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Review

Atropisomers beyond the C–C axial chirality: Advances in catalytic asymmetric synthesis

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SUMMARY

Atropisomers beyond the C–C axis (denoted as X–Y herein) are important addition to the repertoire of axially chiral compounds, which have received much attention in recent years. Compared with conventional C–C axial chirality around biaryl and olefin axes, atropisomerism portrayed by C–N, C–O, C–B, or N–N bond was deemed to be challenging due to the relatively low rotational barriers. However, the intrinsic shorter bond length and electron-repelling effect lead to a congested hetero X–Y axis, resulting in stable axially chiral frameworks. The past two decades, especially the past few years have witnessed a rapid progress of this emerging area. A range of catalytic atroposelective approaches have been reported for the efficient synthesis of these challenging skeletons. The X–Y axially chiral compounds are valuable molecules, and they may be used as new ligands or catalysts in asymmetric catalysis or evaluated for their potential biological activities. We believe that the chemistry of atropisomers beyond C–C axial chirality will be forthcoming and blooming in the near future, taking up an important position in organic chemistry and beyond.

INTRODUCTION

Atropisomerism, stereoisomerism arising from an axially restricted bond rotation, constitutes one fundamentally important chirality element in nature.[1] Since the first report in 1922,[2] atropisomers have found wide applications in asymmetric catalysis, natural products synthesis, drug discovery, and materials science. Among different atropisomers, the C–C atropisomers, e.g., axially chiral biaryls, aryl alkenes, and aryl amides, are the more common frameworks (Figure 1), which have been intensively investigated in the past decades.[1,3–6] For instance, BINOL (1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol)-derived axially chiral ligands and catalysts are tremendously useful in asymmetric catalysis and synthesis.[7] On the other hand, atropisomers beyond the C–C axis, e.g., about the C–N, C–O, C–B, and N–N bonds, have been studied to a much less extent, which may likely due to the reduced rotation barrier induced by the deplanarization of the heteroatom-containing plane.[8] When barriers of rotation about the X–Y bond are more than 23 kcal/mol, atropisomers may exist.[9] Therefore, introduction of heteroatom(s) into the axial axis, through fine tuning of substructures and various forces, such as electronic and steric interactions, hydrogen bonding, and π–π stacking, among others, may lead to the creation of axially chiral molecules containing an X–Y rotatory bond.

Earlier studies on the atropisomers around a X–Y bond were focused on their physical characteristics, such as rotational energy barrier, conformational analysis, and

The bigger picture

As a type of stereoisomerism, atropisomerism represents one fundamentally important chirality element in nature. Atropisomers could vary drastically in their biological activities and functions. Extremely significant in asymmetric catalysis, numerous atropisomers are privileged chiral ligands in asymmetric catalysis. Although atropisomers based on C–C bond rotation, e.g., axially chiral biaryls, have been extensively investigated in the past decades, atropisomers featuring an X–Y axis beyond the C–C bond, e.g., C–N, C–O, C–B, and N–N bonds have been somehow overlooked. In this review, we summarize the development of catalytic asymmetric synthetic approaches to access atropisomers rotating around an axis other than the classic C–C axis.

