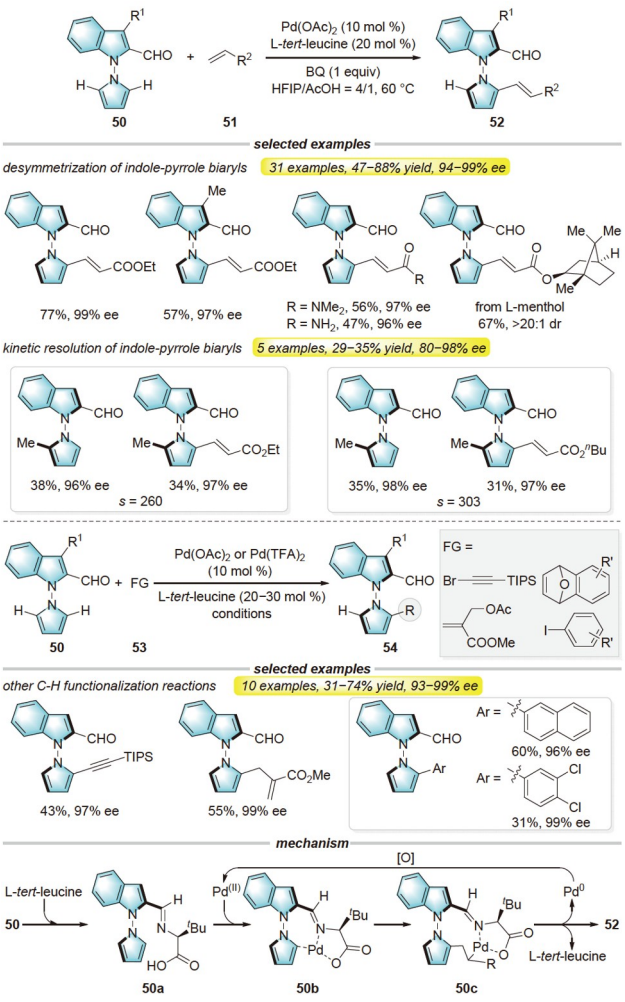


Scheme 13 Atroposelective synthesis of arylpyrroles bearing chiral C–N axis *via* C–H functionalization (color online).

excellent enantioselectivities. Various five-membered heteroarenes, including pyrroles, thiophenes, benzothiophenes, and benzofurans, were competent in this reaction, delivering a range of axially chiral skeletons.

By using above TDG strategy, Liu and co-workers [84] discovered another Pd-catalyzed C–H functionalization of pyrroles for the atroposelective synthesis of indolylpyrroles bearing N–N axis. After extensive screening of different amino acids, they found L-*tert*-leucine to be a suitable TDG in this transformation. As shown in Scheme 14, the C–H olefination reaction of indolylpyrroles **50** with olefins **51** proceeded smoothly to give pyrrole atropisomers **52** efficiently through desymmetrization or kinetic resolution method. Moreover, the reaction was also extended to other coupling partners **53**, including alkynyl bromides, allylic esters, 7-oxabenzonorbornadienes and aryl iodides, delivering various functionalized axially chiral arylpyrroles **54** in moderate to good yields with excellent ee. In their proposed mechanism, indolylpyrrole **50** first condenses with L-*tert*-leucine to generate imine **50a**, which would coordinate with Pd(II) catalyst. Then, C–H activation takes place on the pyrrole ring to give Pd(II) metallacycle **50b**, which facilitates following migratory insertion, β-H elimination and hydrolysis to produce desired product **52**. Notably, most of the axially chiral indolylpyrroles could be synthesized in excellent enantioselectivities.

