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Very Important Publication

Catalytic Synthesis of Atropoisomers via Non-Canonical Friedel-Crafts Reactions

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Abstract: The Friedel-Crafts reaction stands as a powerful synthetic tool for C–H functionalization of aromatic feedstocks, which is conventionally realized through electrophilic alkylation and acylation. The burgeoning interests in axially chiral compounds across diverse fields have spurred extensive exploration of this classic transformation for catalytic atroposelective synthesis. Consequently, the past decade has witnessed the rapid expansion of various non-canonical Friedel-Crafts reactions, including electrophilic arylation, alkenylation, halogenation, sulfenylation, and amination of aryl C–H bonds, thereby delving into new chemical spaces. A range of catalytic atroposelective synthetic methods have been devised for these significant arene C–H functionalization. This review provides a comprehensive overview of the cutting-edge catalytic synthesis of atropoisomers through non-canonical Friedel-Crafts reactions, categorized into three parts based on the type of bond formation on the aromatics: C(sp^2)–C(sp^3) bond formations, C(sp^2)–C(sp^2) bond formations and C-(sp^2)–heteroatom bond formations. The richness of electrophiles and the modulation of atroposelectivity by diverse chiral organocatalysts, particularly chiral Brønsted acids, are elucidated. We anticipate that the repertoire of asymmetric Friedel-Crafts reaction will continue to flourish and to be demonstrated in not only scientific researches but also industrial organic synthesis.

Keywords: Friedel-Crafts reaction; Atropisomers; Axial Chirality; Organocatalysis;

1. Introduction

Since its first report in the late 19th century, the Friedel-Crafts reaction has been extensively explored by the synthetic community and has been indisputably recognized as a textbook reaction of indispensable value for the C–H functionalization of aromatics.[1–3] It typically involves the acid-promoted formation of a highly electrophilic carbocationic intermediate, which is subsequently trapped by π-electrons of the arene partner to repel a proton. The classic Friedel-Crafts reactions can be categorized into acylation and alkylation. The former reactions give rise to aryl ketones that do not generate a stereogenic carbon. In contrast, Friedel-Crafts alkylation reactions connect the aryl moiety to an sp^3-hybridized carbon of central chirality when unsymmetrical groups are attached (Scheme 1A). Given the importance of enantioselective carbon-carbon bond formation in asymmetric synthesis, asymmetric Friedel-Crafts reactions,[4–11] predominantly alkylation reactions, have received great attention in the past decades. Various chiral catalysts, including chiral Lewis acids, Brønsted acids, and enzymes have been devised to control the enantioselectivity, which also overcomes the disadvantage of the stoichiometric use of metal chlorides. In addition, asymmetric Friedel-Crafts reactions have been shown to accommodate a broad range of substrates, such as simple aldehydes or ketones, imines, enamines, α,β-unsaturated aldehydes or ketones, and α,β-unsaturated nitroalkenes.

The significant advancements in Friedel-Crafts reactions mentioned above have led to the exploration of new paradigms for this classic transformation. One area of exploration involves the use of electrophilic partners other than conventional carbon cation or acylium intermediates. This has been demonstrated in the development of arylation, amination, halogenation,

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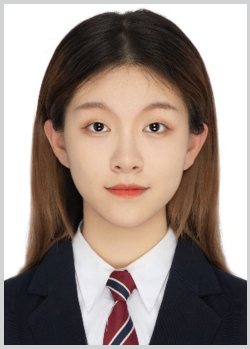

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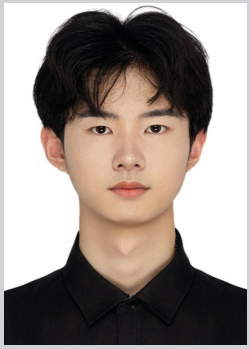

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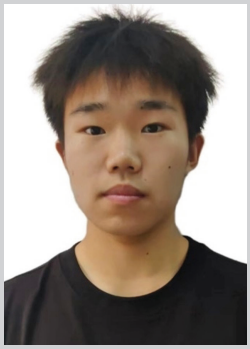

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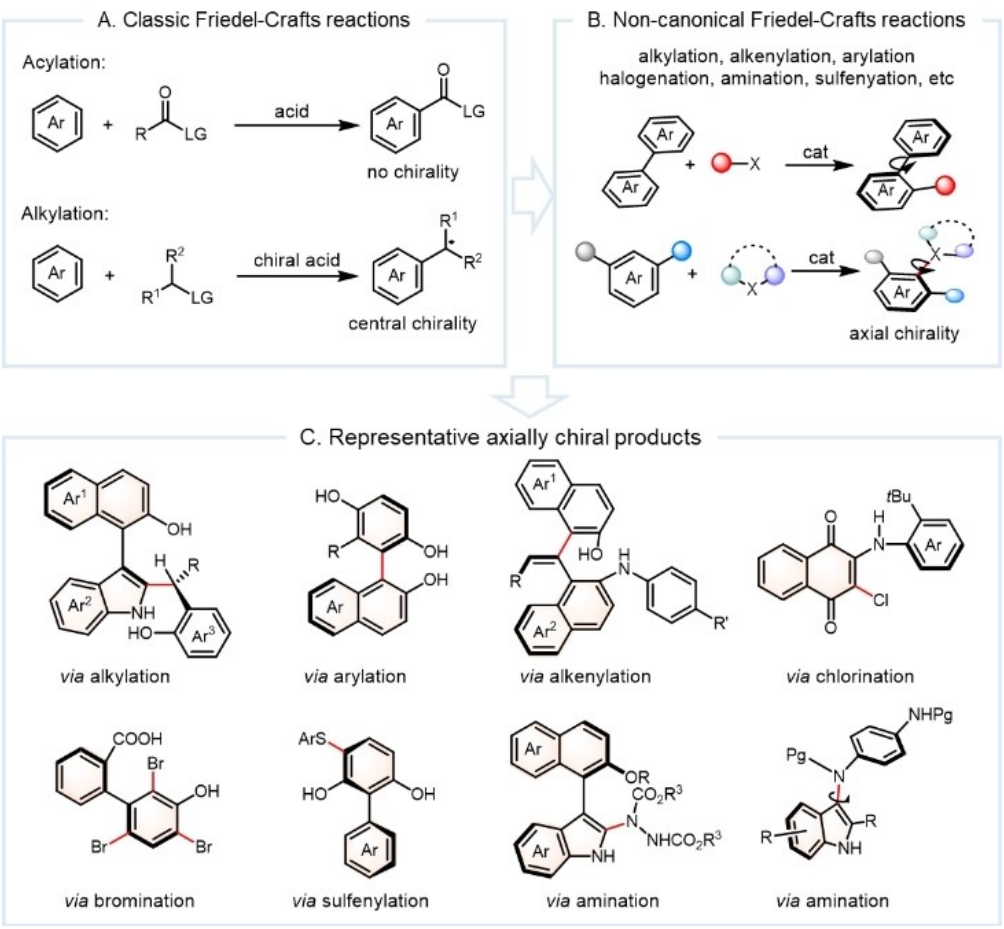
sulfuration, and other non-canonical Friedel-Crafts reactions. These non-canonical reactions greatly enhance the diversity of organic groups that can undergo C–H functionalization on arenes (Scheme 1B). On the other hand, however, in contrast to Friedel-Crafts alkylation reactions, which create a stereogenic sp^3 carbon center, these electrophilic partners are based on heteroatoms or sp^2-hybridized carbons that lack a chiral stereogenic element. Therefore, alternative forms of enantiomerism need to be considered to explore the synthetic potential of these reactions in asymmetric synthesis.

Atropisomerism is a fascinating aspect of stereochemistry that arises from hindered rotation around a single bond, resulting in the formation of distinct stereoisomers.[12] Atropisomers are commonly observed in natural products, pharmaceutical agents, agricultural chemicals, and functional materials.[13–17] The recent exploration of catalytic atroposelective synthesis has opened up exciting opportunities for preparing axially chiral compounds with high levels of stereocontrol.[18–24]

These advancements have shed light on the use of atropisomerism in non-canonical Friedel-Crafts reactions to achieve enantioselectivity. For example, by functionalizing arenes with a heavy halogen, the rotational barrier of an aryl-aryl single bond can be increased,[25] leading to the manifestation of atropisomerism. Similarly, introducing steric demands to the electrophilic amine source enables the construction of a configurationally stable C–N axial bond. Along this line, the Friedel-Crafts reactions have been recently advanced into enantioselective alkylation, alkenylation, arylation, bromination, sulfenylation, and amination reactions that provide accesses to atropo-enantioenriched compounds (Scheme 1C). These catalytic atro-



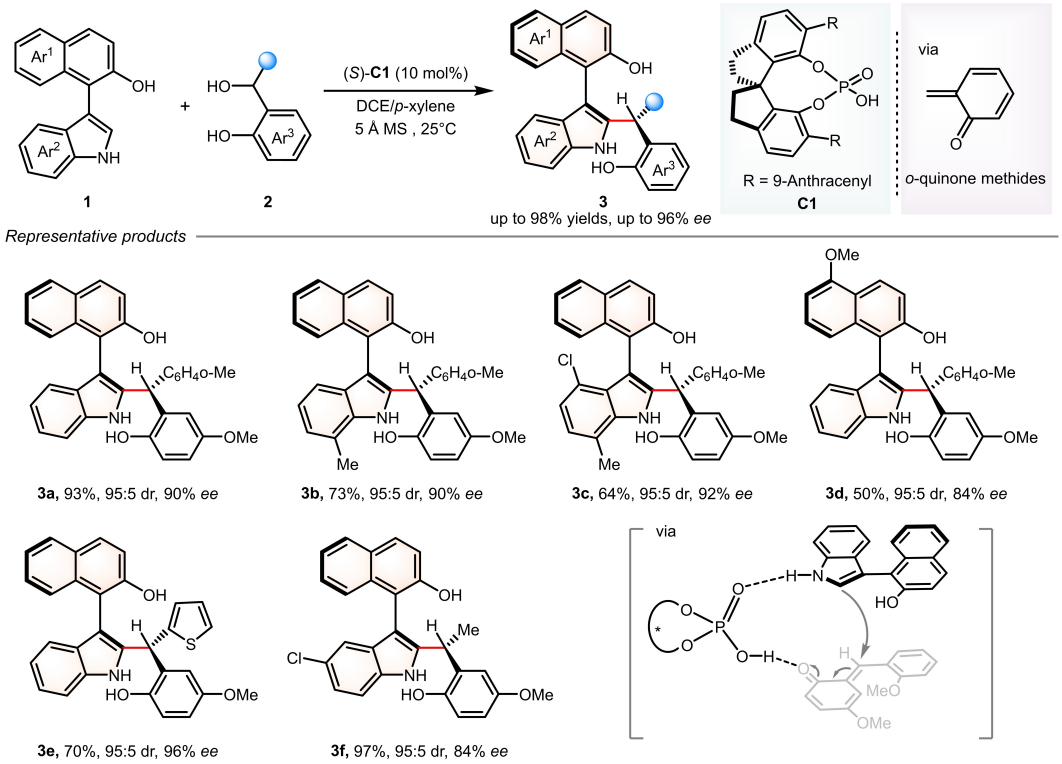
Scheme 1. The Friedel-Crafts reactions: the classic and new development.

poselective C–H functionalization methodologies add to the toolbox of Friedel-Crafts reactions and largely enriched the repertoire for asymmetric organic synthesis. In this review, we summarize recent advances in the aforementioned non-canonical Friedel-Crafts reactions with attempts to illustrate the conceptually fascinating insights including the design of prochiral substrates, innovation of different electrophiles, development of catalytic systems as well as the origin of atroposelectivity.

2. Atropisomers Synthesis via Enantio-Selective Friedel-Crafts Alkylation: C(sp^2)–C(sp^3) Bond Formation

The classic Friedel-Crafts alkylation is a useful method to introduce a C(sp^2)–C(sp^3) bond to aromatic rings, which is intrinsically able to build a stereogenic carbon. This process could be merged with the generation of an additional configurationally stable axis from an existing C–C bond either by increasing the rotational barrier or via desymmetrization, thus affording enantiomerically enriched compounds containing both central chirality and axial chirality. Such an approach significantly expands the diversity of products accessed by Friedel-Crafts alkylation.

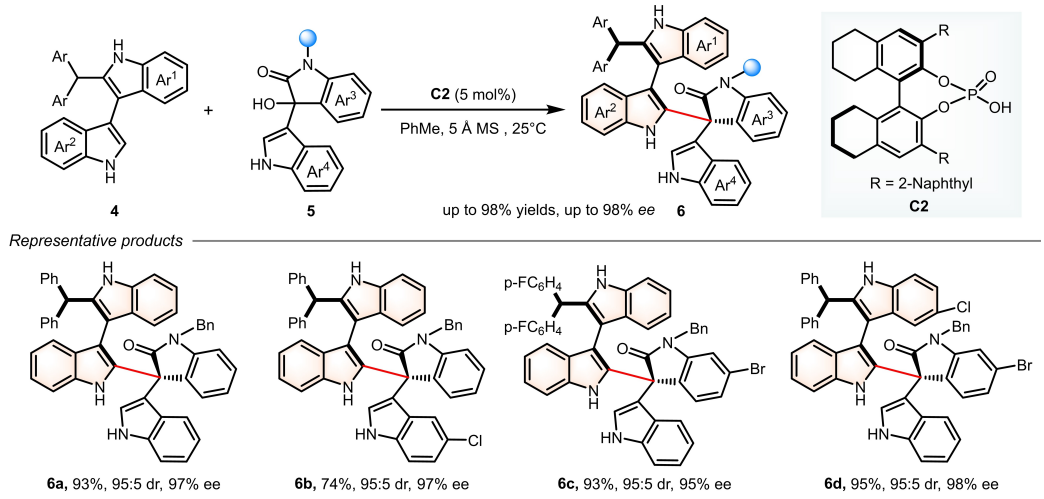
In 2019, Shi and coworkers reported the synthesis of axially chiral paphthyl-indoles via asymmetric addition reaction using a chiral phosphoric acid (CPA) catalyst. The reaction involved the reaction of racemic naphthalene indole **1** with o-hydroxybenzyl alcohol **2** as the electrophile precursor, affording various axially chiral naphthalene indoles containing an additional asymmetric tertiary carbon in good yields and excellent enantioselectivity (Scheme 2).[26] Mechanistically, CPA **C1** preferentially coupled with the substrate **1** of (*Ra*) configuration and *o*-quinone methides (*o*-QM)[27–30] generated in-situ from o-hydroxybenzyl alcohol via hydrogen bonding. The rapid nucleophilic addition between (*Ra*)-**1** and o-QM produced chiral products (*Ra*, *S*)-**3** with stereoselectivity. In contrast, (*Sa*)-**1** is difficult to be activated by CPA (*S*)-**C1** because of their unfavorable spatial organization, but could undergo rapid racemization into (*Ra*)-**1**, thus



Scheme 2. Enantioselective synthesis of axially chiral naphthyl-indoles.

accomplishing a unique Friedel-Crafts alkylatione through efficient dynamic kinetic resolution.

In the same year, the Shi group made further advancements by developing the asymmetric addition of bisindole skeletons **4** with isatin-derived 3-indolylmethanols **5** to synthesize axially chiral 3,3′-bisindole skeletons **6**, which are a dual five-membered ring system (Scheme 3).[31] The success of this reaction relied on the careful selection of the electrophilic reagent. 3-Indolylmethanol **5** was found to be a suitable electrophile due to high reactivity in the presence of CPA catalyst and its large size, resulting in a relatively high rotational barrier. The presence of an acid facilitated the formation of delocalized carbonium ions, which is susceptible to attack by 2-substituted 3,3′-bisindoles. In addition, a large diarylbenzyl group was installed at C2 position of nucleophile **4** to fill the



Scheme 3. Asymmetric addition reactions of 2-substituted 3,3'-bisindoles with 3-indolylmethanols.

space near the axis, thus significantly increasing the rotational barrier.

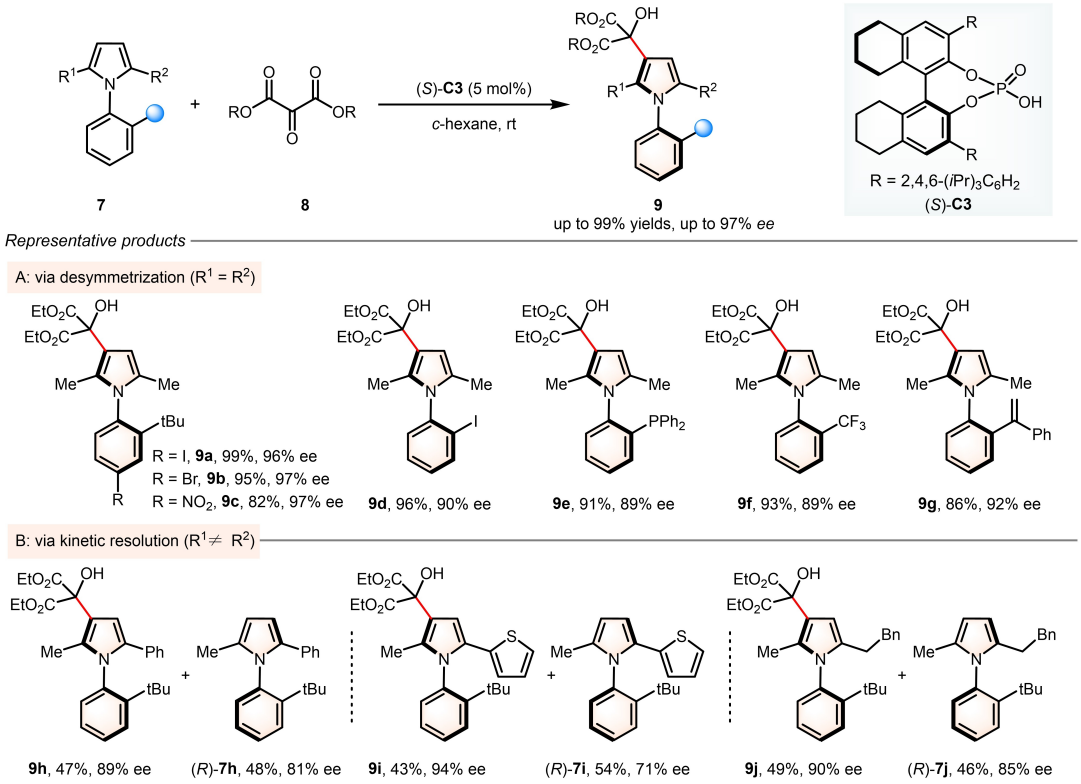
Similar to the use of substituted indole as an arene nucleophile, pyrroles have also been employed in Friedel-Crafts alkylation to access atropisomers. Tan and co-workers disclosed a method to create atropisomerically enriched aryl pyrroles **9** containing a stereogenic C–N axis from *N*-aryl pyrroles **7** and ketomalonates **8** using a chiral CPA catalyst (Scheme 4).[32] This reaction exhibited a broad substrate scope. The reaction involved two different approaches, depending on the symmetry of the substrates. For symmetrical substrates, the reaction proceeded via desymmetrization mediated by CPA **C3**, affording the products **9** in good yield and excellent enantioselectivity (Scheme 4A). Due to the relatively high configurational stability of *N*-aryl pyrroles **7**, those unsymmetrical substrates underwent kinetic resolution (Scheme 4B). In this case, catalyst (*S*)-**C3** matched the transformation of substrate (S)-7 over its enantiomer, leading to the formation of atropisomers **9** with excellent enantiomeric excess value.