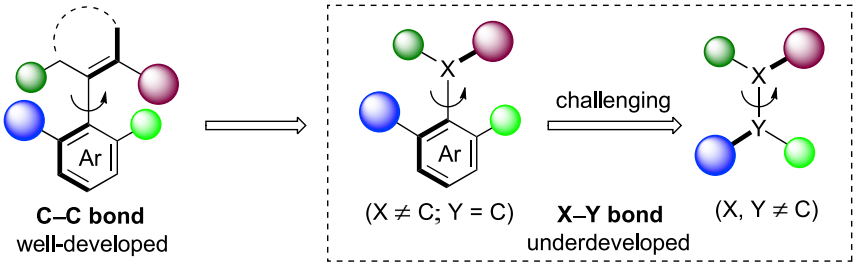

Figure 1. Different types of atropisomers

spectroscopic studies.[10–12] The wide presence of X–Y bond-induced axial chirality in natural products, bioactive molecules, and chiral ligands triggered extensive investigations toward their catalytic asymmetric synthesis (Figure 2). In early 2000s, the groups of Taguchi[13] and Curran[14] independently reported asymmetric synthesis of C–N axial anilides through a Pd-catalyzed *N*-allylation of achiral N–H anilides, although the reported enantioselectivities were low. Following these pioneering investigations, a good range of catalytic asymmetric approaches for the synthesis of atropisomeric molecules containing a heteroatom-carbon axis via either transition metal catalysis or organic catalysis have emerged.[15–19] In this review, we aim to provide an updated summary of catalytic asymmetric synthetic strategies toward the construction of molecules containing an X–Y axial axis, and we organize the review by elaborating various catalytic approaches taken for the synthesis of different types of non-C–C axial chiral molecules. The literature reports covered herein are up to the end of year 2021, and biocatalytic methods and approaches employing chiral substrates are not within the scope of this review. Among various synthetic strategies, catalytic enantioselective desymmetrization of prochiral substrates represents a direct approach to access C–X axial chirality, whereby the desymmetrization may take place at the aromatic rings or heterocyclic aryl ring systems (Figure 3A). Through C–X bond formation, asymmetric cross-coupling reaction serves as an efficient method for the synthesis of C–X atropisomers (Figure 3B). Specifically, for the C–N atropisomers, their catalytic asymmetric *de novo* synthetic methods have been developed (Figure 3C). Another common strategy to prepare C–N atropisomers is through atroposelective N–H functionalizations, including *N*-arylation, *N*-alkylation, *N*-allylation, and *N*-acylation reactions. Alternatively, enantioselective C–H bond functionalization has also been proven powerful in creating C–N axial chirality (Figure 3D). Although there are a few reports making use of kinetic resolution (KR) for catalytic atroposelective synthesis, we chose not to include KR in our collection of general catalytic atroposelective synthetic strategies. Since vast majority of the literature reports in this review concern with asymmetric synthesis of C–N atropisomers, we will first be focusing on this type of atropisomers and discussing various catalytic synthetic strategies toward their efficient asymmetric synthesis. We will then move on to discuss approaches taken for the creation of C–O, C–B, and N–N bond axial chiral compounds. Strategies that employ either enantiopure starting materials or multistep reactions are not within the scope of this review.[20,21] We hope to provide our readers a timely overview of this dynamic and fast-developing research field, stimulating more creative work for the construction of axially chiral compounds beyond the traditional C–C axial chirality, facilitating the advancement of various science domains, such as asymmetric catalysis, natural product synthesis, and drug discovery.

ATROPISOMERS AROUND C–N BOND

The existence of atropisomerism about a C–N bond has long been known; however, their catalytic asymmetric synthesis has not drawn much attention until