Very recently, You and co-workers [85] developed an iridium(I) catalytic system to achieve the highly enantioselective C–H alkylation of arylpyrroles. As illustrated in Scheme 15, arylpyrroles **55** reacted efficiently with acrylates **56** to forge alkylated axially chiral product **57** in the presence of $[Ir(cod)Cl]_2$/(*R*)-DM-BINAP catalyst. It is worth mentioning that, acrylates bearing relatively complex structures, such as *L*-menthol, (−)-borneol, *D*-ribofuranoside, testosterone, estrone and ergosterol, were well tolerated in

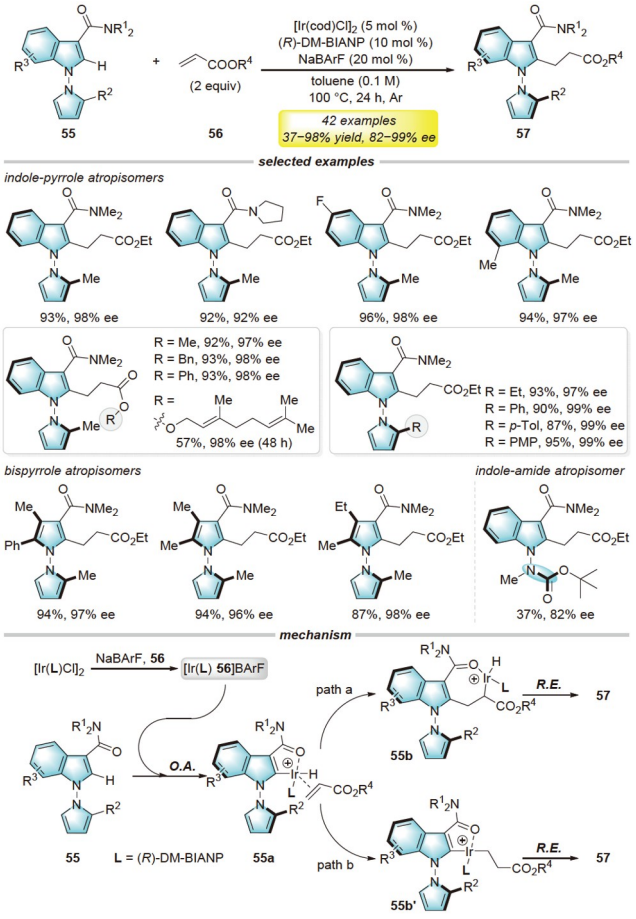


Scheme 14 Atroposelective synthesis of indolylpyrroles bearing chiral N–N axis *via* C–H functionalization (color online).

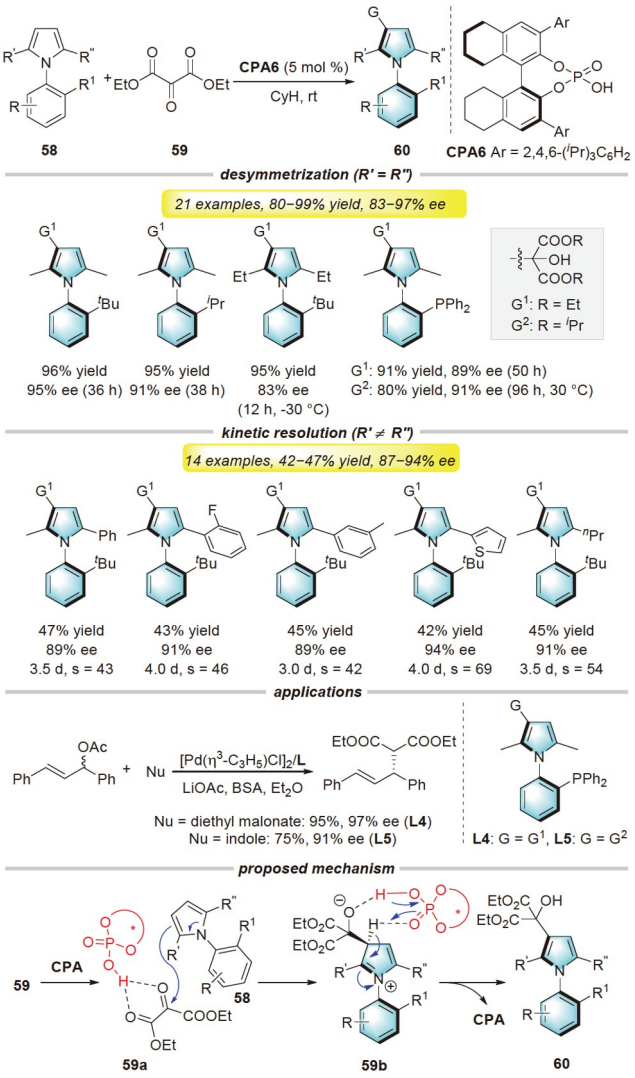
this oxidant-free protocol. Deuterium labeling experiments have been performed to explore the reaction mechanism. As proposed in Scheme 15, the reaction starts with the coordination of substrates with Ir(I) catalyst and carbonyl group-directed oxidative addition to give Ir(III)–H intermediate **55a**. Next, migratory insertion of acrylate into Ir(III)–C bond or Ir(III)–H bond takes place, followed by reductive elimination to produce the desired arylpyrrole **57**. Importantly, the constructed axially chiral arylpyrroles containing chiral N–N axis demonstrated high rotational barriers and good configurational stability.