In the above Friedel-Crafts alkylation of *N*-aryl pyrroles, replacement of the *N*-aryl group with another pyrrole moiety could potentially establish a novel type of atropisomers containing a stereogenic *N*-*N* axis. *N*-*N* bonds containing motifs are important and ubiquitous in natural products and bioactive compounds..[33–37]

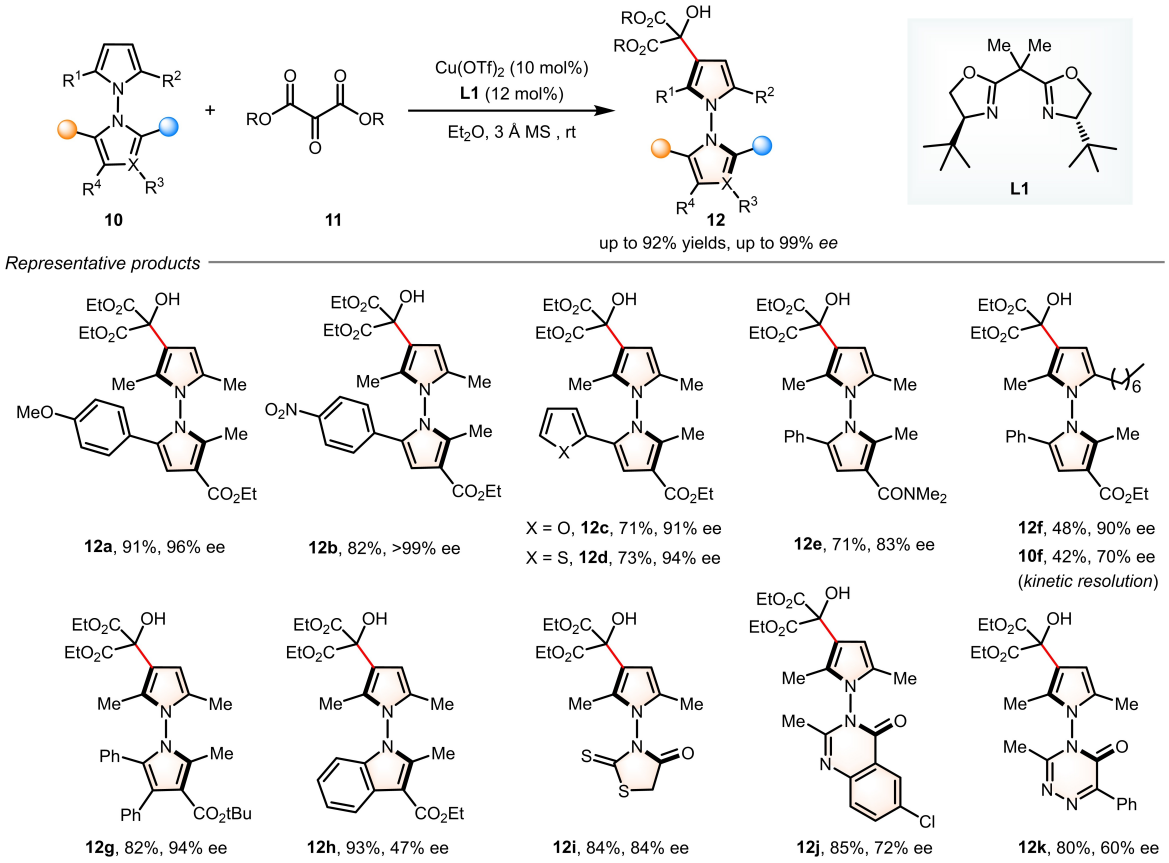
However, this type of atropisomerism is largely overlooked compared with C–C and N–C atropisomers. Liu and co-works developed Cu-bisoxazoline-catalyzed Friedel-Crafts alkylation for enantioselective synthesis of various *N*-*N* bis-pentatomic heteroaryl atropisomers (Scheme 5).[38] The coordination of Lewis acidic Cu(II) complex with ketomalonate rendered much higher electrophilicity than CPA catalyst. The reaction worked under mild conditions with broad substrate scope to provide various bis heteroaryl atropisomers **12** in good yields and ee value. Heating experiments showed that the axially chiral bisazaheterocycles prepared by this method have high rotational barriers.

In addition to the use of reactive ketones as electrophiles, imines can also serve as reaction partners in Friedel-Crafts alkylation. Huang and co-workers described the synthesis of axially chiral 3-indolyl pyrazole derivatives from 3,4′-indole-pyrazolyl acetate **13** and imine electrophile **14** (Scheme 6).[39] The key step is the chiral acid **C4**-catalyzed stereoselective C–C bond formation via a Mannich reaction, allowing for cooperative installation of both axial chirality and a quaternary stereocenter with excellent diastereoselectivity and enantioselectivity.

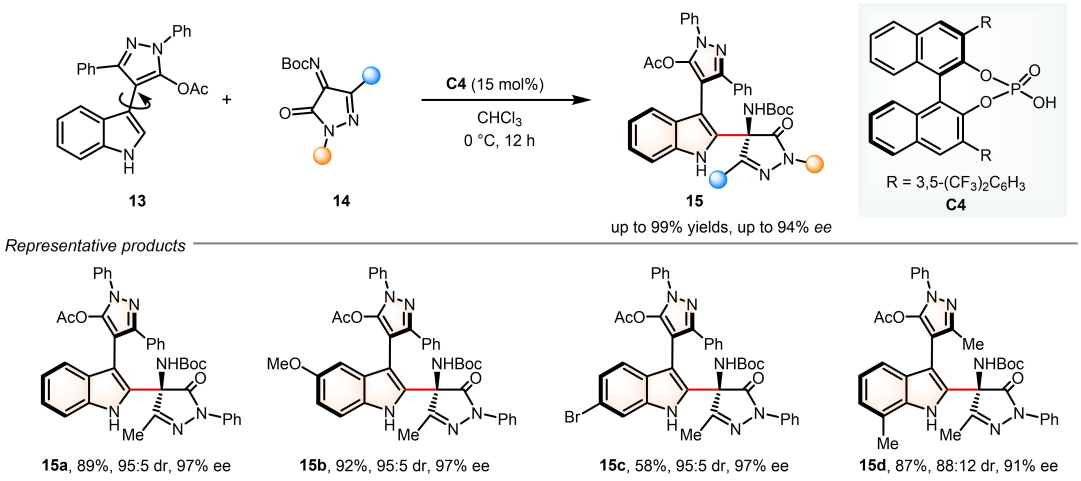
The Pictet-Spengler cyclization[40–42] is a versatile and efficient method for the construction of biologically important heterocycles proceeding via intra-



Scheme 4. Strategy to access enantioenriched axially chiral arylpyrroles.

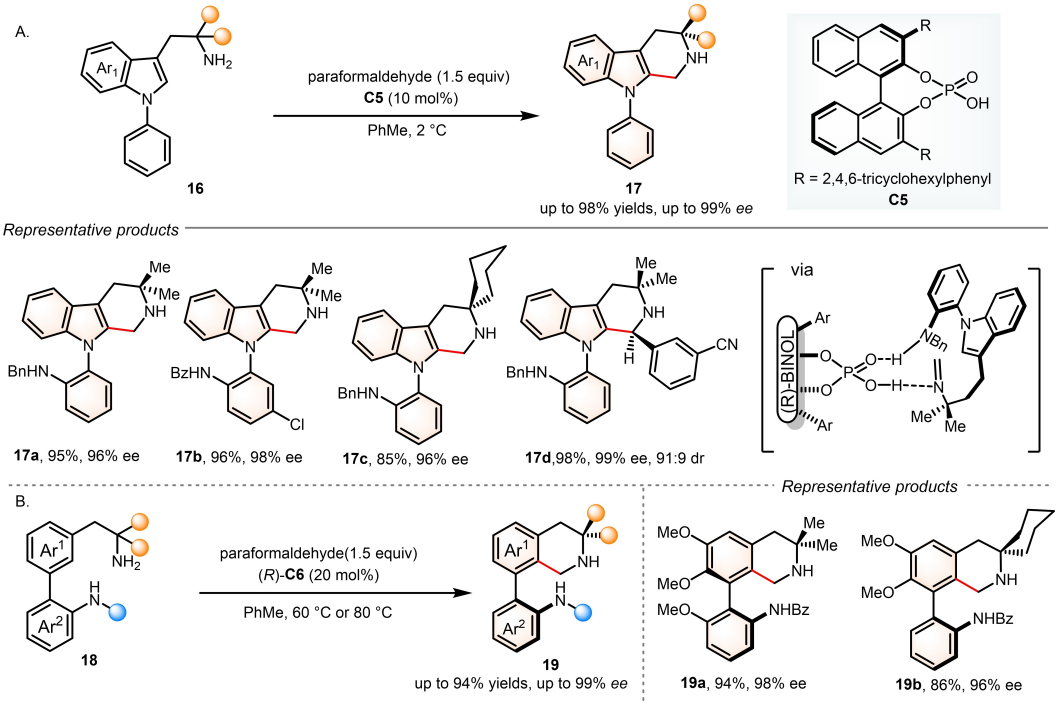


Scheme 5. Cu-bisoxazoline-catalyzed enantioselective synthesis of N–N biaryl atropisomers.



Scheme 6. Asymmetric construction of axially chiral 3,4'indole-pyrazole derivatives.

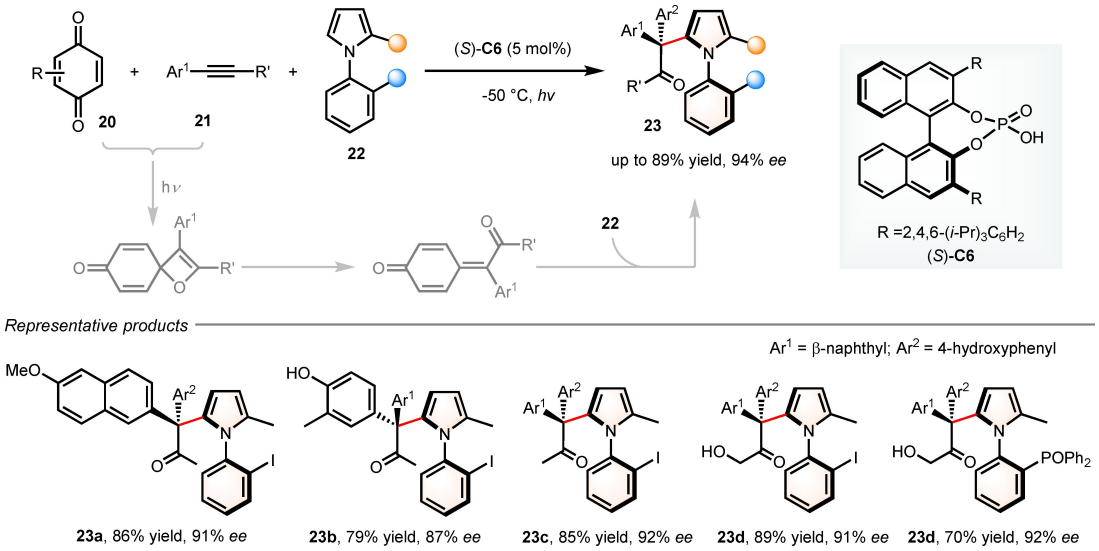
molecular Friedel-Craft reaction typically mediated by acid. The newly formed ring system can impose steric hindrance to an existing bond in vicinity, thus increasing its rotational barrier. In 2021, a CPA-catalyzed atroposelective Pictet-Spengler reaction of *N*-arylindoles was developed by Kwon and co-workers (Scheme 7A).[43] Axially chiral C–N bond-containing *N*-aryl-tetrahydro-beta-carbolines **17** were obtained with high optically purity. The introduction of an amide hydrogen bond donor in the aromatic ring provides a secondary interaction with a phosphoryl oxygen, which plays a crucial role in achieving high enantioselectivity. Catalyst **C5** enhanced the cyclization process by forming an iminium-phosphate ion



Scheme 7. Atroposelective Pictet-Spengler reaction of *N*-arylindoles and tetrahydroisoquinoline.

pair. Later on, the same group applied this similar Pictet-Spengler reaction for atoposelective cyclization of tetrahydroisoquinoline **18** through dynamic kinetic resolution (Scheme 7B).[44]

More recently, Lu's group developed a three-component reaction of quinone **20**, alkynes **21** and *N*-arylpyrroles **22** through a sequential photocycloaddition and enantioselective Friedel-Crafts alkylation, which accomplished the synthesis of functionalized *N*-arylpyrrole atropisomers (Scheme 8).[45] Different from previous Friedel-Crafts alkylations using thermochemically formed electrophiles as a reaction partner, Lu's work skillfully made use of photochemical [2+2] cycloaddition between quinone carbonyl with alkyne, which generated spiro-oxetenes as versatile intermediates. These highly strained four-member ring system



Scheme 8. CPA-catalyzed three-component reaction for atroposelective synthesis of *N*-arylpyrroles.

readily underwent ring opening reaction to in-situ form highly electrophilic *p*-quinone methide intermediate, and the subsequent nucleophilic addition with *N*-arylpyrroles **22** delivered axially chiral *N*-arylpyrrole products **23** with both central and axial chirality with up to 89% yield and 94% ee. The intrinsic advantages of multicomponent reaction in this reaction system facilitated convenient introduction of various functionalities into the products, thus significantly adding to the molecular diversity of the optically pure *N*-arylpyrroles.

3. Atropisomers Synthesis via Enantioselective Friedel-Crafts Arylation: C(sp^2)–C(sp^2) Bond Formation

The direct construction of a configurationally stable axis between two sp^2-hybridized carbons via Friedel-Crafts arylation is a straightforward but challenging strategy for atroposelective synthesis. The use of large site-blocking aryl reagents is necessary to secure high bond rotational barrier but also often impose challenges in reactivity. In this regard, earlier synthetic efforts were mainly devoted to the construction of axially chiral compounds with two six-membered aromatic hydrocarbons such as naphthols and naphthylamine derivatives.[16] In recent years, synthetic attentions have been moved to the use of more challenging five-membered aromatic hydrocarbons such as indole. On the other hand, selection of electrophile partners suitable for this strategy are mainly limited to quinones and their derivatives.[46,28] Expanding the pool of electron-deficient substrates is a key challenge in this synthetic strategy. Discovering new electron-deficient substrates that can participate in axial bond formation would greatly broaden the scope and applicability of this synthetic approach.

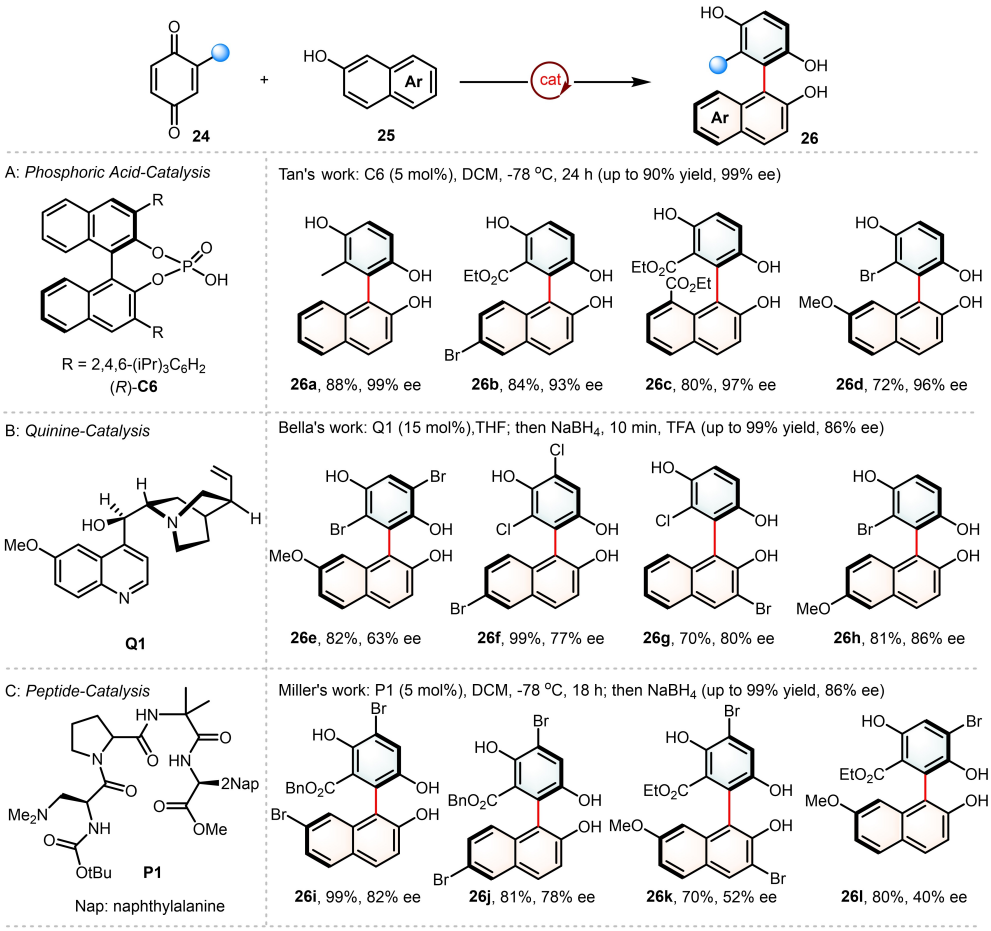
3.1. Atroposelective Biaryl Formation

Functionalized biaryls with axial chirality such as 1,1′-binaphthyl-2,2′-diol (BINOL) and its derivatives are versatile chiral ligands/catalysts widely used in asymmetric synthesis and natural product synthesis, as demonstrated in the landmark compounds such as BINAP,[47,48] phosphoric acids.[49–52] Synthesis of axially chiral biaryldiols conventionally relied on the approaches of metal-catalyzed asymmetric oxidative cross-coupling reactions and kinetic resolution,[19,53–55] which often focused on the symmetric biaryldiols derivatives. Recent studies have been switched to the preparation of the nonsymmetric counterparts, for which the Friedel-Crafts arylation of quinone and its derivatives represents a versatile approach.

In 2015, Tan, Liu and coworkers developed the first CPA-catalyzed Friedel-Crafts arylation of 2-naphthols **25** and electrophilic quinone derivatives **24** (Scheme 9A).[56] The reaction afforded a class of axially chiral biaryldiols **26** in up to 90% yields and 99% ee under very mild reaction conditions. In this reaction, CPA activated both reaction partners through hydrogen bonding interactions to facilitate nucleophilic addition with effective control of C/O selectivity with respect to 2-naphthols. The resulting biaryldiols bear an additional halogen or carboxylate group on the aromatic ring, providing opportunities for adjust their steric/electronic properties. Indeed, the obtained axially chiral biaryldiols were found be show higher enantioselectivity than the classic BINOL in the model reaction of enantioselective addition of diethylzinc to aldehydes, highlighting the excellent synthetic potential of these chiral biaryldiol products. The strategy was further extended into p-quinone phosphonates for construction of chiral biaryl monophosphorus ligands by Zhang, Wang and co-workers.[57] Shortly after, Moliterno and co-workers disclosed a similar transformation by using quinine **Q1** as catalyst (Scheme 9B).[58] It is noteworthy that quinine was also proposed to act as bifunctional catalyst that synergistically interacted with both naphthol and quinone carbonyl is hydrogen bonded to the 9-hydroxyl group on the quinine. In generally, low enantioselectivities were recorded therein compared to CPA catalysis. Moreover, due the high susceptibility of the biaryldiol toward oxidation, the atroposelective Friedel-Crafts arylation in their system was often coupled with oxidation to form quinone products. Therefore, a subsequent reduction using $NaBH_4$ was employed to obtain the desired biaryldiol atropisomers.

In addition to the use of CPA and quinone catalyst described above, a tetrameric peptide featuring the Lewis-basic residue β-dimethylaminoalanine was designed and applied for atroposelective coupling of ester-containing quinones and naphthols by Miller and co-workers in 2020 (Scheme 9C).[59] The reaction yielded a series of nonsymmetric biaryls in good to excellent yields under mild conditions. Although the atroposelectivity obtained in this study was not satisfactory, this catalytic system demonstrates the potential of enzyme catalysis for this type of Friedel-Crafts arylation the synthesis of atropisomeric compounds.