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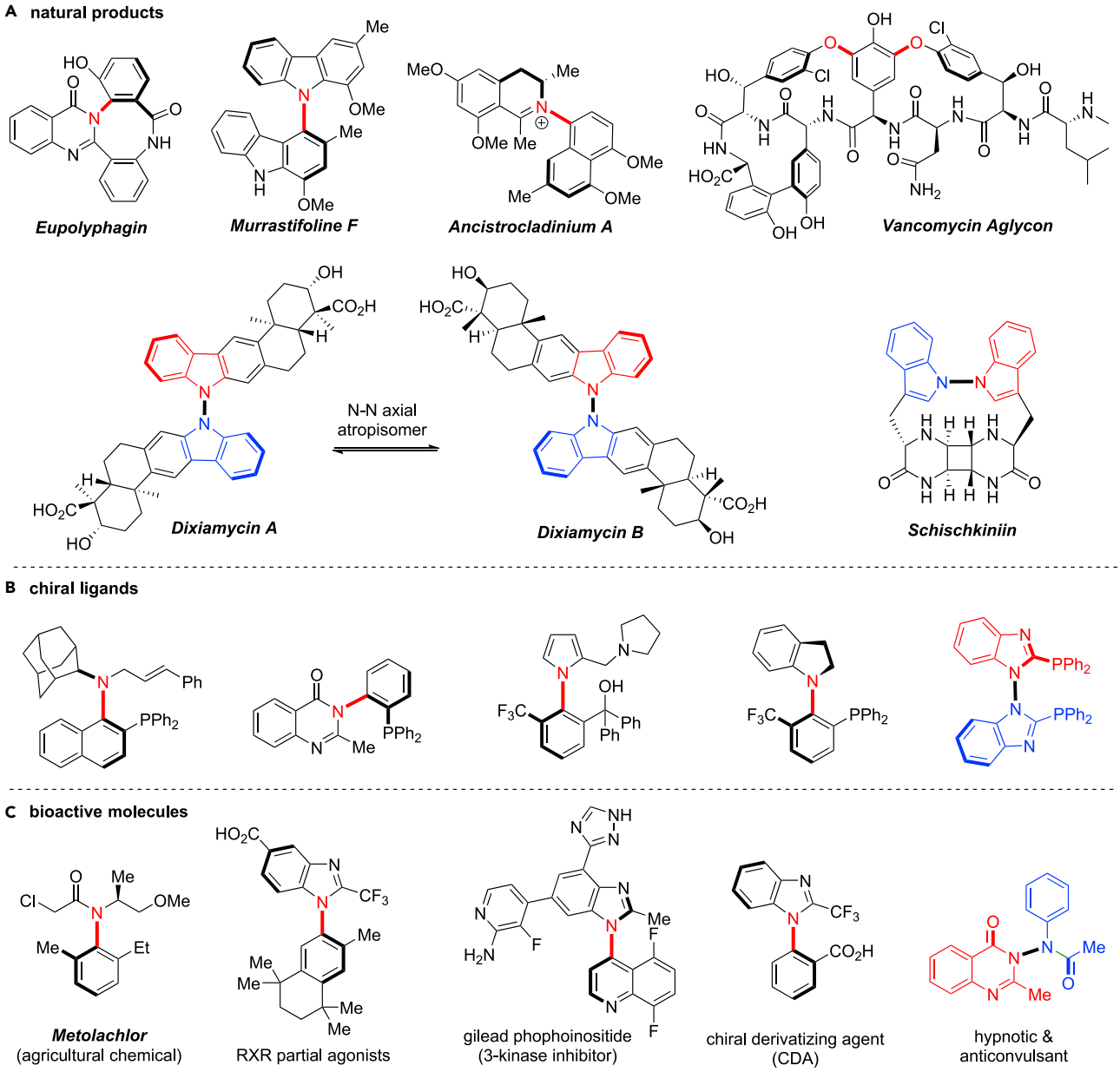

Figure 2. Representative atropisomeric molecules around an X–Y bond

(A) Natural products.

(B) chiral ligands.

(C) bioactive molecules.

recently. Intrinsically, it is well perceived that the construction of different types of atropisomers around a C–N bond could be very challenging. For biaryl structures containing a nitrogen heterocycle, such as *N*-aryl pyrroles and *N*-aryl indoles, the five-membered ring structure tends to reduce the rotational barrier of the C–N axis, since the substituents are more remote from the chiral axis in such biaryls. The *N*-disubstituted anilides are another class of common C–N atropisomers. However, the presence of a nitrogen-containing plane is expected to induce deplanarization, resulting in a less stable C–N axis. Remarkable progress has been made in this research area, with many