3.2 Organocatalytic transformations

Compared with transition-metal catalysis, the organocatalytic approaches are more challenging and have been relatively less studied. In 2019, Tan's group [86] reported a highly efficient organocatalytic strategy to synthesize enantioenriched axially chiral arylpyrroles by using atroposelective desymmetrization and kinetic resolution. As shown in



Scheme 15 Atroposelective synthesis of arylpyrroles bearing chiral N–N axis *via* C–H functionalization (color online).

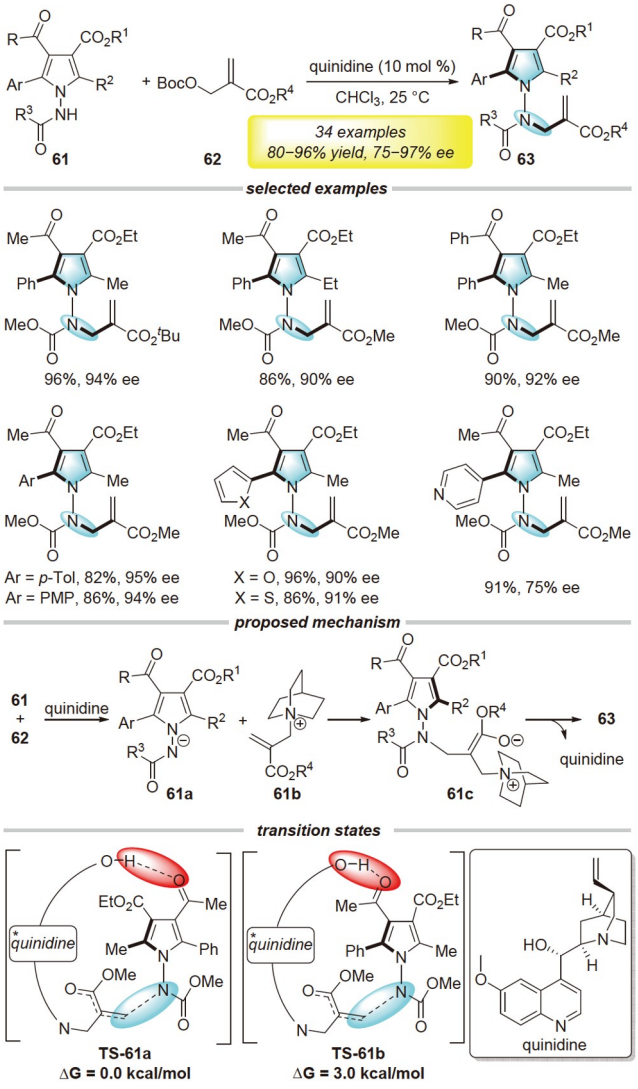


Scheme 16 Atroposelective synthesis of *N*-arylpyrroles bearing chiral C–N axis *via* desymmetrization or kinetic resolution (color online).

Scheme 16, the reaction of arylpyrroles **58** with ketomalonates **59** in the presence of H8-BINOL-derived CPA catalyst generated various functionalized axially chiral arylpyrroles **60** efficiently. The symmetric or asymmetric arylpyrrole substrates could undergo desymmetrization or kinetic resolution respectively, and produce the desired products in good to excellent enantioselectivities. Importantly, the synthesized structural motifs were proven to be potentially useful as chiral ligands in asymmetric catalysis.