Since the pioneering work by Tan and Liu on the CPA-catalyzed atroposelective Friedel-Crafts arylation using benzoquinone derivatives, other quinone equivalents and electron-rich arenes were employed to further develop this methodology. The direct construction of five-membered ring biaryls via Friedel-Crafts arylation has been relatively slower compared to six-membered ring biaryls, primarily due to the lower rotational energy barrier and other factors. In 2019, the Tan′s group successfully achieved CPA-catalyzed



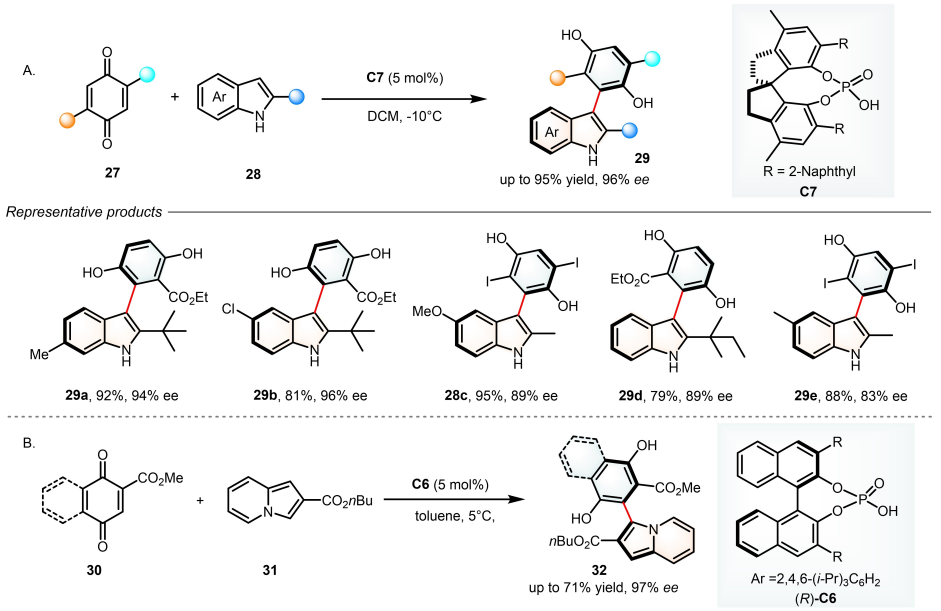
Scheme 9. Atroposelective arylation of 2-naphthols with quinone derivatives.

atroposelective coupling of indoles **28** and quinone derivatives **27** (Scheme 10A).[60]

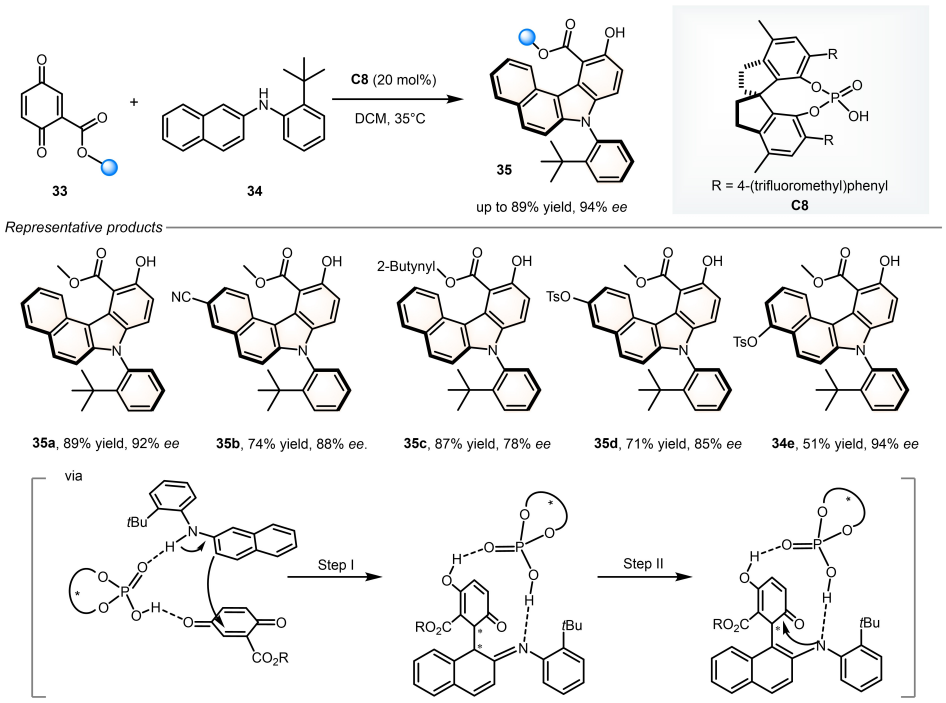
The catalytic system worked quite smoothly to provide a series of structurally novel heteroaryl atropisomers **29** with good group tolerance in good to excellent yields and enantioselectivities. The marked atropostability of the products arises from the introduction of sterically bulky alkyl at the C2 position of indoles or quinone ring, which is also beneficial to avoiding the competing [3+2] cyclization reaction after the first nucleophilic addition event. Later, a similar work was latterly achieved by metal catalysis. Chen and Tu disclosed the copper-catalyzed asymmetric coupling of iodoles and quinone derivatives utilization of the spirocyclic pyrrolidine oxazoline (SPDO) ligand for construction of axially chiral 3-arylindoles.[61] In 2022, Song and Li realized the atroposelective coupling of indolizines **31** and *p*-quinone esters **30**.[62] The reaction delivered diverse axial chiral 3-arylindolizine **32** in good to excellent yields and stereocontrol (up to 97% ee) under mild reaction conditions (Scheme 10B).

Very recently, Zhou and co-workers developed an efficient CPA-catalyzed coupling of *N*-naphthalen-2-amines **34** with quinone esters **33**. Unlike the aforementioned Friedel-Crafts arylation reactions wherein quinone moiety ultimately formed diphenols via tautomerization, in this reaction the enone intermediate of central chirality was subsequently condensed with intramolecularly pendent naphthylamine that led to the formation of carbazole derivatives **35**. Similar cascade transformations of quinones have been disclosed in [3+2] cycloadditions for the assembly of polycyclic indole derivatives.[63–65] Given the presence of sterically demand in proximity to the nitrogen atom, the condensation and dehydration transferred central chirality information to axial chirality of the C–N bond. With this strategy, a series of C–N axially chiral carbazole derivatives were also constructed in moderate to good yields (36–89% yield) with moderate to excellent atroposelectivities (44–94% ee) (Scheme 11).[66]

The quinone electrophiles could be replaced by *p*-quinone monoimines, of which the properties could be potentially adjusted by the protecting group at the

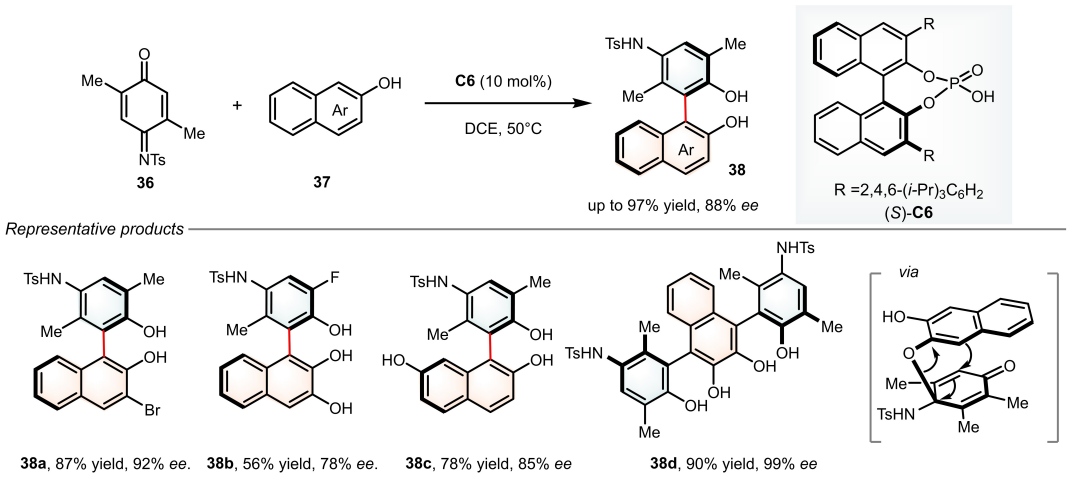


Scheme 10. Atroposelective arylation of indoles and indolizines with quinone derivatives.



Scheme 11. Atroposelective synthesis of carbazoles from naphthalen-2-amines and quinone esters.

nitrogen atom. In this regard, Xu and Kürti reported the first study on atroposelective direct arylation of phenols/naphthols **37** with *p*-quinone monoimines **36** based on CPA catalysis (Scheme 12).[67] The stragegy enabled synthesis of diverse non-C2 symmetric 2,2′-dihydroxy-1,1′-binaphthalenes **38** with broad substrate scope in up to 97% yield and 99% ee. The reaction was amenable to double arylation that delivered product **38 d** with two chiral C–C axes. Interestingly, the authors proposed that the reaction proceeded via sequential aminal formation, [3,3]-rearrangement and rearomatization. They found that the symmetry of the earliest formed aminal intermediate had a significant effect on the enantiomer induction level of the final product. Aminals with a plane of symmetry resulted in significantly low enantiomeric excess, suggesting that

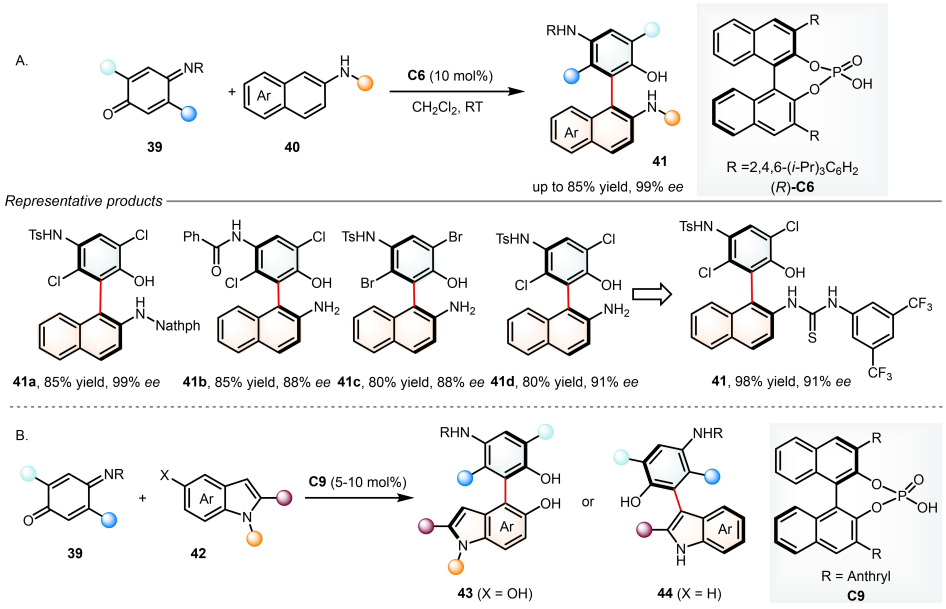


Scheme 12. Atroposelective of arylation phenols/naphthols with quinone monoimines.

asymmetric induction in the sigmatropic rearrangement step is more challenging than the aminal formation, and the central chirality transfers into axial chirality is with high fidelity in the rearomatization step.

The Friedel-Crafts arylation for the combination of *p*-quinone monoimines and 2-naphthylamines was also established. In contrast to the extensive studies on the enantioselective synthesis of BINOL and its derivatives,[19] the counterparts on axially chiral biaryl amino alcohols, which also constitute a class of versatile ligand or oganocatalyts,[68] remained underexplored. In 2017, the Tan's group reported synthesis of axially chiral biaryl amino alcohols via direct atroposelective arylation of 2-naphthylamines **40** with quinone monoimines **39** in the presence of CPA (Scheme 13A).[69] A various of axially chiral biaryl amino alcohols **41** were obtained easily with broad functional groups in good to excellent yields and enantioselectivities. In addition to the coupling with 2-naphthylamines, the use of *p*-quinone monoimines has facilitated a few other atroposelective Friedel-Crafts arylation with other nucleophilic aromatic compounds, such as functionalized indoles (Scheme 13B).[60,70] These methodologies enrich the structural diversity of axially chiral biaryl scaffolds.

In contrast to the broad use of *p*-quinones as electrophiles in enantioselective Friedel-Crafts arylation for the synthesis of enantioenriched axially chiral biaryls, *o*-quinones has been much less studied. This fact could presumably be ascribed to its high reactivity



Scheme 13. Atroposelective arylation of 2-naphthylamines with iminoquinones.

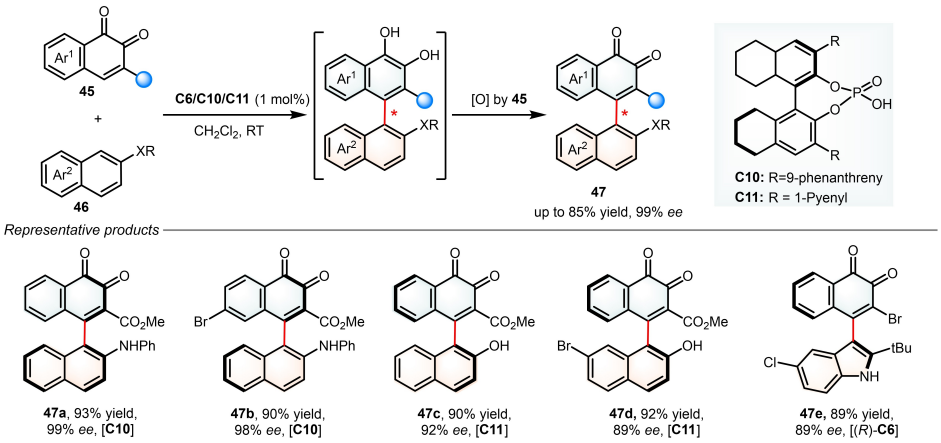
and relative low stability.[71–73] Ring fusion (e.g., o-naphthoquinone) or introduction of stabilizing steric hindrance is generally required to overcome lability of *o*-quinones. In fact, *o*-quinones do occur in bioactive natural products,[74] making this motif interesting targets in synthetic chemistry.

In 2019, Tan's group reported CPA-catalyzed atroposelective coupling of various nucleophilic aromatics including 2-naphthylamines, 2-naphthols and indoles with *o*-naphthoquinone **45** (Scheme 14).[75] These reactions took place with excellent regioselectivity that the C3 position of *o*-naphthoquinones were functionalized, resulting in axially chiral naphthalene-1,2-diol. However, the intermediate was unstable and easily oxidized by *o*-naphthoquinone **45** to form a class of unique axially chiral arylquinone **47**. The protocol gave a rapid access to *o*-naphthoquinones. This protocol features mild conditions, broad substrate scope, high yields and enantioselectivities.

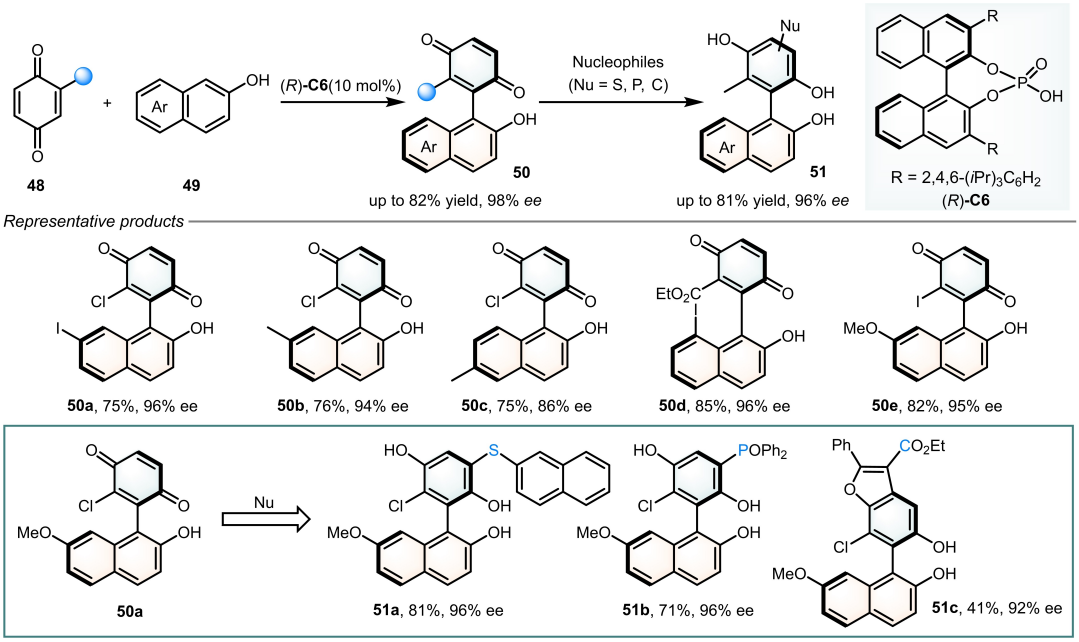
The Friedel-Crafts arylation/oxidation cascade provides a promising strategy for diversity-oriented synthesis of a wide range of highly functionalized non-C_2 symmetric biaryldiols with preservation of the chirality. For instance, by oxidizing the phenol moiety of Friedel-Crafts arylation products, highly electrophilic quinone moiety could be restored in the products, thus allowing downstream 1,4-addition to introduce different nucleophiles. This strategy was demonstrated by Tan in the CPA-catalyzed Friedel-Crafts arylation of 2-naphthol derivatives to p-quinones, wherein the restored *p*-quinones bearing a chiral C–C axis was used as arylation reagent to introduce a range of S-, P- and C-nucleophiles. This protocol provides a platform for rapid difunctionalization of readily available *p*-quinones into non-C_2 symmetric biaryldiols **51** (Scheme 15).[76]

The further development of atroposelective Friedel-Crafts arylation has been driven by the search for new electrophilic reagents beyond quinones. In this pursuit, the Tan's research group made a breakthrough by discovering that azobenzene derivatives can serve as effective electrophilic reagents. In 2018, they demonstrated the asymmetric arylation of indoles **53** using azobenzenes **52** (Scheme 16).[77] In this strategy, the azo group not only acts as an activting group to decrease the electron density of the aromatic ring but also serves as a hydrogen bonding site with chiral phosphoric acid (CPA). This interaction with CPA enhances the enantioselectivity of the reaction. By employing CPA **C12/C13** as a catalyst, the reaction successfully provided a wide range of axially chiral arylindoles in good yields and with excellent enantioselectivities under mild reaction conditions. Interestingly, when 2-methyl indoles were used, unexpected products in the form of axially chiral aniline-indoles were achieved through an arrangement process. The mechanism of this transformation involves chiral phosphoric acid activating both the indole and azo substrates, promoting stereoselective nucleophilic attack. The in situ generated reactive intermediate **55** underwent immediate re-aromatization to make the thermodynamically more stable arylhydrazine intermediate **56**, since the cyclization of B was blocked due to steric effect, and subsequent re-aromatization facilitated an efficient center-to-axial chiral transition.

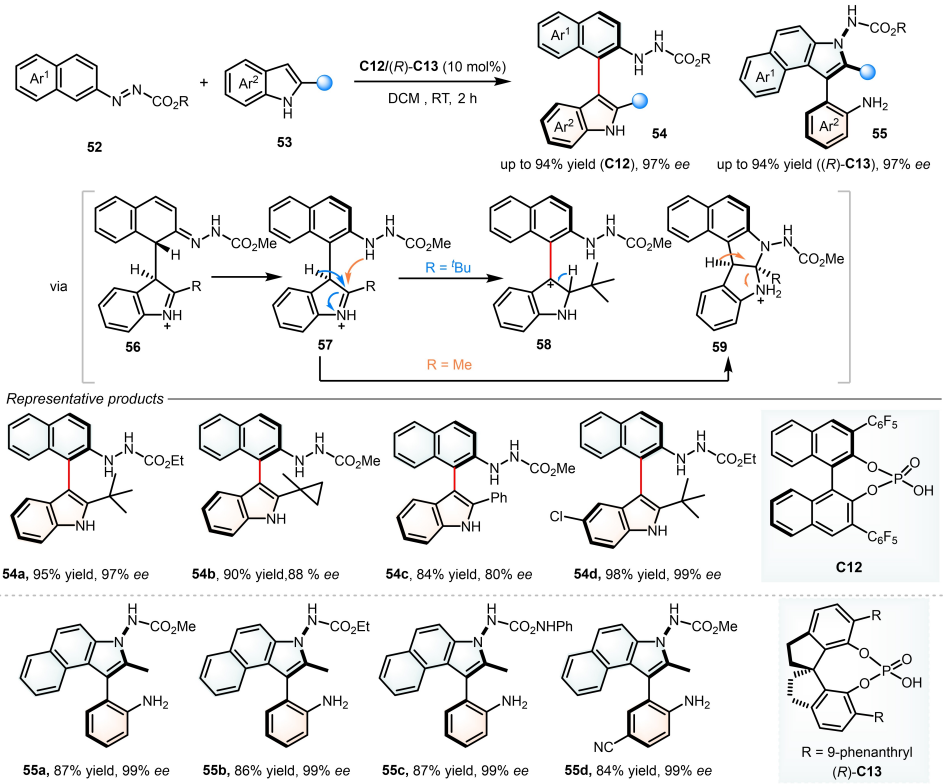
In their continuous exploration of site-selective C–H functionalization of azo-tethered aryl substrates, the Tan's group further reported CPA salts-catalyzed atroposelective Friedel-Crafts arylation of naphthols and 2-naphthylamines (Scheme 17).[78] Additionally, the group developed an alternative protocol using the $Ni(OTf)_2$/chiral bis(oxazoline) ligand catalytic system for the synthesis of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) and 1,1′-binaphthyl-2,2′-diamine (BINAM) derivatives. These two complementary catalytic systems offer a highly attractive approach for the rapid access to a wide range of NOBIN and BINAM derivatives (Scheme 17).



Scheme 14. Atroposelective arylation of *o*-naphthoquinones with 2-naphthylamines, 2-naphthols.