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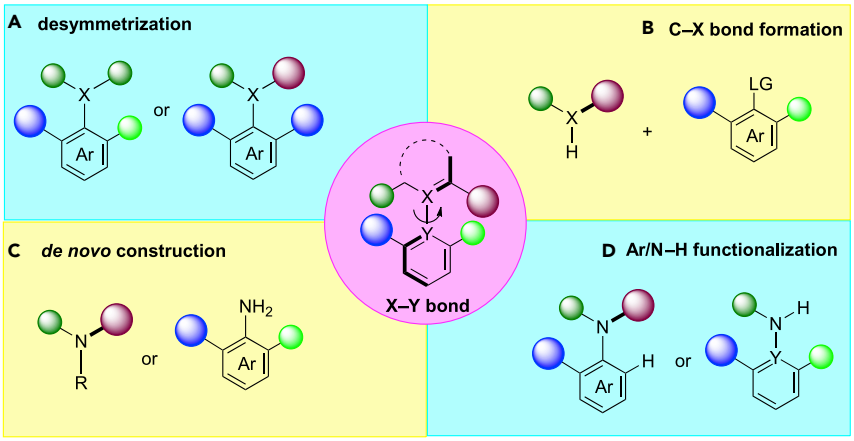


Figure 3. Different strategies for catalytic asymmetric synthesis of X–Y axially chiral compounds

(A) Desymmetrization.

(B) C–X bond formation.

(C) *de novo* construction.

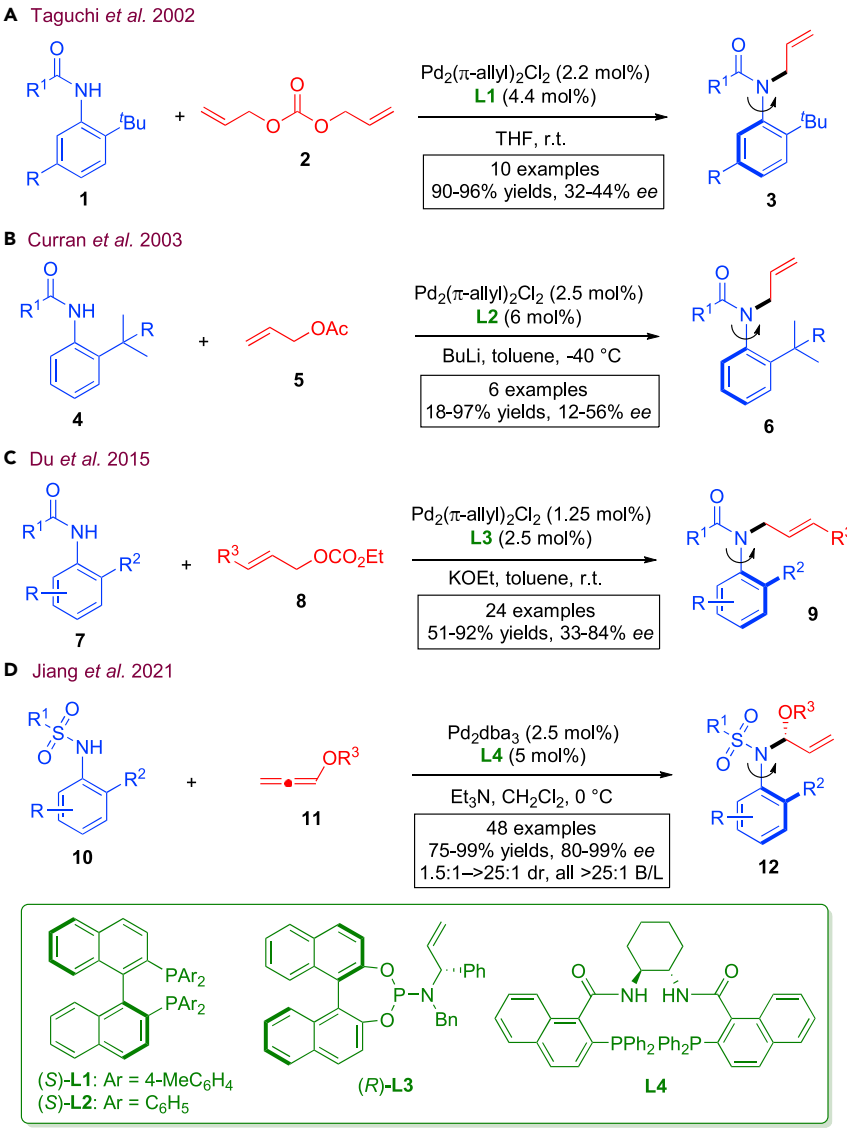
(D) Ar/N–H functionalization.