As proposed in Scheme 16, the hydrogen bonding between ketomalonate and CPA is pivotal to form the chiral pocket for the induction of chirality. The pyrrole substrate **58** undergoes a nucleophilic addition onto CPA-ketomalonate intermediate **59a** to form intermediate **59b**. Finally, CPA promoted aromatization takes place to give the final product **60** and regenerate the chiral catalyst. The addition of pyrrole onto CPA-ketomalonate intermediate was considered as the enantio-determining step.

Beyond arylpyrroles, an alternative organocatalytic reaction was reported to construct another type of axially chiral pyrroles. In 2021, the asymmetric N–H functionalization of pyrrole-based scaffolds has been invoked to synthesize N–N axially chiral pyrroles bearing amide groups [87]. Lu and coworkers [87] discovered a quinidine catalyzed *N*-allylic alkylation of 1-aminopyrroles **61** with Morita-Baylis-Hillman (MBH) adducts **62**, leading to the convenient assembly of N–N axially chiral 1-aminopyrroles **63**, which is distinctly different with arylpyrroles in above reports (Scheme 17). Initially, the substitution of quinidine with MBH adduct **62** produces intermediate **61b** and releases BocO-anion. Further decomposition of BocO-anion and deprotonation of 1-aminopyrrole **61** leads to nitrogen anion **61a**. Subsequent nucleophilic attack of nitrogen anion **61a** onto **61b** affords chiral adduct **61c**. Finally, the axially chiral 1-aminopyrrole **63** forms through elimination, with catalyst regeneration. The authors rationalized the observed enantioselectivity by DFT calculations, and the calculated energy barrier matches well with the observed ee value. This reaction provides an efficient methodology for the synthesis of the rarely explored axially chiral 1-aminopyrroles.



Scheme 17 Atroposelective synthesis of 1-aminopyrroles bearing N–N axis *via* *N*-allylic alkylation (color online).

4 Conclusions and outlook

During the past decades, significant advances have been made in the construction of axial chirality. Among them, axially chiral pyrroles are important organic frameworks, which widely exist in functional molecules with biological activities and catalytic utilities. Due to the lower rotational barriers of pentatomic heteroaryl atropisomers, the synthesis of axially chiral pyrroles is challenging. By using organocatalytic and metal-catalyzed reactions, diverse synthetic strategies were reported based on *de novo* synthesis of pyrroles, kinetic resolution of racemic arylpyrroles, and desymmetrization of prochiral arylpyrroles. These protocols provide powerful and efficient methods for the rapid assembly of valuable axially chiral pyrroles, especially for arylpyrroles.

Despite these achievements, there is still room for further exploration: (1) Synthetic methods towards asymmetric *de novo* preparation of pyrroles are largely limited to some similar reactions, such as Paal-Knorr reaction, Attanasi reaction, and Barton-Zard reaction. The development of more types of catalytic reactions for the preparation of axially chiral pyrroles is highly desirable. (2) In the kinetic resolution and desymmetrization of arylpyrroles, relatively complex biaryls were employed as starting materials. To improve the utility of these reactions, simpler reactants and more efficient catalytic methods should be imperative, such as multicomponent reactions and cascade reactions. (3) Most of the reported reactions constructed axially chiral arylpyrroles, thus other categories of axially chiral compounds, such as axially chiral alkenyl pyrroles, pyrryl amides, and pyrryl imides, need to be investigated. (4) In most of these transformations, high catalyst loadings are required, especially for organocatalytic reactions. Therefore, it is vital to discover new catalytic systems with much higher efficiency. (5) Further research on the application of axially chiral pyrroles should be conducted, including drug discovery, asymmetric catalysis, and their application in material science. It is our expectation that, this review will attract more interest from the chemistry community and stimulate deeper investigations into the synthesis and application of axially chiral compounds.

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Conflict of interest The authors declare no conflict of interest.

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