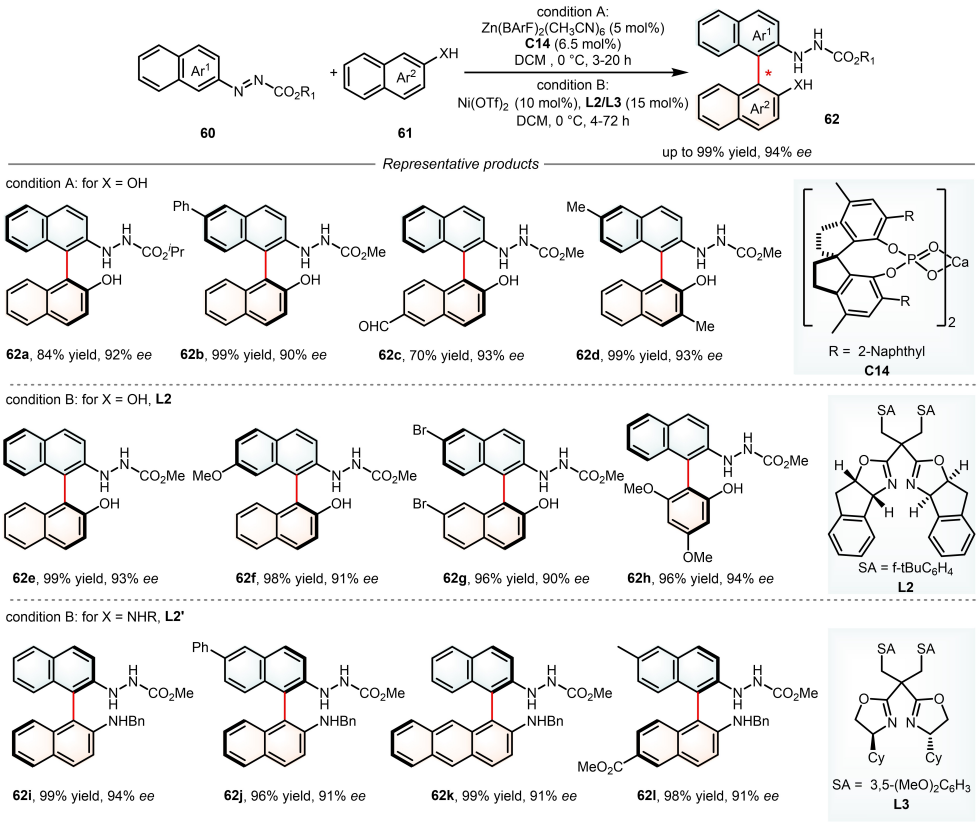


Scheme 15. Enantioselective construction of axially chiral (hetero)aryl-p-quinone frameworks.

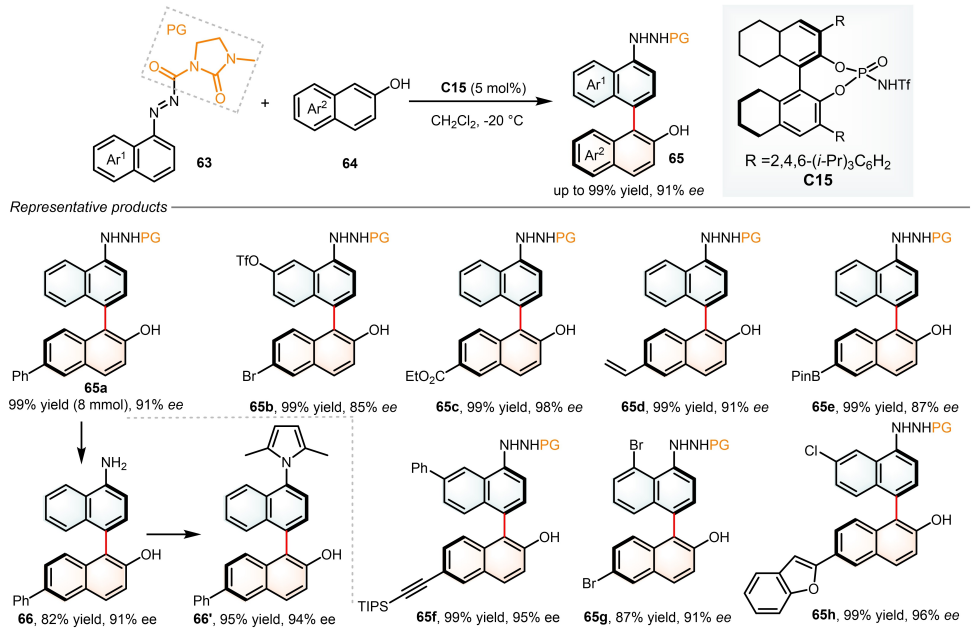


Scheme 16. Atroposelective arylation of azonaphthalenes as electrophiles and indoles.

Very recently, the same research group achieved asymmetric cross-coupling between 1-azonaphthalenes **63** and 2-naphthols **64** through atroposelective Friedel-Crafts arylation, demonstrating high efficiency and exclusive C4-selectivity (Scheme 18).[79] The success of this reaction can be attributed to the identification of the acylimidazolinone auxiliary, which effectively activates the azo group, enables remote coordination of



Scheme 17. Atroposelective arylation of naphthols and azonaphthalenes.



Scheme 18. Atroposelective Cross-Coupling of 1-Azonaphthalenes and2-Naphthols.

the chiral Brønsted catalyst, and takes advantage of the arene resonance effect. This reaction delivered the axially chiral binaphthyl derivatives **65** in excellent enantioselectivity with broad spectrum of functional groups. The utility of this method is further demonstrated through the transformation of the resulting

products into other binaphthyl compounds while perfectly retaining their axial chirality.

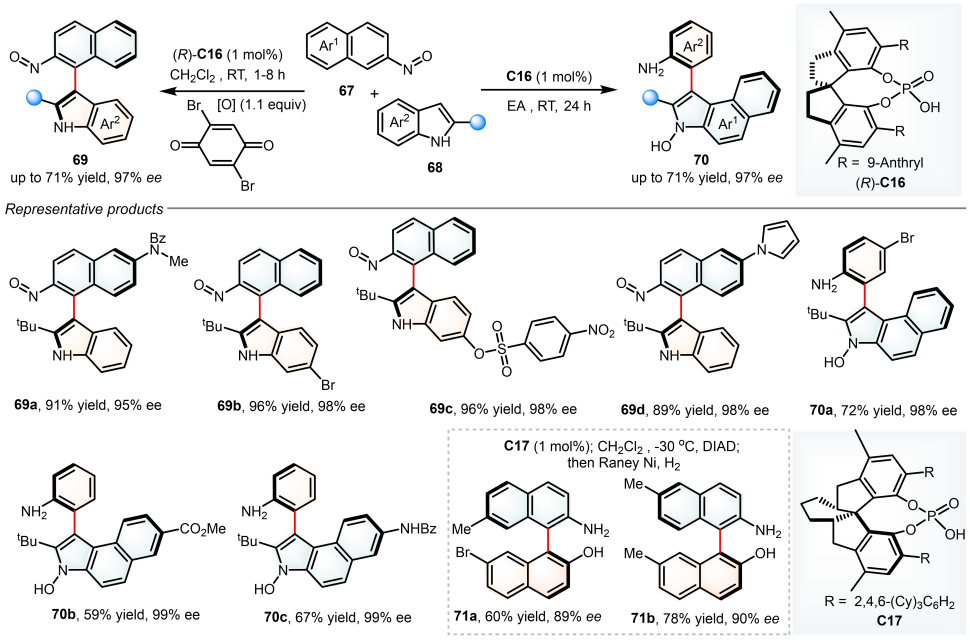
With the aid of computational screening on naphthalene bearing a range of substitute groups, Tan's group found that a nitroso group showed great potential for the similar coupling transformation as azo group (Scheme 19).[80] Density functional theory (DFT) calculations revealed that the hydrogen-bond interaction between phosphoric acid and 2-nitrosonaphthalene can lower the LUMO energy, thereby increasing the reactivity of the nitro compound as an electrophilic reagent. Guided by these findings, they successfully realized the CPA catalyzed atroposelective arylation of nitrosonaphthalenes **67** with indoles **68**. Under the mild conditions, a wide range of indoles and nitrosonaphthalene were compatible to give axial chirality indole-naphthalene skeleton **69** in excellent yields and enantioselectivities in the presence of oxidant using acetate as solvent via a subsequent cascade process. Notably, when the reaction was carried out in the absence of oxidant with ethyl acetate as solvent, the aniline-Indole derivatives **70** were obtained via a similar arrangement as in their previous work with azonaphthalenes.[77] Additionally, the transformation was successfully applied to 2-naphthols, allowing for the synthesis of various valuable axially chiral 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) compounds through a one-pot, two-step process involving C–C coupling and reduction.

In addition to using quinones, quinone monoimines, azoarene and 2-nitrosonaphthalene as electrophilic partners in atroposelective Friedel-Crafts arylation, the Shi group has developed a new strategy by using C3-electrophilicity of 2-indolylmethanols (Scheme 20).[81] Indolylmethanols have proven to be versatile reactants for enantioselective synthesis of chiral indole derivatives because they are easily transformed into carbocation, vinyliminium, and delocalized cation intermediates under the catalysis of an acid.[82–85] The C3-position of 2-indolylmethanols displayed unusual electrophilicity due to resonance effect, which could be attacked by nucleophiles to accomplish organocatalytic indole-Nu couplings. By introducing bulky diaryl substituents and the employment of CPA activation, Shi and coworkers successfully established an axially chiral indole-aryl framework **74** through atroposelective coupling of 2-naphthols **73** with 2-indolylmethanols **72** (up to 99% yield, 97:3 e.r.).

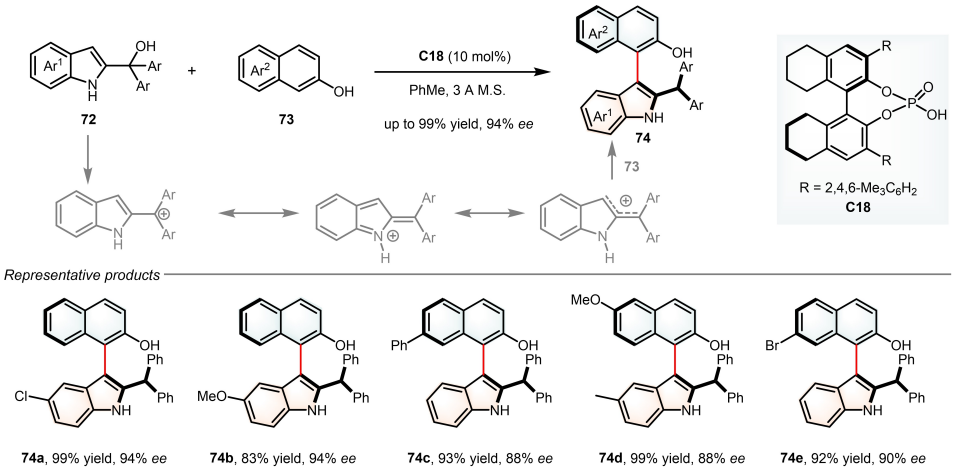
3.2. Formation of Arylalkene Atropisomers

The majority of earlier studies on catalytic atroposelective synthesis were centered on the formation of axially chiral biaryl scaffolds. The catalytic asymmetric construction of axially chiral alkene-arene frameworks is much more challenging due to the lower rotational barriers, lower configurational stability and difficulty in controlling the (*E*/*Z*)-selectivity and enantioselectivity. Thus, the axially chiral alkene-arenes have been much less investigated until recent years.[86–89]

As a class of intermediate similar to the prominent *ortho*-quinone methides, Vinylidene *ortho*-quinone methides (VQMs) feature axial chirality due to their orthogonal π-bonds forming an allene motif. The disturbed aromaticity of the VQM led to its high



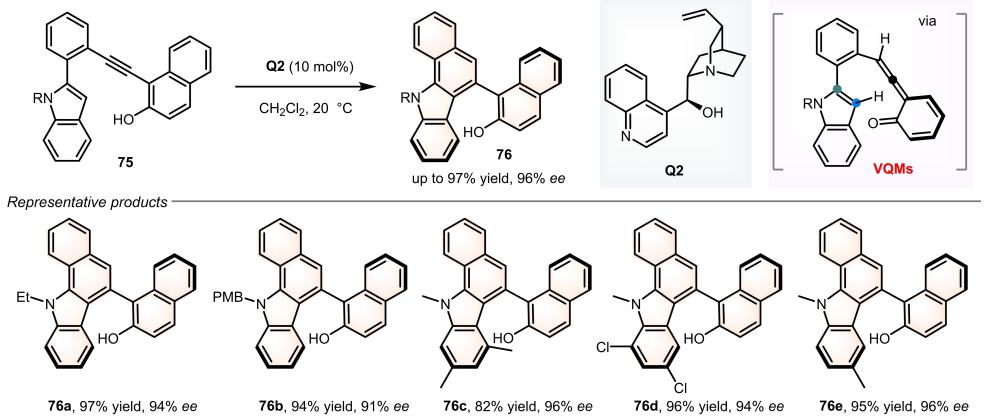
Scheme 19. Atroposelective arylation of nitrosonaphthalenes and indoles.



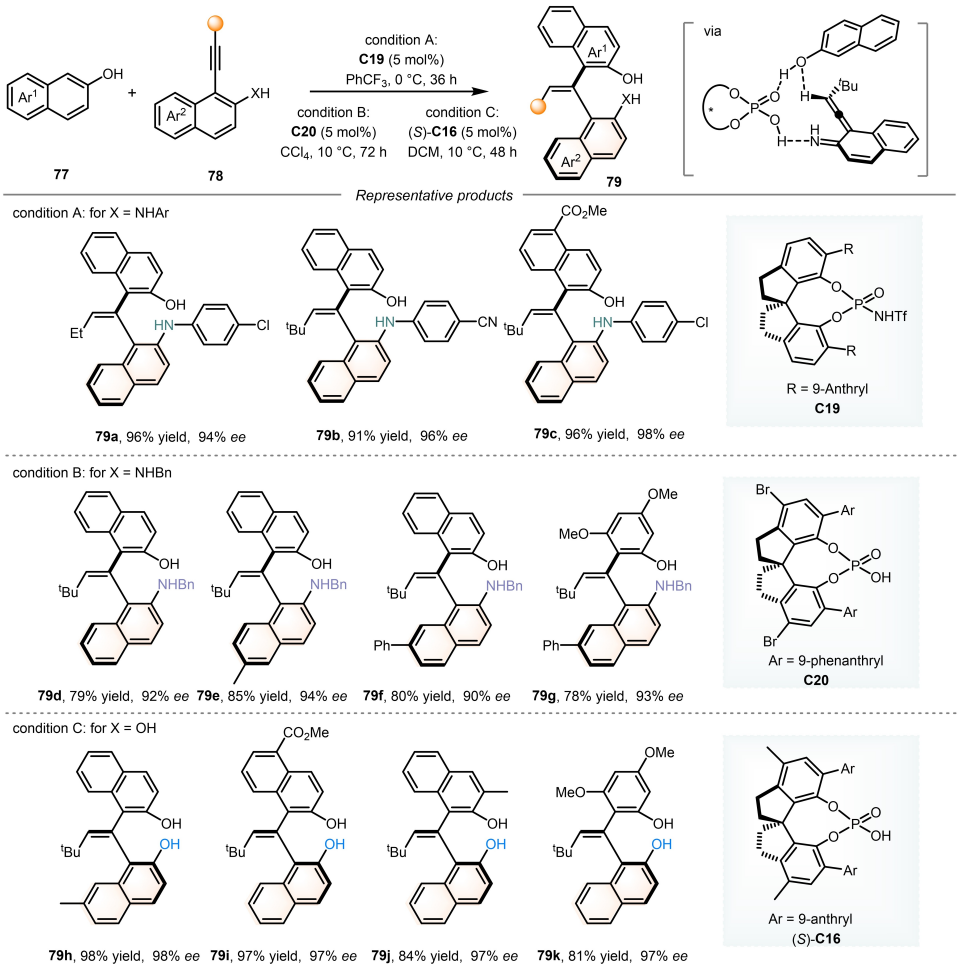
Scheme 20. Catalytic Asymmetric Synthesis of Axially Chiral 3,3′-Bisindoles.

reactivity as an electrophile, which has been demonstrated as high versatile and reactive intermediates in asymmetric catalysis.[24,90,91] VQMs can be generated through a prototropic tautomerization of 2-(phenylethynyl)phenol under basic conditions. By making use of these features, Irie and co-workers established a novel synthetic approach to access axially chiral benzocarbazole derivatives **76** through a sequence of enantioselective tautomerization of 2-(indolylethynyl)phenol **75** that generated an axially chiral VQM and stereospecific Friedel-Crafts alkenylation. The tautomerization of 2-(indolylethynyl)phenol **75** was mediated by the naturally occurring cinchonidine alkaloid, and the formal alkenylation of tethered indole virtually delivered aromaticity-extended axially chiral benzocarbazoles (48–97% yields with 90–96% *ee*) through axial-to-axial chirality transformation (Scheme 21).[92]

The highly electrophilic VQMs can undergo intermolecular trapping with an aromatic ring, resulting in the formation of 1,1-diaryl alkenes. If appropriate steric hindrance is introduced, these alkenes can exhibit a chiral axial configuration. Building upon this concept, Tan and his colleagues in 2019 developed an atroposelective synthesis approach for disubstituted 1,1′-(ethene-1,1-diyl)binaphthol (EBINOL) derivatives **79**. This was achieved through enantioselective Friedel-Crafts alkenylation of 2-naphthols **77** with VQMs generated in situ from *o*-alkynyl-naphthylamines **78** using CPA catalysts. The reaction accommodated not only *N*-aryl alkynylnaphthylamines but also *N*-benzyl alkynylnaphthylamines and *o*-alkynylnaphthols, all demonstrating excellent yields, enantioselectivities, and *E/Z* selectivities (Scheme 22).[93] DFT calculations revealed that the VQM intermediate was generated through a concerted 1,5-H transfer, and the hydrogen bonding between the chiral acid catalyst and the alkyne substrate was crucial for the observed atroposelectivity. The potent application of the structural scaffold developed for the synthesis of EBINOL derivatives is demonstrated by its effectiveness in catalyzing a series of asymmetric reactions.



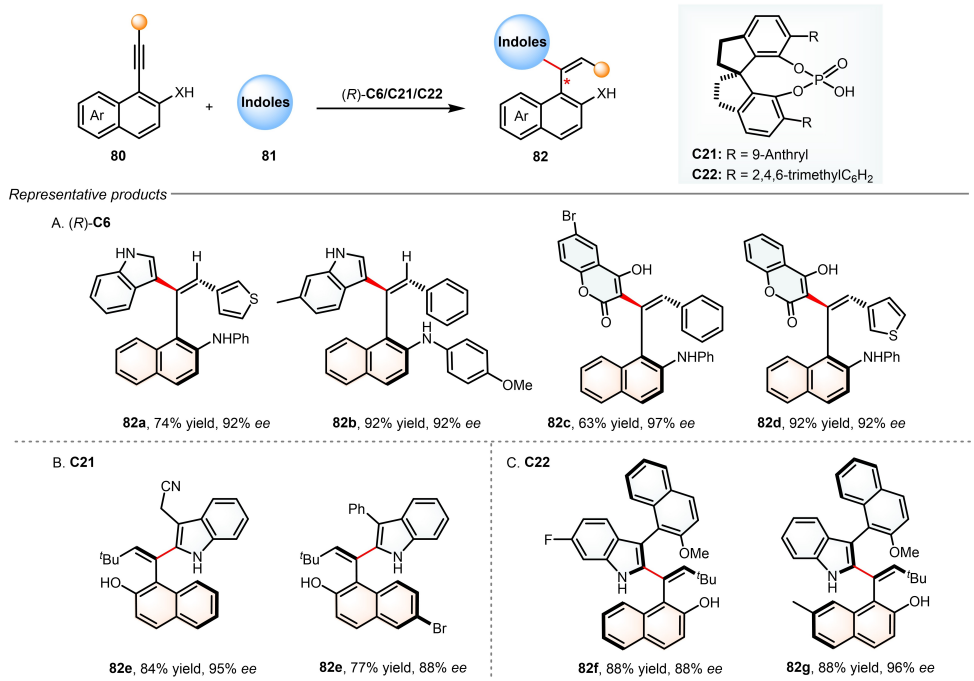
Scheme 21. Asymmetric Synthesis of Axially Chiral Benzocarbazole Derivatives.



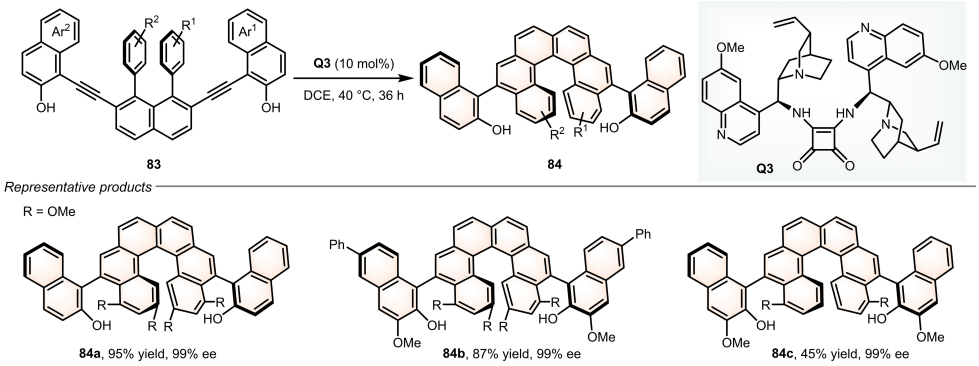
Scheme 22. Atroposelective alkenylation of 2-naphthols to *ortho*-alkynyl-naphthylamines.