impressive reports only appearing in the past few years, as we shall elaborate in the following sections.

Catalytic asymmetric N–H functionalization

The seminal contributions were from the laboratories of Taguchi and Curran in early 2000s.[13,14] They independently achieved catalytic enantioselective synthesis of axially chiral anilides around the C–N bond via a palladium-catalyzed Tsuji-Trost allylation reaction. The BINAP-palladium complex displayed a high catalytic efficiency for constructing axially chiral anilides **3** and **6**. In spite of low enantioselectivity, those two reports represent the first catalytic asymmetric synthesis of C–N axially chiral compounds (Scheme 1A & 1B). In 2015, Du et al. further developed the palladium-catalyzed asymmetric allylic amination reaction.[22] By using a phosphorus amidite–olefin ligand **L3**, the axial anilides were obtained with modest-to-good enantiomeric excesses (Scheme 1C). The less efficient asymmetric induction in the above examples may be rationalized mechanistically; the attack of anilide anion to π-allyl carbon occurs at the side opposite to the chiral ligands in the palladium complex.[16,23] In a very recent example, Zhou, Zhang, Jiang, and coworkers accomplished an enantioselective construction of C–N axially chiral sulfonamides **12** via palladium-catalyzed atroposelective hydroamination of allenes.[24] A simple oxidation of the *N,O*-acetals enabled the creation of axially chiral sulfonyl anilides with high stability (Scheme 1D).

A plethora of organocatalytic asymmetric transformations of the Morita-Baylis-Hillman (MBH) adducts have been developed in the past two decades, which are now reliable synthetic tools in organic chemistry.[25,26] When the construction of central chirality is concerned, asymmetric allylic alkylation (AAA) reaction of prochiral nucleophiles with achiral rather than racemic MBH adducts is considered to be challenging, as the chirality center is not formed at the bonding site; thus, remote stereochemical control is required.[27] The atroposelective AAA reaction was first reported by Li and coworkers in 2018, when they derived axially chiral anilides through an *N*-alkylation reaction with an achiral MBH carbonate.[28] In the presence of biscinchona alkaloid **C1**, a broad range of C–N axially chiral anilide products **15** were obtained in good yields with excellent enantioselectivities (Scheme 2). Shortly after, the Zhao



Scheme 1. Palladium-catalyzed asymmetric *N*-allylation

(A) Taguchi *et al.* 2002.

(B) Curran *et al.* 2003.

(C) Du *et al.* 2015.

(D) Jiang *et al.* 2021.

group reported an enantioselective approach to access axially chiral sulfonamides **16**.[29] Further extending their initial report, the Li group subsequently developed asymmetric synthesis of axially chiral phosphamides **17**,[30] as well as axially and centrally chiral sulfonamides **18**.[31] Notably, all the above atroposelective synthesis of C–N axially chiral compounds made use of asymmetric *N*-allylic alkylation reaction, under the catalysis of different cinchona alkloaids (**C2–C4**). The axially chiral *ortho*-iodine phosphamides of type **17** were also evaluated as a hypervalent iodine(III) catalyst for asymmetric oxidative spirolactonization of phenols.