The electron-rich arenes utilized intermolecular trapping of VQMs intermediates for construction of axially chiral styrenes have been extended into indole derivatives and others. In 2020, Zhu, Zhang and co-workers developed a CPA-catalyzed atroposelective construction of axially chiral naphthylamine heterocycles with *ortho*-alkynyl-naphthylamines by employing indoles and 4-hydroxycoumarins as the nucleophiles (Scheme 23A).[94] The π–π interaction and hydrogen-bonding network synergistically control the stereoselectivity, resulting in excellent enantioselectivity. Later, Lv's group reported the atroposelective coupling of *ortho*-alkynylnaphthols with various 3-substituted indoles via a C2 Friedel–Crafts alkylation under mild conditions (Scheme 23B).[95] The reaction system was also applicable to the 2-substituted indoles. Very recently, Lin reported the chiral phosphoric acid catalyzed enantioselective Friedel-Crafts alkenylation of 3- naphthyl-indoles **81** with o-alkynylnaphthol **80**, realizing the atroposelective synthesis of axially chiral styrenes bonded to an axially chiral element (Scheme 23C).[96] Under the mild condition, a range of such axially chiral styrenes were obtained in good yields with up to 99.9% ee, >20 : 1 dr and >99 : 1 *E*/*Z*. The reaction could be easy scalable with almost same yields and stereoselectivities as small scale.

In 2019, the Yan group successfully established an organocatalytic method for the asymmetric synthesis of molecules containing helicenes and stereogenic axes through successive intramolecular Friedel-Crafts alkenylations (Scheme 24).[97] This method was established through two steps based on bisquinine squaramide-catalyzed formation of VQMs. The first cyclization of VQMs with pendent benzene ring produced a reaction intermediate containing a stereogenic axis, followed by dynamic kinetic resolution of this helix intermediate in a second cyclization, thus resulting in a class of helically and axially chiral compounds **84** in yields up to 98% with up to 99% ee. Based on the same strategy, they reported a quinine-derived thiourea-catalyzed atroposelective construction of axially chiral biaryl-triols, a class of compounds possessing potential applications as organocatalyst demonstrated in asymmetric Petasis reaction and enantioselective addition.



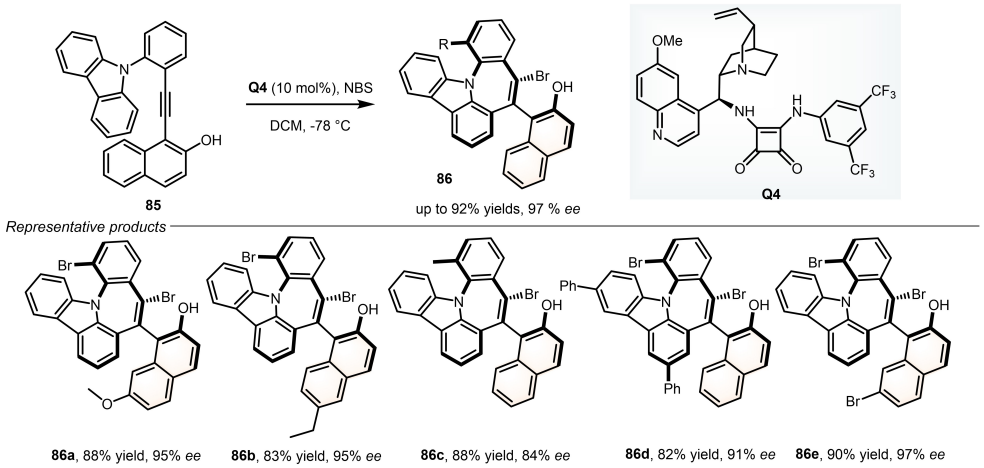
Scheme 23. CPA catalyzed Enantioselective couplings of indoles with o-alkynylnaphthols/amines.



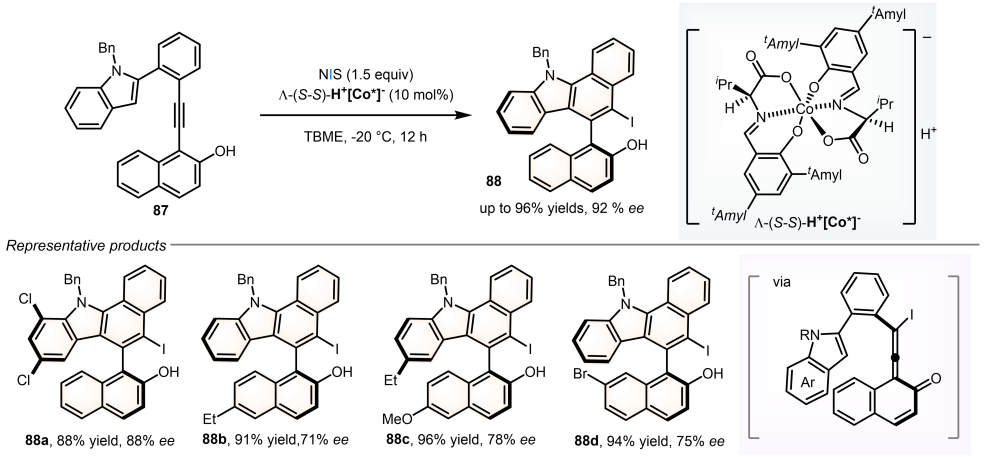
Scheme 24. Atroposelective construction of axially chiral nonsymmetric biaryltriols.

In 2021, the Yan′s group established another organocatalytic Friedel-Crafts alkenylation for the preparation of polychiral molecules **86** bearing four types of stereogenic elements in fused azepines (Scheme 25).[98] In the presence of chiral phosphoric acid, the carbazole moiety **85** undergwent intramolecular electrophilic aromatic substitution with the in situ generated chiral VQM intermediates, exhibiting a wide substrate scope with up to 92% yield, 97% ee and excellent diastereoselectivity (>20:1 dr). The method also demonstrates excellent diastereoselectivity, with diastereomeric ratios exceeding 20:1, and high enantioselectivity, with enantiomeric excesses up to 97%. The derived compounds possess unique optical properties, likely stemming from their helical and axially chiral structures. The optical properties and Ru^{3+}-induced fluorescence responses of these compounds suggest their potential applications in optoelectronic materials and detection of heavy metal ion.

Expanding on a similar approach, Yu and collaborators have successfully achieved the enantioselective synthesis of novel axially chiral iodobenzocarbazole derivatives **86** (Scheme 26).[99] This reaction was accomplished through the intramolecular iodoarylation of indole with intramolecular alkynyl naphthalene-2-ol **85**, employing a cobalt(III)-complex catalyst with chirality-at-metal. The reaction proceeded via the formation of an axially chiral iodinated vinylidene *o*-quinone methide (IVQM) intermediate. This protocol provides 21 examples in excellent yields with good to high enantioselectivities (up to 96% yield, 98% ee). Furthermore, the introduced iodine atoms can easily be



Scheme 25. Organocatalytic Asymmetric Annulation for Construction of Chiral Azepine.

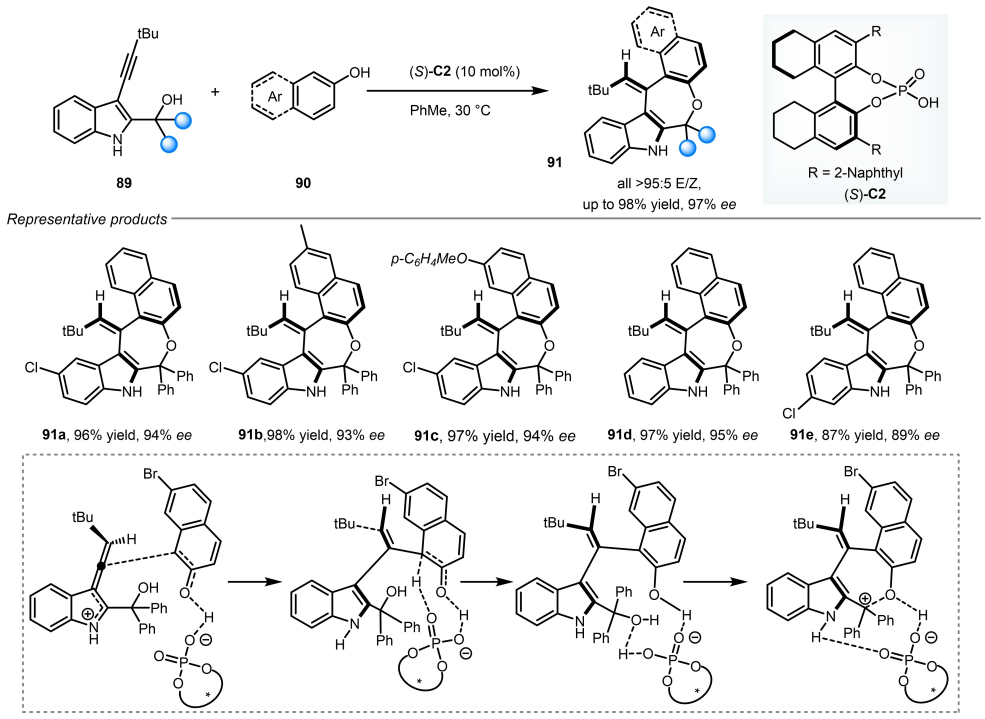


Scheme 26. Cobalt(III)-Catalyzed Iodoarylation of Alkynes for Enantioselective Construction of Axially Iodobenzocarbazole Derivatives.

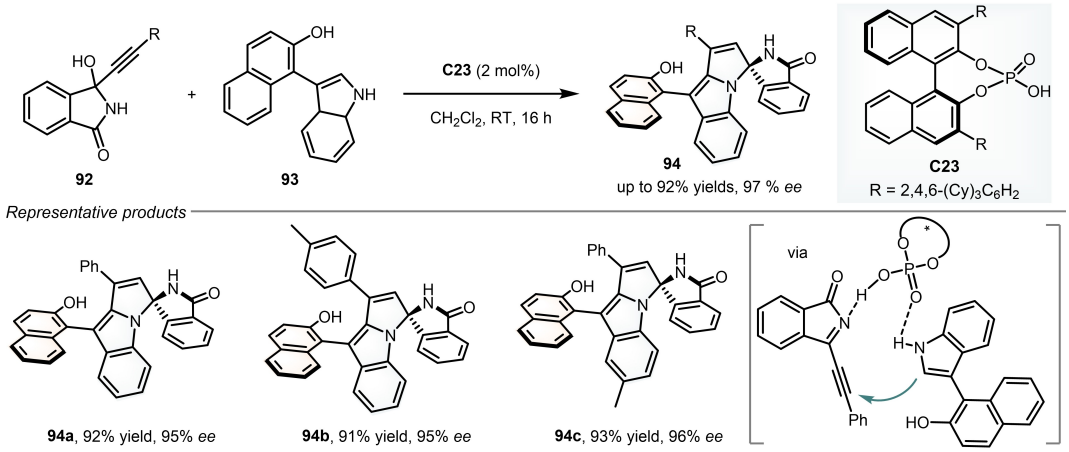
converted into other functional groups. Moreover, the introduced iodine atoms in the synthesized compounds can be readily transformed into other functional groups, further expanding the synthetic versatility and potential applications of these molecules.

In their continuous research on indolylmethanols,[83,85] the Shi group further designed 3-alkynyl-2-indolylmethanols **89** as a new class of indolylmethanols that can serve as 1,4-dielectrophiles building blocks. In the presence of acid catalyst, 3-alkynyl-2-indolylmethanols would generate the C–C double bond when using a nucleophile to attack the alkynyl group. Building on this strategy, 2-naphthols/phenols **90** were employed as 1,3-dinucleophiles that first underwent atroposelective Friedel-Crafts alkenylation with an axially chiral allene-iminium intermediate and subsequent naphthol rearomatization, yielding 3-alkenylindole with axial chirality. Then CPA-catalyzed intramolecular dehydration and etherification proceeded to give formal [4+3] adducts (Scheme 27).[100] Proposal of these multistep sequence was supported by DFT studies. The entire process is characterized by excellent yield and selectivity (all > 95 : 5 *E/Z*, up to 98% yield, 97% ee). This reaction also represents the first catalytic asymmetric construction of axially chiral alkene-heteroaryl scaffolds, which will add a new member to the atropisomeric family.

Recently, Li and coworkers realized CPA-catalyzed [3+2] cycloaddition of α- (3-isoindolinonyl) propargylic alcohols **92** with 1-(3-indolyl)naphthalen-2-ols **93**, affording a broad scope of pyrrolo[1,2-a]indoles bearing both enantioenriched spiroisoindolinone-indoline and atropisomeric naphthalenol frameworks (Scheme 28).[101] These products feature chiral spiro *N*,*N*-acetal carbon stereocenters and a chiral C–C axis. Mechanistically, the reaction was initiated by dehydration of propargylic alcohol **92** to give propargylic *N*-acylimine intermediate, followed by asymmetric 1,4-



Scheme 27. Enantioselective cyclization of 3-alkynyl-2-indolylmethanols with 2-naphthols.



Scheme 28. Asymmetric organocatalytic [3+2] annulation for spiro isoindolinone-indoline and atropisomeric naphthalenol frameworks construction.

addition of 2-(3-indolyl)naphthalenol **93** to form axially chiral allene. Protonation of allene and subsequent enantioselective intramolecular annulation furnished the desired product **94** and regenerated catalyst **C23**.

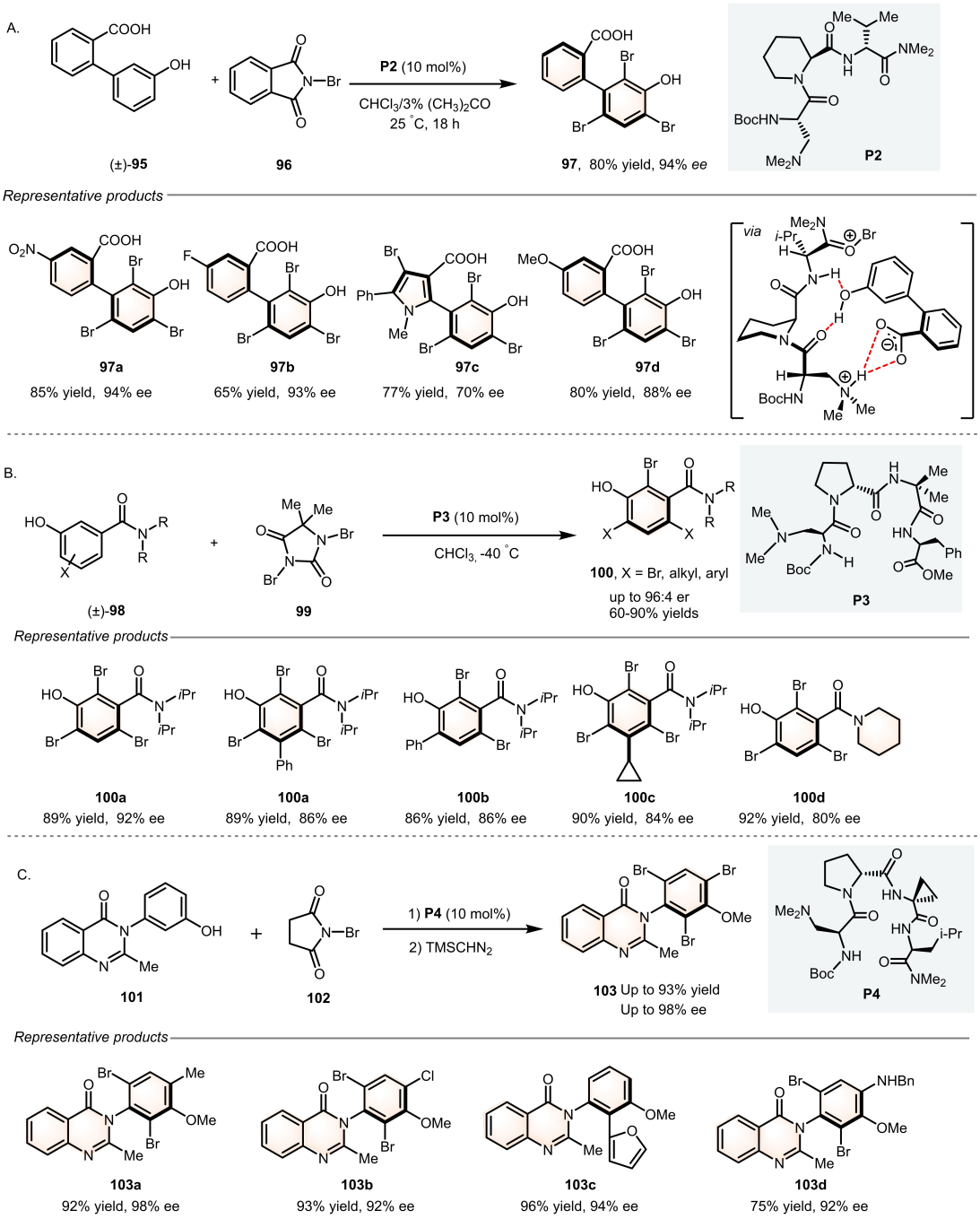
4. Atropisomers Synthesis via Friedel-Crafts C(sp^2)-Heteroatom Bond Formation

4.1. Enantioselective Friedel-Crafts Halogenation

In the realm of constructing atropisomers via the Friedel-Crafts halogenation reaction, the establishment of the carbon-halogen bond as the chiral axis remains unknown. However, by introducing halogens, it becomes possible to enhance the rotational energy barrier of a specific axis, thereby conferring stable chirality.[25]

This is primarily achieved through bromination reactions. One key factor contributing to the predominance of bromination is the relative ease with which electrophilic bromination reactions can be conducted. Additionally, the larger size of bromine atoms plays a significant role in augmenting the rotational energy barrier. Consequently, bromination serves as the primary method for increasing the stability of configuration, minimizing the likelihood of racemization. Friedel-Crafts halogenation provides a novel avenue for the creation of atropisomers, opening up new avenues for exploring the synthesis and applications of atropisomers.

In 2010, the Miller group accomplished the first dynamic kinetic resolution Friedel-Crafts bromination for the construction of biaryl atropisomers by designer peptide catalysts (Scheme 29A).[102] Notably, the tripeptide-derived small-molecule catalyst **P2** exhibited selective binding to one configuration of the substrate through intermolecular hydrogen bonding. This facili-



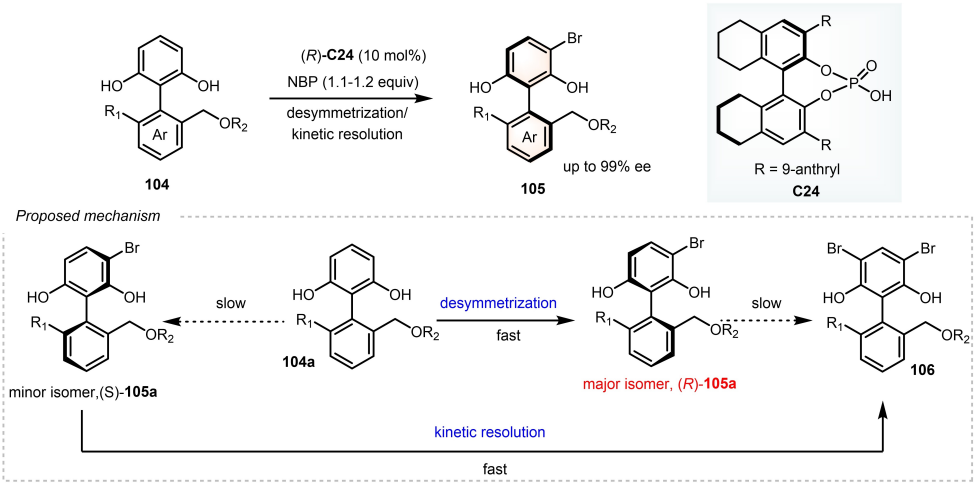
Scheme 29. Friedel-Crafts bromination to construct biaryl atropisomers.

tated the bromination reaction of the substrate with electrophile *N*-bromophthalimide, effectively enhancing the configurational stability of the chiral C–C axis. The desired product with *R*-configuration was obtained with an impressive isolated yield of 80% and enantiomeric excess of 94%. This reaction exhibited remarkable substrate tolerance, accommodating substrates containing methoxy, nitro, and fluorine atoms (**97a**, **97b**, **97d**). It was suitable for heterocyclic aromatic hydrocarbon substrates (**97c**). Molecular docking suggested that the substrate underwent a specific conformational arrangement facilitated by the formation of a salt bridge between the β-*N*,*N*-dimethylamino alanine tertiary amine and the substrate carboxylic acid. This arrangement disposed a putative O-bromonium ion toward formation of the observed stereoisomer.

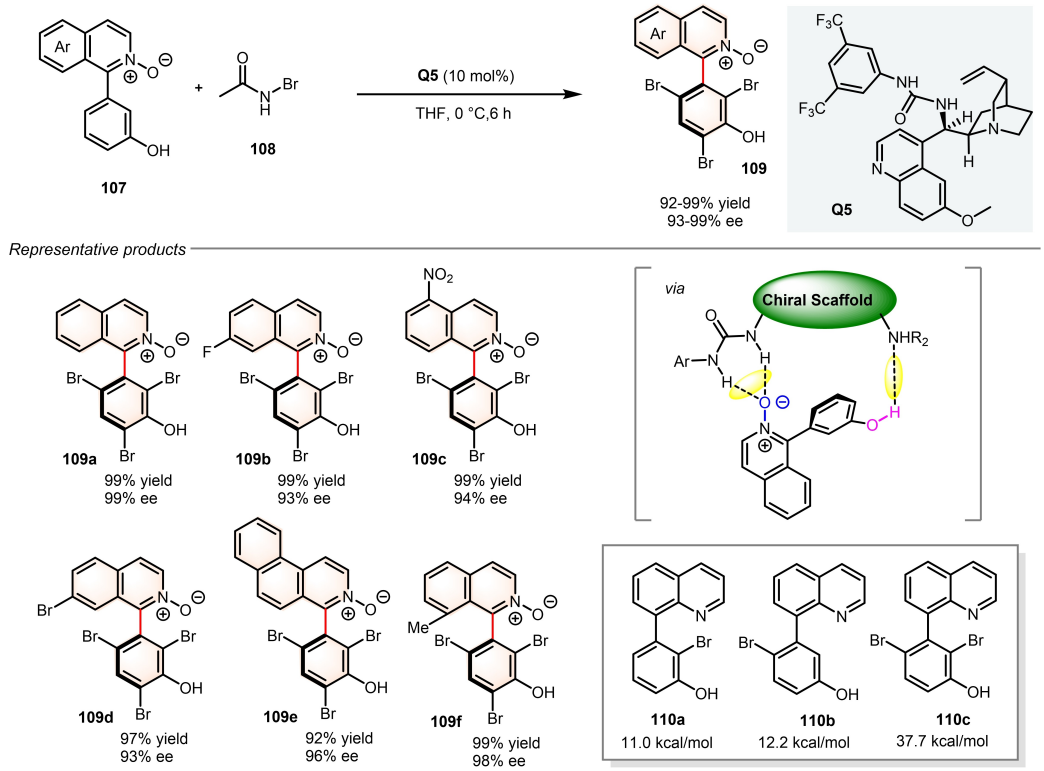
The use of polypeptide catalysts has continued to shine in subsequent research efforts. Tertiary aromatic amides with appropriate substitution may exhibit axial chirality about the carbonyl carbon-aryl carbon bond axis. Differential biological activity has been noted for isolated enantiomers of chiral benzamide drugs and drug candidates.[14,15] In 2013, the Miller group successful developed enantioselective synthesis of atropisomeric benzamides through peptide-catalyzed bromination (Scheme 29B).[103] A tetrapeptide catalyst **P3** containing a tertiary amine was used, and tertiary benzamides exhibited sufficiently high barriers to racemization after *o*-bromination, which were isolated in up to 90% yield with 92% ee. In 2014, Miller extended their exemplary peptide catalysis to the construction of unsymmetrical amides exhibiting two asymmetric axes. These axes are defined by a benzamide substructure and differentially *N*,*N*-disubstituted amides, respectively.[104]

In 2015, Miller developed a tertiary amine-embedded β-turn peptide and further extended the above peptide-catalyzed system to the atroposelective bromination of pharmaceutically relevant 3-arylquinazolin-4(3H)-ones **103** (Scheme 29C).[105] The Friedel-Crafts o-bromination determined the stereochemistry of the product, and the second bromination further increased the rotational energy barrier. The low rotational energy barrier of the reactants (18.8 kcal/mol) allowed for continuous racemization of the reactants during the slow stepwise addition of N-bromosuccinimide, thus achieving an enantiomeric excess of 94% in the manner of dynamic kinetic resolution. The reaction has good tolerance to the substituents at different positions of the substrate, and the installed bromo group facilitated downstream conversion into other atropisomerically defined products of interest without erosion of enantiopurity.

Apart from the previously mentioned polypeptide catalysts, there has been notable progress in the development of organic small molecule catalytic systems, particularly those involving chiral cinchona alkaloids and CPA. In 2013, Takahiko et al. successfully realized the enantioselective synthesis of multi-substituted biaryl derivatives by chiral phosphoric acid catalyzed asymmetric bromination (Scheme 30).[106] The efficient tandem of desymmetrization and kinetic resolution processes provides the reaction with excellent enantioselectivity (up to 99%). The effective hydrogen bonding interaction between the substrate and the CPA catalyst plays a key role in it. Then in 2015, Matsubara reported highly atroposelective aryl bromonination reactions by using a bifunctional quinidine-urea catalyst, which afforded axially chiral isoquinoline N-oxides **109** with a broad substrate scope (Scheme 31).[107] The enantioinduction of this process relied on hydrogen-bonding interactions between N-



Scheme 30. Friedel-Crafts bromination to construct multisubstituted biaryl derivatives.



Scheme 31. Highly enantioselective synthesis of axial chiral biaryl products by quinine catalysis..

oxide and urea groups and that between phenol and amine groups, which twisted the molecule in one direction. Electrophilic bromination at the *ortho*-position of the axis determined the chiral conformation of the product, but only when both *ortho*-positions of the axis are brominated the rotational energy barrier is sufficient to stabilize the molecular configuration. This atroposelective bromination strategy was found to be also applicable to the asymmetric construction of an axially chiral cyanoarene skeleton.[108]

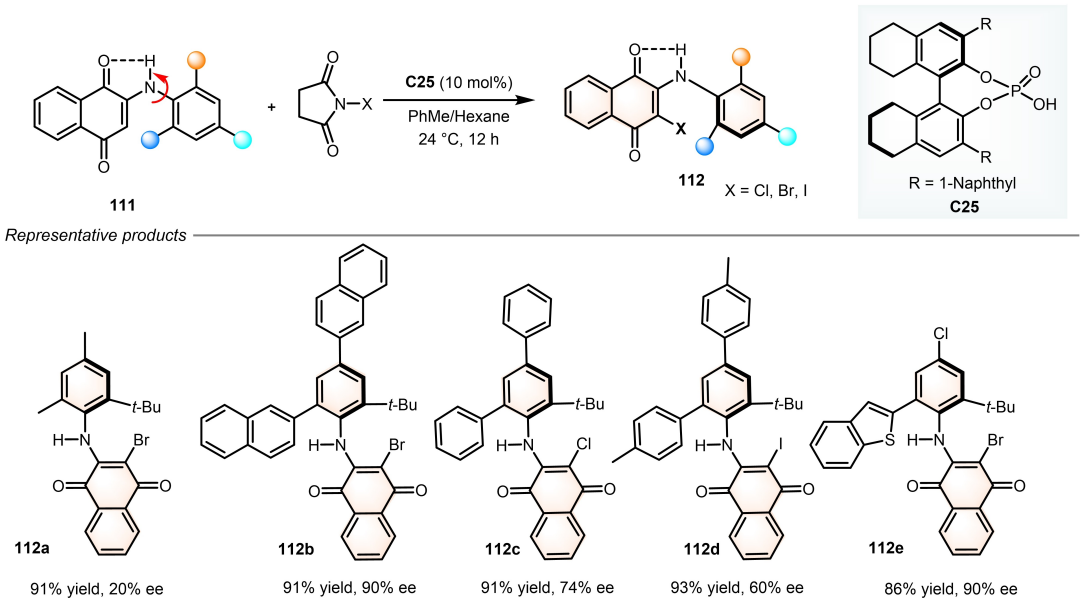
Diarylamines and related scaffolds are highly prevalent in modern drug discovery. Enantioselective synthesis has been largely unexplored due to the inherent stereochemical instability of the potential two axes. In 2020, the Gustafson group successfully developed a CPA-catalyzed atroposelective Friedel-Crafts halogenation method for *N*-aryl quinoids **111**, which bear structural analogous to diarylamines. This method enabled the efficient synthesis of a diverse range of stereochemically stable *N*-aryl quinoids **112** with excellent yields and atroposelectivity. The high configurational stability is attributed to the presence of strong intramolecular N–H–O hydrogen bonding interaction, effectively locking one of the chiral axes into a planar conformation. This advancement opens the door to further exploration and utilization of diarylamine-based compounds in drug discovery. (Scheme 32).[109]

In addition to bromination, an atropselective iodination of 2-amino-6-arylpyridines catalyzed by chiral disulfonimides (DSIs) was disclosed by Denmark and co-workers very recently. In this work, the machine learning methods was applied to screen suitable chiral catalysts. By using high-level data fusion technology, they successfully predict the performance of the catalyst and established a series of DSI catalysts with high stereoselectivity and versatility to obtain the desired product **114** with >99% yield and 82% ee (Scheme 33).[110]

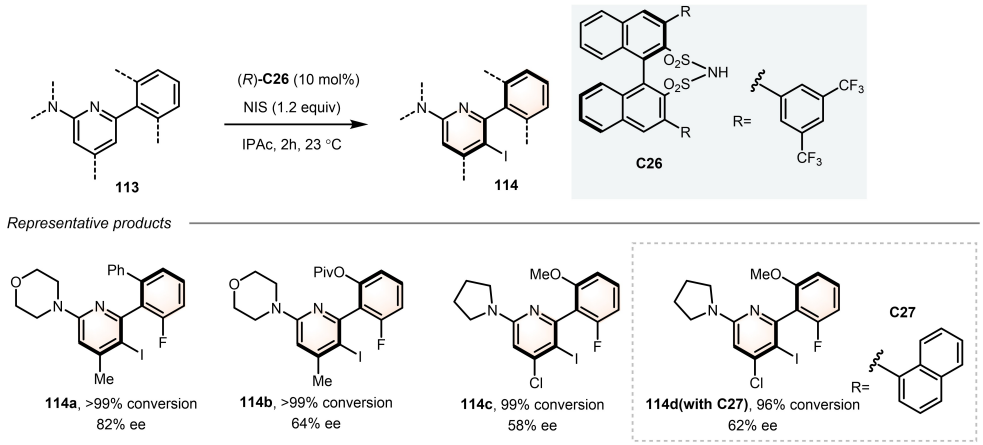
4.2. Formation of Atropisomers via Enantioselective Friedel-Crafts Sulfenylation

Chiral organosulfur compounds are widely found in pharmaceuticals, bioactive natural products and are useful chiral organocatalysts and ligands.[111–114] Enantioselectively catalyzed electrophilic sulfenylation reactions are a straightforward and efficient strategy for the synthesis of chiral organosulfur compounds. In contrast to widely exploration on enantioselective electrophilic sulfenylation for centrally chiral organosulfur compounds synthesis,[114–116] the enantioselective construction of axially chiral sulfur-containing compounds based on this strategy is underdeveloped.

In 2020, Zhao and co-workers reported the first example of clytic enantioselective sulfenylation by



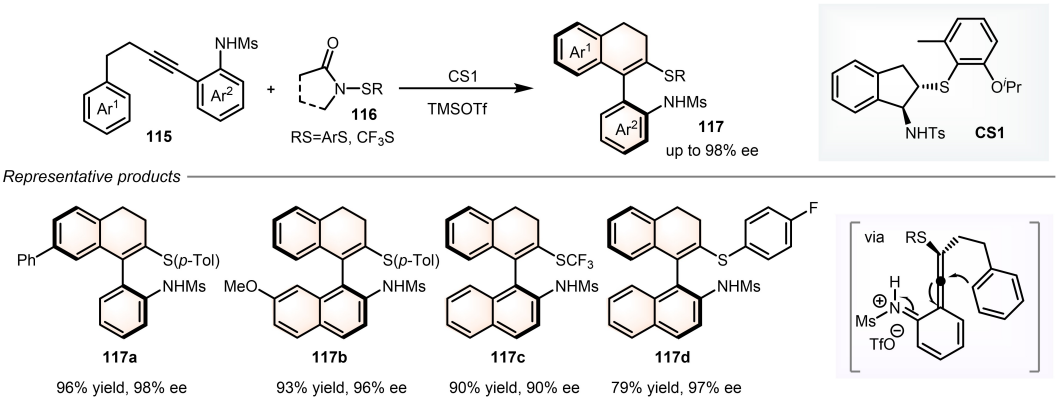
Scheme 32. Atroposelective synthesis of diarylamine-like backbones via chiral phosphoric acid catalysis.



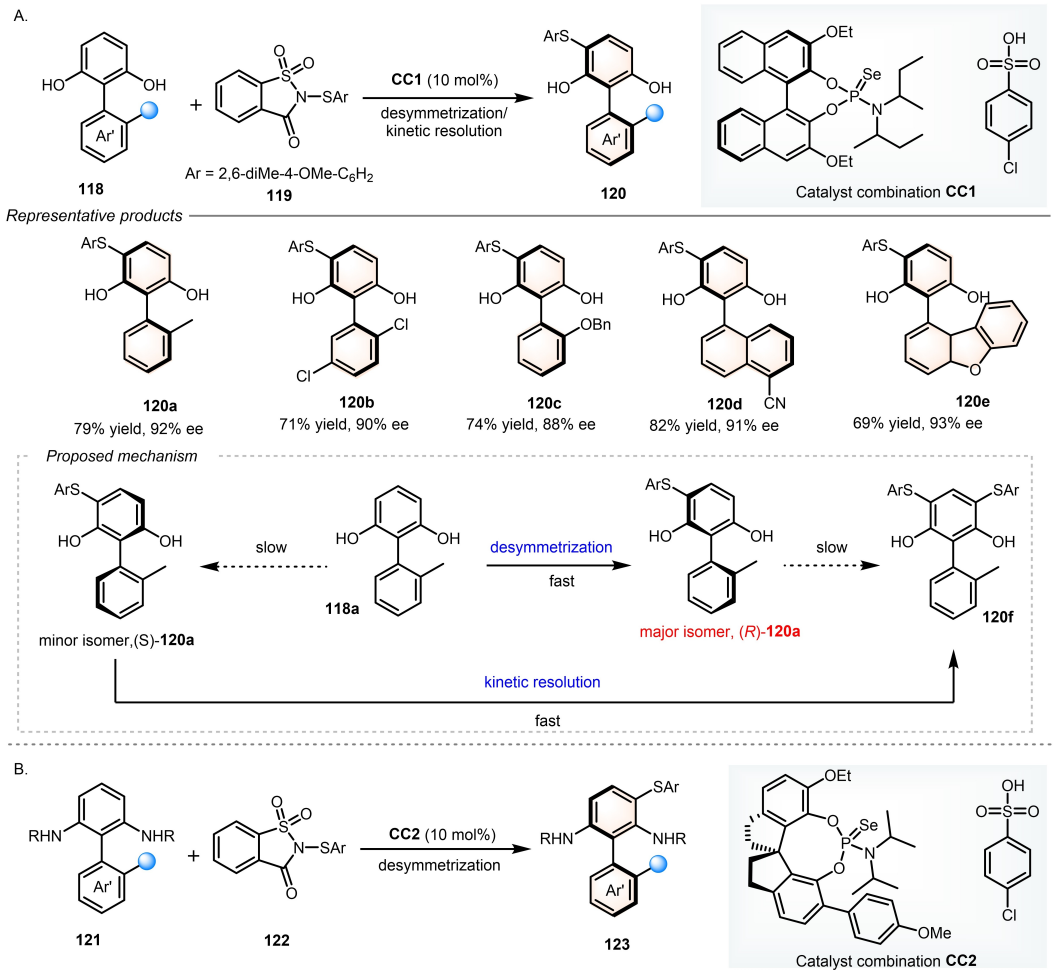
Scheme 33. Discovery of atropselective iodination catalyst guided by high-level data fusion.

employing their developed indane-based chiral aryl chalcogenide catalyst **CS1**, accomplishing the synthesis of axially chiral amino sulfides in good yields with high enantioselectivities from the Ms-protected *ortho*-alkynylaryl amines **115** (Scheme 34).[117] Both the electrophilic aryl sulfide and trifluoromethylsulfide reagents **116** were both applicable in the reaction. The H-bonding network between the substrates and the catalyst was slightly affected by the amine protecting group, therefore, the proper selection of protecting group is crucial to achieve high enantioselectivity. The products could be easily converted into other valuable axially chiral compounds such as biaryl amino sulfides, biaryl phosphine sulfides, etc.

In 2022, Chen and co-workers disclosed the enantioselective electrophilic sulfenylation of biphenol compounds **118** for construction of axial chiral sulfur-containing diphenylene oxides **119** via a desymmetrization strategy, employing the catalyst combination of a novel 3,3′disubstituted BINOL-derived selenides and achiral sulfonic acids (Scheme 35A).[118] The optimized catalysts exhibited moderate to good yields with excellent enantioselectivities over the range of substrates evaluated. The choice of added acids and its amount in the reaction are both important for the enantioselectivity because of its crucial role in the hydrogen bonding network. Further mechanism studies revealed that a tandem process of desymmetrization and kinetic resolution was involved in the system, which is also the source of the high enantioselectivity of the reaction. Very recently, this strategy was successfully applied to synthesis of axially chiral



Scheme 34. Chiral sulfide-catalyzed Enantioselective carbothiolation for construction of axially chiral amino sulfides.



Scheme 35. Construction of axially chiral sulfur-containing diphenyl ethers.

sulfur-containing biaryl anilines through electrophilic sulfenylation of biaryl anilines by the same group (Scheme 35B).[119]

In this work, only a desymmetrization process was involved in the system. In addition to the aforementioned works, Chen's team also reported an antropose-lective electrophilic thiocyanation of indole compounds with *N*-thiocyanatosaccharin for construction of axially chiral SCN-containing 3-aryl indoles via kinetic resolution approach. However, only moderate enantioselectivity was achieved.[120]

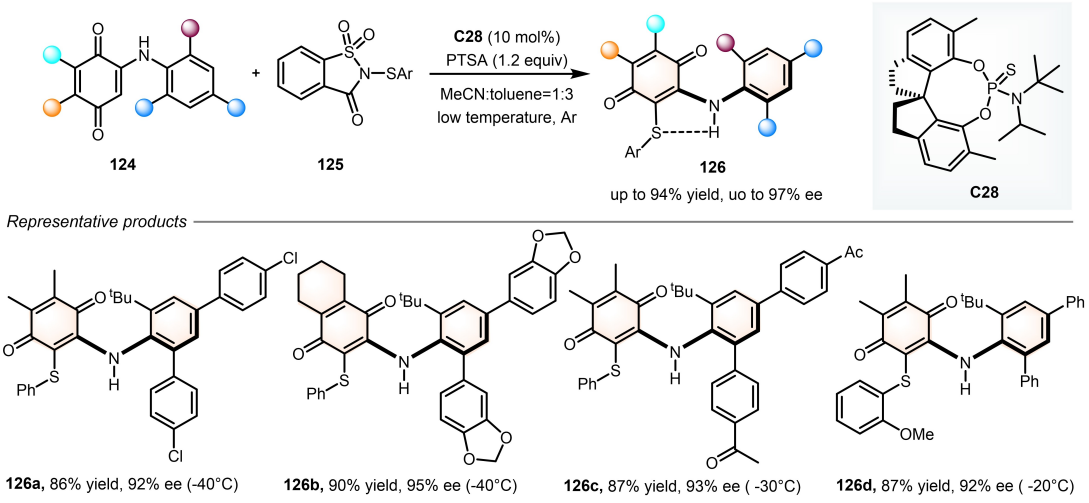
Comparing to the extensively studies on construction of the C–N axes between C(sp^2) atoms and acyclic tertiary amides or tertiary cyclic amino groups,[20,121,122] the construction of C–N axial chirality in diarylamines and related scaffolds is less developed. In 2022, the group of Chen developed an enantioselective electrophilic sulfenylation of *N*-arylaminoquinone derivatives **124** with sulfenylating reagent **125** (Scheme 36)[123] in the presence of p-toluene sulfonic acid (PTAS) by employing the newly designed chiral 6,6′-disubstituted SPINOL-derived sulfide as catalyst. Under mild conditions, the reaction afforded a range of axially chiral sulfur-containing diarylamine derivatives in moderate to excellent yields and enantioselectivities. The introduced sulfur-containing group could act as a hydrogen bond acceptor into the substrate molecule to form an intramolecular five-membered ring N–H···S hydrogen bond, thereby fixing one of the C–N axes in the five-membered ring plane. Thus, the other C–N axis can be more easily blocked to stabilize the C–N axis.

4.3. Formation of Atropisomers via Enantioselective Friedel-Crafts Amination

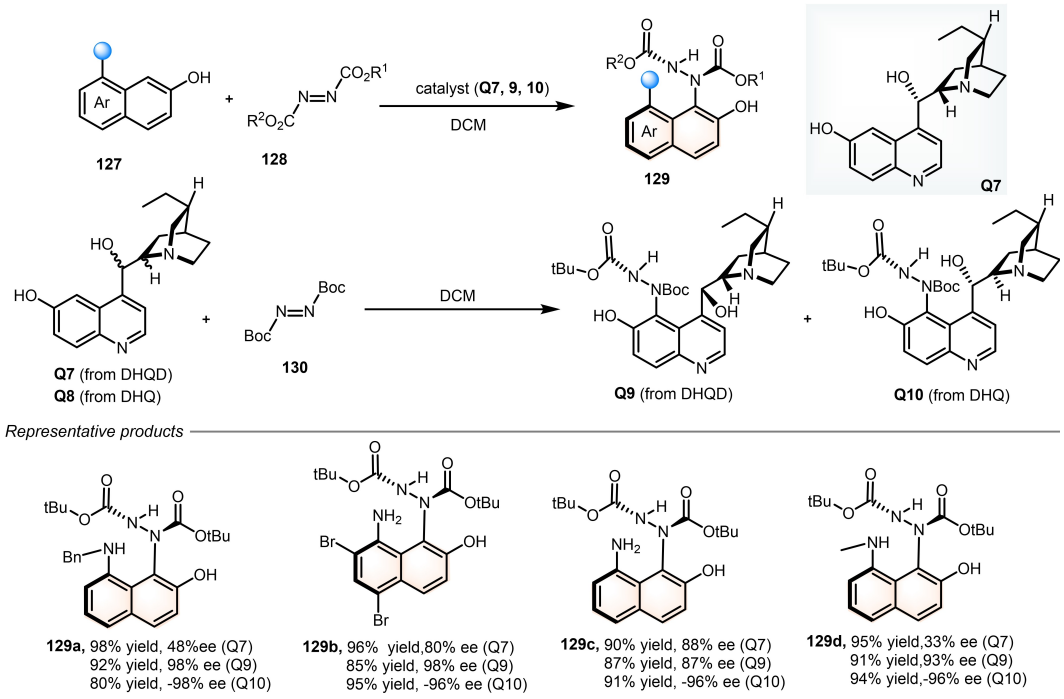
In addition to the aforementioned approach, another approach employed in the field is the utilization of Friedel-Crafts amination. Currently, there are two main strategies. One involves direct formation of a new chiral C–N axis by catalytic C–H amination, which requires introducing large sterically hindered nitrogen-containing side groups to increase the rotational energy barrier. Alternatively, atropisomers can also be achieved by C–H amination that increases the rotation barrier of an existing axis.

Azodicarboxylates represent a versatile amination reagent and essential building blocks with high electrophilicity for the synthesis of complex molecules.[124] In 2006, Jørgensen's group constructed a new class of non-biaryl axial chirality skeleton through direct asymmetric Friedel-Crafts amination reaction of 8-amine-2-naphthol **127** and azodicarboxylates **128** catalyzed by cinchona alkaloids (Scheme 37).[125] Although amination of activated naphthalenes with azodicarboxylates has been known for a century, these products were recognized as chiral compounds. Jørgensen found that the amino group at the C8 position of the naphthalenes was crucial in stabilizing the chirality of the axis. Interestingly, the authors further discovered that cinchona alkaloids **Q7** and **Q8** underwent Friedel-Crafts amination with **130**, giving rise to modified alkaloids **Q9** and **Q10**, which were suitable catalysts for a series of amino-2-naphthol derivative substrates with excellent yield and enantioselectivity recorded. This serendipitous discovery demonstrated the potential of this Friedel-Crafts amination with azodicarboxylates for late-stage C–H functionalization.

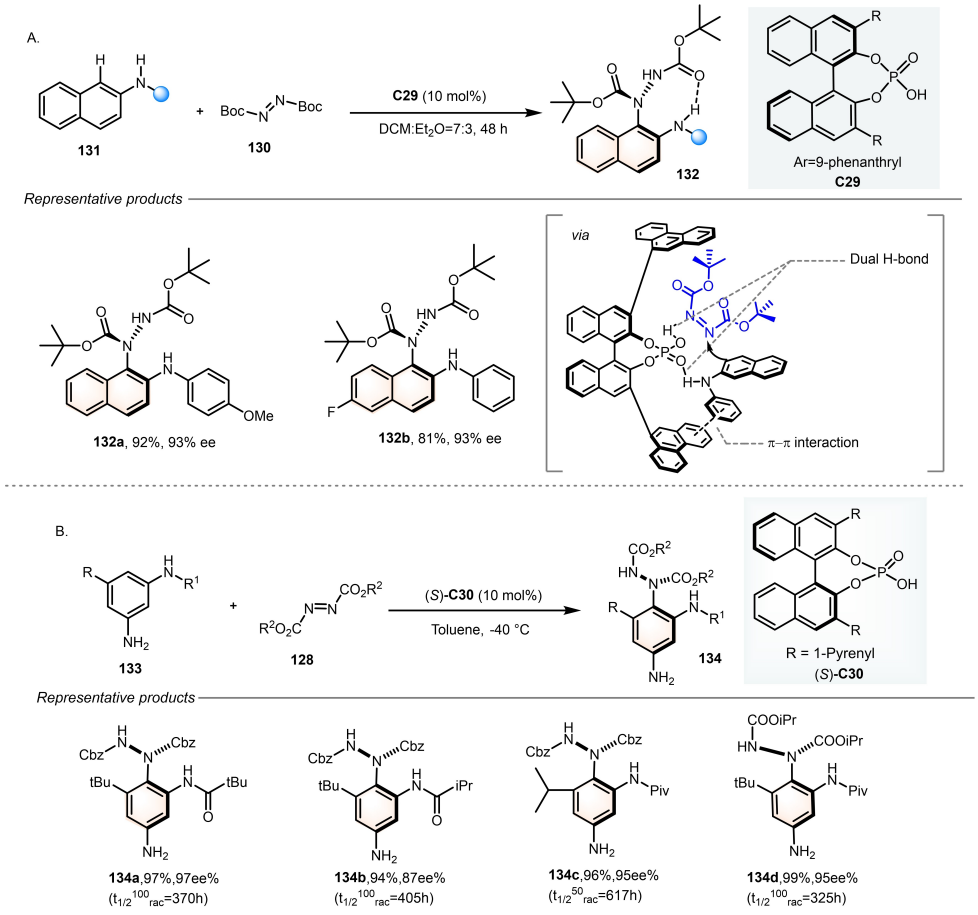
The direct atroposelective Friedel-Crafts amination was not further explored until the CPA-catalyzed enantioselective C–H amination of N-aryl-2-naphthylamines **131** and azodicarboxylates **130** disclosed by Zhang in 2019.[126] Di-*tert*-butyl azodicarboxylate was used as the aminating reagent taking advantage of its large steric hindrance, and the configurational stability of the newly formed C–N axis of products **132** was benefited from intramolecular hydrogen bond between naphthylamines NH and the carbonyl of the Boc group. The stereoselectivity was proposed to be originated from synergistic π–π interaction and dual H-bond between CPA and both reactants (Scheme 38A). In 2020, Yang and coworkers extended a similar CPA-catalyzed asymmetric Friedel-Crafts amination for functionalizing 1,3-benzenediamines also using azodicarboxylate. The resulting benzenetriamine framework exhibited remarkably high atropostability with a



Scheme 36. Enantioselective electrophilic sulfenylation of N-arylaminoquinone derivatives.



Scheme 37. Construction of non-biaryl axial chiral framework through asymmetric Friedel-Crafts amination.



Scheme 38. CPA-catalyzed enantioselective C–H amination..

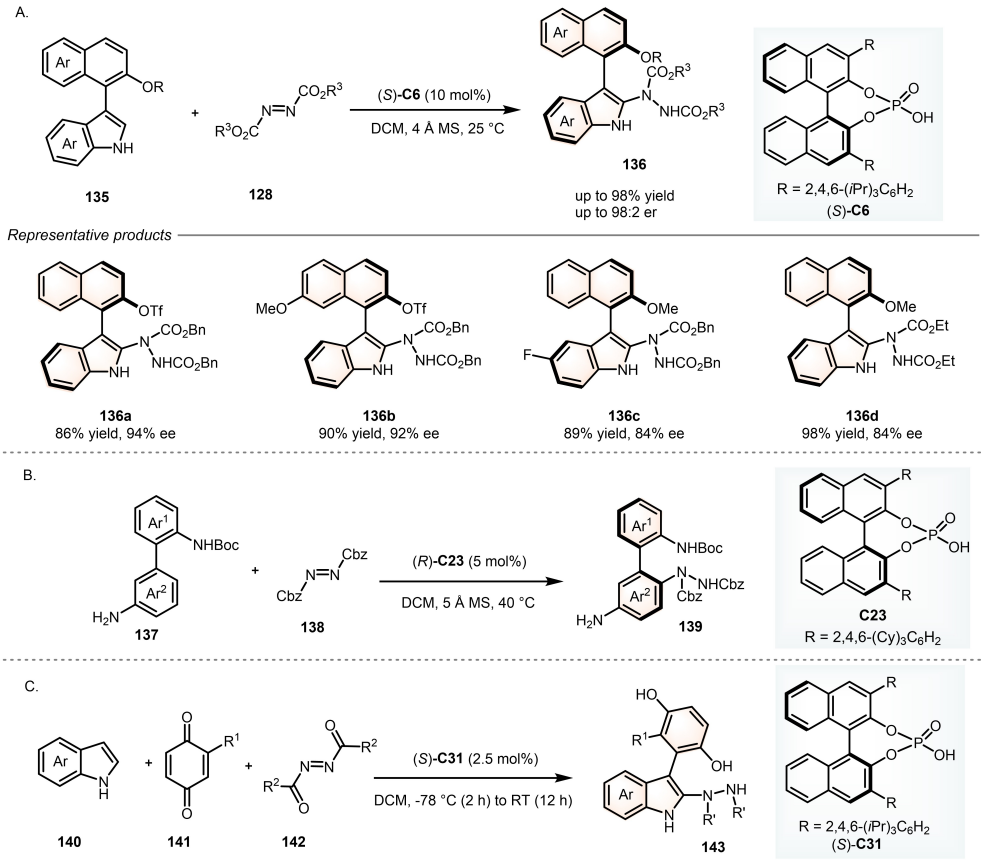
racemization half-life of up to 405 hours at 100 °C (Scheme 38B).[127]

While the reactivity of azodicarboxylates could be harnessed to generate a chiral C–N axis provided a bulky group of sufficient steric hindrance is attached nearby, they were more extensively used to enhance the atropostability of existing axes through Friedel-Crafts amination. For instance, in their continuous studies on atroposelective synthesis of axially chiral indole derivatives, Shi applied this Friedel-Crafts amination strategy to functionalize C2 position of naphthyl-indoles **135**, affording atropomerically stable naphthyl-aminoindoles **136** in good yields and enantioselectivities. used the electrophilic Friedel-Crafts reaction of racemic naphthylindole **135** with bulky and electrophilic azodicarboxylates **128** to construct optically active axial chiral naphthylindole **136** (Scheme 39A).[26] The similar strategy was also reported and applied for asymmetric synthesis of biaryl diamines by Yang (Scheme 39B).[128] And in 2024, by generation of 3-naphthyl-indoles in-situ, Lu and coworkers realized the construction of axially chiral indole-containing molecules through the 2,3-difunctionalization of simple indoles with benzoquinone and azodicarboxylates in one-pot (Scheme 39C).[129]

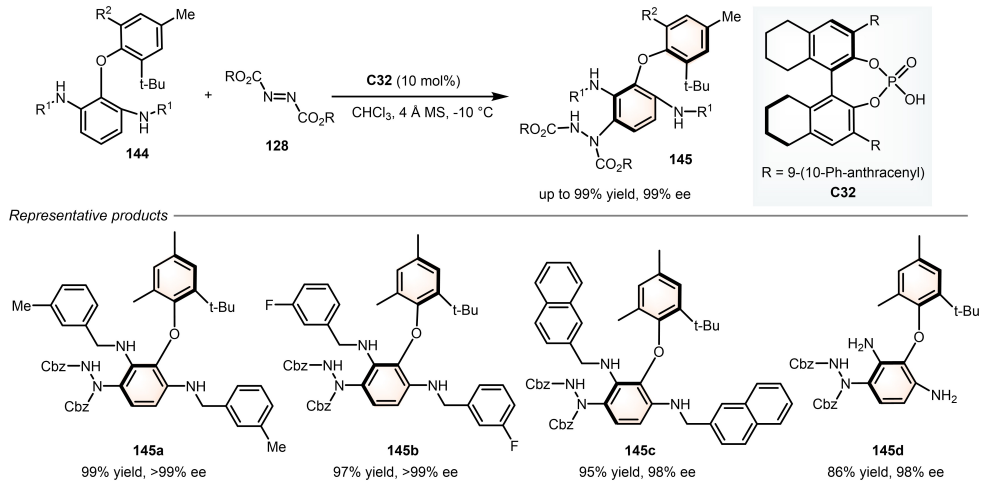
Axially chiral diaryl ethers constitute a class of unique atropisomers bearing two potential axes with potential applications various research fields. However, compared to the catalytic asymmetric synthesis of biaryl or other types of atropisomers, the enantioselective synthesis of these diaryl ether atropisomers has received limited attention.[130,131]

In 2023, Yang and coworkers accomplished the asymmetric synthesis of a range of axially chiral diaryl ether atropisomers **145** using a desymmetry strategy (Scheme 40).[132] The process involved CPA-catalyzed asymmetric Friedel-Crafts amination of arylamines **128**, resulting axially chiral diaryl ether in excellent yields and enantioselectivities. They further demonstrated facile derivatization of these products into a series of novel azaarene-containing diaryl ether atropisomers.

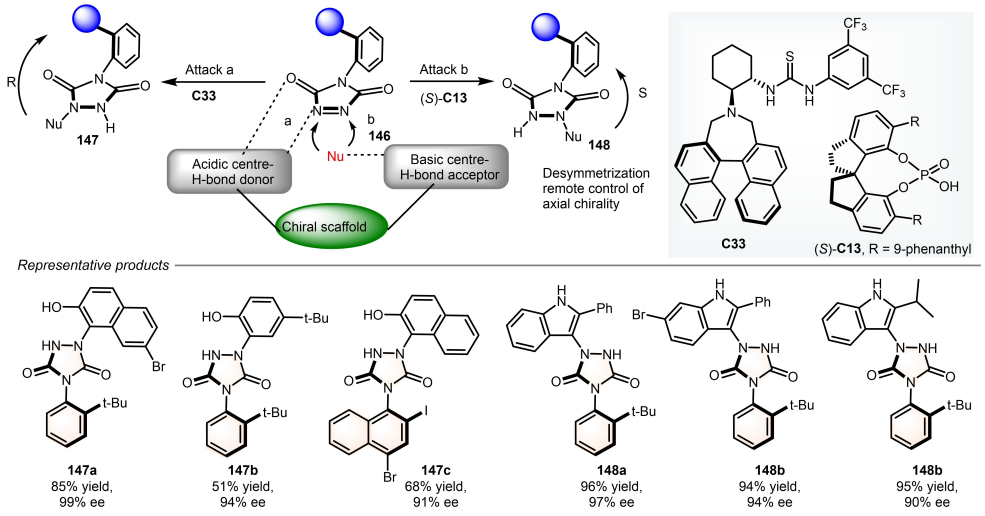
As can be seen above, the discovery of efficient electrophilic amination reagents and the design of prochiral substrates are of high importance in the atroposelective Friedel-Crafts amination. In 2016, Tan and Liu presented an enantioselective C–N amination method for phenols and indoles utilizing *N*-aryl urazoles (Scheme 41).[133] This reaction was inspired by the tyrosine click reaction developed by Barbas, where a specific class of cyclic triazodiones reacted



Scheme 39. Construction of axial chiral naphthalene indoles & biaryl diamines through Friedel-Crafts amination.



Scheme 40. Symmetric synthesis of axial chiral diaryl ether atropisomers through Friedel-Crafts amination.



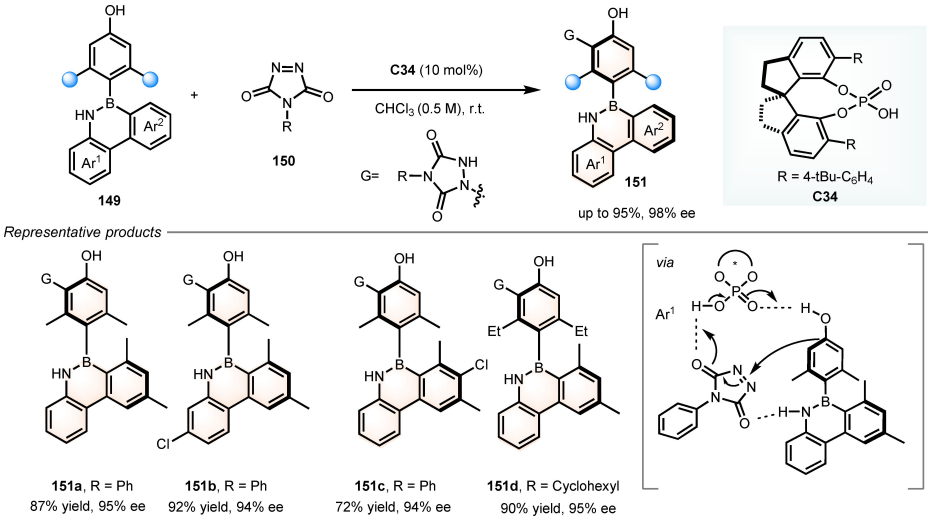
Scheme 41. Atropisomerized *N*-aryl urazoles through asymmetric Friedel-Crafts amination.

selectively and rapidly with the phenol side chain of tyrosine in the field of bioconjugate chemistry. For this enantioselective C–N amination, chiral bifunctional thiourea-tertiary amine **C33** was employed as the organocatalyst for phenols, while CPA (*S*)-**C13** served as the organocatalyst for indoles. These catalysts effectively discriminated between the two reaction sites in the N–N double bond and facilitated the activation of both the electrophile and nucleophile through hydrogen bonding. This led to fidelious transfer of the stereochemical information of the catalyst to the *N*-Ar axis, which is located at a significant distance from the reaction site.

In 2021, Tan and collaborator established the catalytic enantioselective construction of axially chiral *B*-aryl-1,2-azaborines **151** with a C–B chiral axis through asymmetric Friedel-Crafts amination by employing cyclic triazodiones (Scheme 42).[134] The 1,2-Azaborine subunit was known as the isosteric and isoelectronic surrogate of a benzene ring generated from the replacement of the C═C with a B–N subunit in a monocyclic 6-membered arene. The potential of 1,2-azaborines in material science and medicinal chemistry have spurred increasing interest to explore the construction of axially chiral C–B bond.

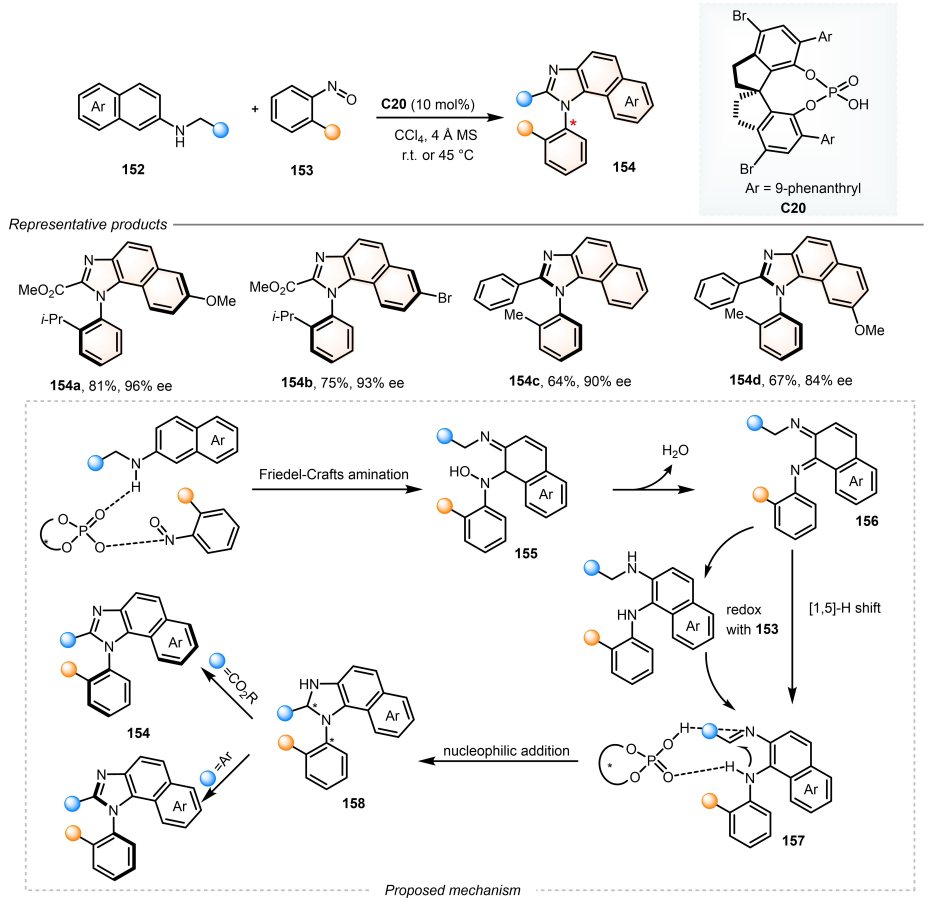
The authors took the approach of on locking the free rotation around an existing C–B stereogenic axis through atroposelective C–H amination of prochiral aryl-1,2-azaborines. The remote chiral chemical control is also achieved through the multi-point hydrogen bond interaction between CPA catalyst and the two substrates.

In seeking to alternative approaches to synthesize atropisomeric benzimidazoles, Tan and collaborators designed an elegant domino reaction based on the unique chemistry of nitroso compounds



Scheme 42. Catalytic enantioselective construction of axially chiral B-aryl-1,2-azaborines.

(Scheme 43).[135] This process started from CPA-catalyzed Friedel-Crafts amination of 2-naphthylamine derivatives **152** with nitrosoarene **153** as the electrophile in high chemoselectivity and regioselectivity, rendering the formation of the dearomatized hydroxylamine **155**. Dehydration of this intermediate gave rise



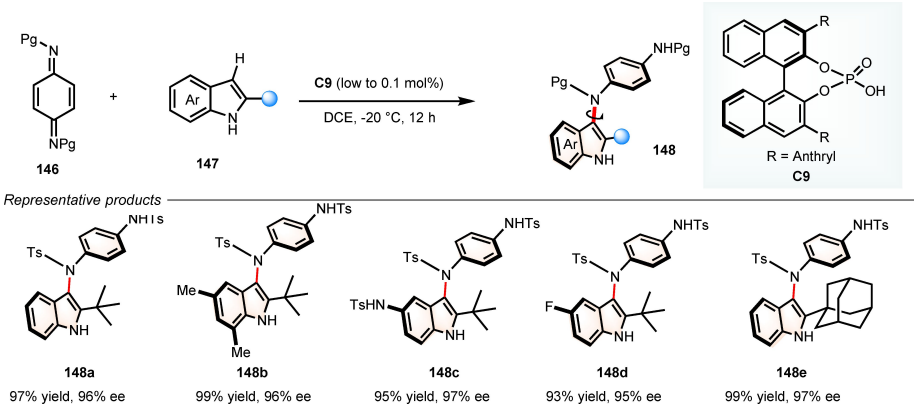
Scheme 43. A unique domino reaction construct of N-arylbenzimidazole atropisomers.

to diimine **156**, which was proposed to transform into aromatized intermediate **157** either via successive redox or direct [1,5]-H migration. Promoted by CPA, subsequent intramolecular asymmetric addition of amine to imine provided the annulated intermediate **158** containing a chiral carbon center and a chiral C–N axis. This C–N bond formation process was the stereoselectivity determination step in the whole process. Finally, nitrosoarene **153** served as an oxidant that facilitated the oxidative aromatization and afforded axially chiral *N*-arylbenzimidazoles **154**. Interestingly, the use of 2-naphthylamine derivatives **152** bearing an ester or an aryl group led to products **154** with opposite absolute configuration despite the same enantiomer of CPA catalysts were used for them. This observation may originate from different non-covalent interactions between the substrate and the catalyst. The triple role of nitrosoarenes **153** providing an electrophilic site (N) for the initial C–N bond formation, a nucleophilic site (N), and additionally as an endogenous oxidant underpinned the domino process.

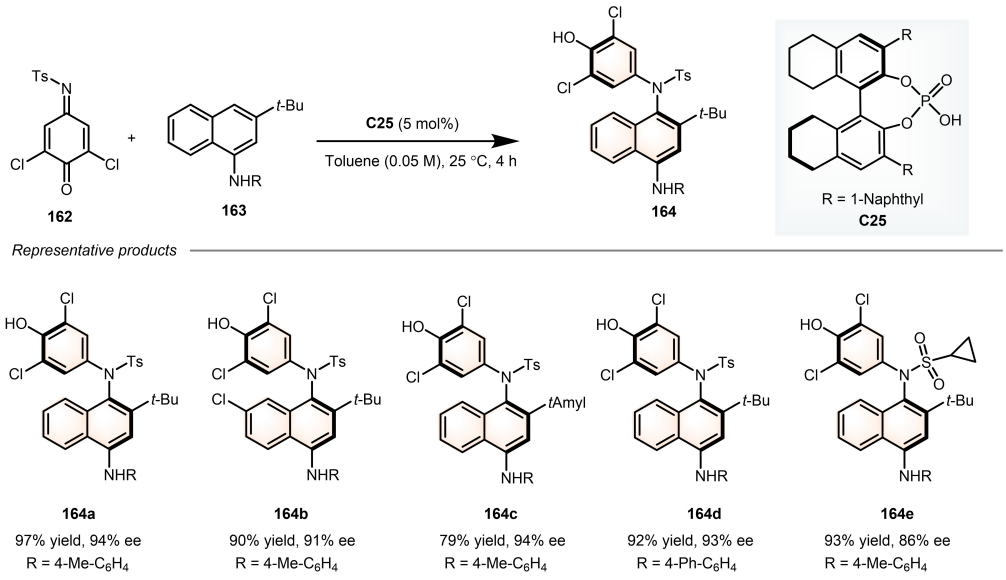
In 2022, Zhong and coworkers serendipitously discovered that *p*-benzoquinone diamine **159** could serve as an amination reagent for indole C–H functionalization through unprecedented CPA-catalyzed asymmetric nucleophilic 1,6-addition, thus affording a range of atropisomeric *N*-sulfonyl-3-arylaminoindoles containing a newly formed C–N axial (Scheme 44).[136] The presence of bulky substituent, e.g., *tert*-butyl, at C2 position of indoles was found to be highly crucial to secure high atropostability. Mechanistic experiments suggested that this Friedel-Crafts amination likely involved an ionic nucleophilic addition rather than a radical mechanism. Computational calculations revealed that the preference of 1,6-addition regiospecificity than the 1,4-addition commonly observed in other quinone derivatives might arise from the high electrophilicity of the imine nitrogen induced by the strong inductive sulfonyl protecting group, high degree of aromaticity of the 1,6-addition transition state and intermediate, and more exergonic driving force for the C–N bond formation than the C–C coupling. This amination reaction featured low catalyst loading (low to 0.1 mol%), richness in functional group tolerance and excellent atroposelectivity (up to 98% ee). Notably, preliminary biological studies revealed that the obtained enantioenriched 3-aminoindoles exhibited significant anticancer activities.

Lately in 2023, Tan et al. reported another work of constructing the C–N chiral axis. By using a similar strategy to the above work, they successfully achieve the addition of C–N chiral axis between iminoquinone **162** and naphthalene rings **163** under **C25** catalyzed conditions (Scheme 45).[137] The strong electron-withdrawing group attached to the imine can significantly enhance its umpolung reactivity through electronegativity and aromatic character, thus providing good yield and enantioselectivity for the reaction. This reaction has good tolerance to different modifications of the amine substituents on the naphthylamine and different decoration pattern and electronic property on the aromatic ring(**164 a**–**e**). This work successfully developed the construction of C–N atropisomers between iminoquinone and naphthalene.

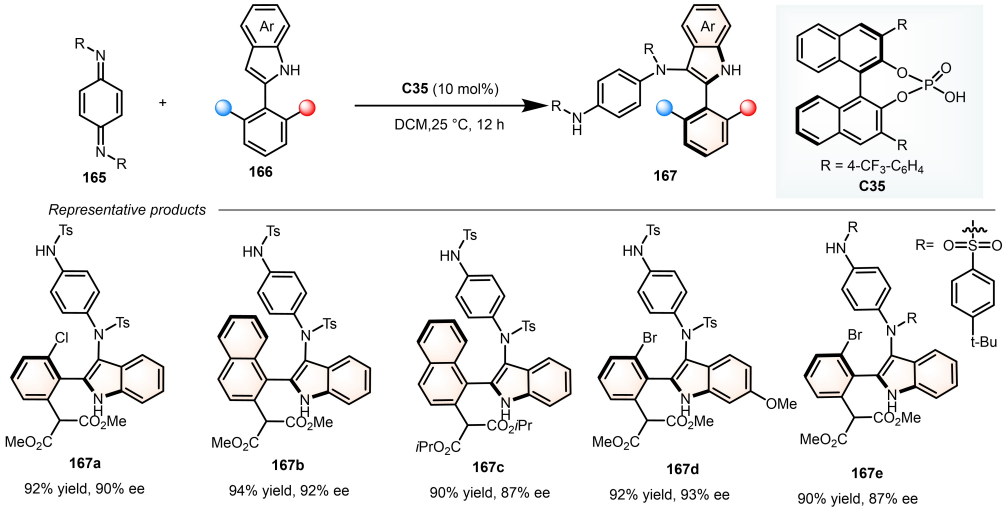
At the same time, they reported an example of constructing another indole-based atropisomer. They significantly increased the rotation energy barrier of the adjacent C–C axis by introducing a large sterically hindered aryldiimine group at the third position of indole, which makes the axis to be configured as a chiral axis (Scheme 46).[138] The malonate group adjacent to the chiral axis of the product plays an indispensable role in its high enantioselectivity, which may be due to the additional interaction or hydrogen bonding between the ester group and the CPA catalyst. This reaction shows good tolerance to p-quinodiimine and the *ortho*-substituent substituted at the second position of the benzene ring of indole(**167 a**–**e**). This work successfully constructed the chiral axis between



Scheme 44. CPA-catalyzed atroposelective Friedel-Crafts amination of indole.



Scheme 45. Construction of C–N atropisomer by umpolung reaction of imines



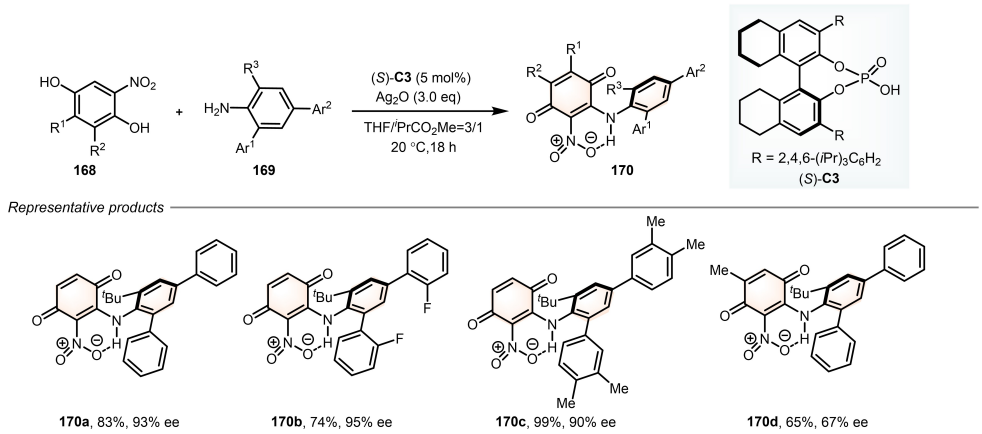
Scheme 46. Direct amination of indole to construct 2-arylindoles.

a simple five-membered ring and a six-membered ring without the involvement of large-volume skeletons on both sides.

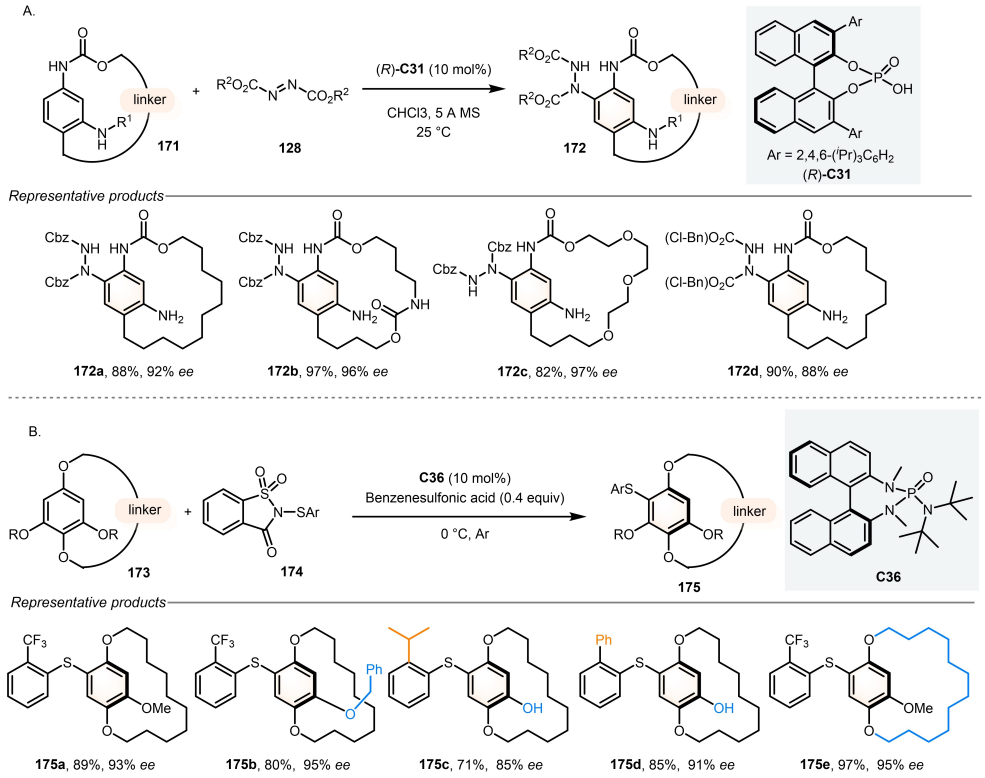
Unlike the previous works to construct C–N bond with N as electrophile, Li and co-workers recently disclosed a new synthetic strategy for axially chiral diarylamines (Scheme 47)[139] by employing N as nucleophile. In this work, axially chiral diarylamines were achieved through the nucleophilic addition of amines to the *in-situ* generated quinones from 1,4-diol under the catalysis of CPA and subsequently oxidation, which shows excellent yields (up to 99%) and enantioselectivities (up to 99% *ee*). Notably, the "NO_2···H–N" hydrogen bonds in the products is quite essential for high enantioselectivity, which stabilized one of the planar axial conformations.

4.4. Supplement: Synthesis of Planar Chiral Macrocyclic Compounds

In addition to the above work, the synthesis of planar-chiral macrocycles is also a unique branch of building axial chiral compounds. Among them, the enantioselective synthesis of sulfur- and nitrogen-containing macrocycles is challenging, which has stimulated the interest of researchers. A great breakthrough in this field was achieved by Xue's group in 2022 (Scheme 48A).[140] They developed an efficient method for the asymmetric synthesis of planar-chiral macro-



Scheme 47. Enantioselective Synthesis of "NO_2···NH" Hydrogen Bond-Stabilized Diarylamines.



Scheme 48. Construction of atropisomers containing planar chiral macrocycles.

cycles derivatives with high enantioselectivity (up to 99% ee) through enantioselective electrophilic aromatic aminations with azodicarboxylates enabled by chiral phosphoric acid catalysis (CPA). Very recently, the same group described the synthesis of planar-chiral sulfur-containing cyclophanes (up to 97% yield and 95% ee) through a catalytic asymmetric electrophilic sulfenylation reaction by employing the new Lewis base catalysts C36 (Scheme 48B).[141]

5. Conclusion and Outlook

The examples discussed in this article highlight recent progress in the development of asymmetric Friedel–Crafts reactions for the preparation of atropisomerically enriched compounds. This progress is driven by rapidly growing interests in axially chiral compounds, which typically originate from a rotationally restrained σ-bond connected to an arene moiety. This nature overlaps with the realm of Friedel–Crafts reactions for arene C–H functionalization. Indeed, classic Friedel–

Crafts alkylation has be harnessed for atropisomer synthesis, generating optically active compounds containing both an sp^3-hybridized chiral center and a chiral axis. Compounds bearing multiple stereogenic elements are emerging as synthetic targets in asymmetric synthesis. On the other hand, exploration into the diversity of electrophiles has paved the way for the development of Friedel–Crafts atroposelective arylation, halogenation, sulfenylation, and amination. These non-canonical Friedel–Crafts reactions allow for access to molecular complexity with atropisomerism, either based on reinforcing an existing axis or through the direct formation of a new stereogenic axis. All these processes largely expand the repertoire of the asymmetric Friedel-Crafts reaction, making it an enhanced synthetic toolbox for atroposelective C–H functionalization.

Among atroposelective Friedel–Crafts reactions, a significant focus has been on C–H arylation. This dominance can be attributed to the value of the resulting biaryl atropisomers and their relatively high configurational stability. However, the majority of these reactions have been achieved using electrophilic quinones and their derivatives as building blocks, which are often constrained by issues such as reagent stability and availability. Atroposelective Friedel–Crafts arylation through oxidative cross-coupling directly using phenols might be a viable solution to enhance sustainability and structural diversity. In addition, carbon-heteroatom axially chiral compounds are important additions to the pool of atropisomers. However, their asymmetric synthesis, particularly through Friedel–Crafts reactions, is largely underexploited. While the carbon-halogen bonds are intrinsically unlikely to constitute a chiral axis, known examples have only included C–B and C–N axially chiral compounds. There are certainly possibilities to construct other classes of carbon-heteroatom axes, such as C–P, C–O, and C–Se, among others. Such scarcity is caused by the dearth of suitable heteroatom-centered electrophiles, which require research efforts from the synthetic chemistry community. Moreover, the scope of arene nucleophiles has been largely limited to electron-rich arenes in the leading Friedel-Crafts reactions. Innovative strategies need to be devised to tackle electron-neutral or even electron-deficient substrates, expanding the substrate scope for atroposelective Friedel-Crafts reactions.

With respect to catalysts, chiral Brønsted acids are predominantly used in atroposelective Friedel–Crafts reactions, which typically operate bifunctionally by activation of both arene and electrophile partners. Notably, 1–10 mol% catalyst loading were typically seen in the example described in this review. Not to mention the mediation of enantioselectivity, this also represents a huge step forward in comparison to the original Friedel–Crafts reactions performed under harsh conditions with super-stoichiometric quantities of aluminium trichloride. In addition, biocatalysis is becoming a promising tool for asymmetric Friedel-Crafts reactions,[10–11] which are actually known in nature for the biosynthesis of amino acids and alkaloids. This has shed light on the development of biocatalytic atroposelective Friedel-Crafts reactions. In 2022, Lewis and coworkers reported directed evolution of flavin-dependent halogenases for site- and atroposelective Friedel-Crafts halogenation of 3-aryl-4(3H)-quinazolinones.[130] The best variant exhibited 91-fold improved site selectivity, 25-fold improved conversion, and >98% ee for the major brominated atropisomer relative to the parent enzyme. This example highlights the vast chemical space of biocatalysis and also power of directed evolution to shape enzymes for abiological atroposelective Friedel-Crafts reactions. Along with the development of bioinformatics and computer modeling-aided catalyst optimization, it would be able to parameterize and predict the performance of catalysts, which has been preliminarily demonstrated in structurally flexible β-turn-containing peptide catalysts.[131]

Last but not the least, one should always in mind the practical values of the synthetic axially chiral products when considering further development of atroposelective Friedel-Crafts reactions apart from their scientific significance. Historically, Friedel-Crafts alkylation and acylation reactions are undoubtable a fundamental pillar in industrial organic processing. As the field of sustainable synthesis continues to evolve, further advancements in atroposelective Friedel-Crafts reactions are expected to play a pivotal role in expanding the synthetic toolbox and driving innovation in the fields of asymmetric catalysis, pharmaceuticals, and materials science.

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