In 2005, Taguchi, Kitagawa, and their coworkers reported an atroposelective *N*-arylation reaction of anilides, which represented the first highly enantioselective and practical

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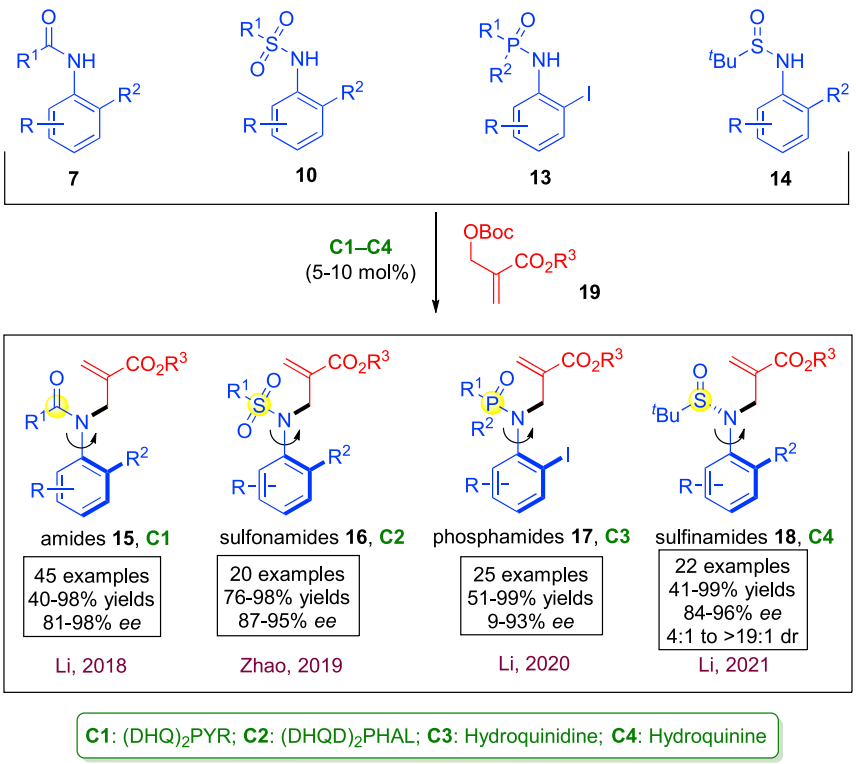

Scheme 2. Organocatalytic asymmetric *N*-allylic alkylation
Li *et al*. 2018; Zhao *et al*. 2019; Li *et al*. 2020; Li *et al*. 2021.

catalytic synthesis of C–N axially chiral compounds.[32,33] Asymmetric Buchwald-Hartwig amination reaction of *ortho*-*t*-butyl anilides **1** with 4-nitroiodobenzene readily occurred in the presence of **L5**-Pd complex, delivering various C–N axially chiral anilides **20** with excellent enantioselectivities (Scheme 3A). An intramolecular variant of the reported method was also developed for the synthesis of optically enriched atropisomeric lactams. To account for the high enantioselectivity for such palladium-catalyzed N–C coupling reaction, the authors reasoned the stereochemical determining reductive elimination of the palladium amide complex (**TS-1**) takes place near chiral ligands, thus offering good stereochemical control. The asymmetric alkylation reaction via the nucleophilic substitution of alkyl halides represents one of the most fundamental organic transformations. In this connection, Maruoka and coworkers reported a highly enantioselective synthesis of C–N axially chiral 2-iodoanilides **22** via an asymmetric *N*-alkylation process.[34] In the presence of the Maruoka chiral phase-transfer catalyst **C5**, both benzyl and allyl bromides served as suitable alkylation reagents, affording a series of chiral 2-iodoanilides bearing C–N axis in a highly enantioselective manner. In their following studies,[35] the same authors extended their protocol to the asymmetric synthesis of other *o*-substituted anilides, such as *o*-*tert*-butyl and *o*-bromoanilide (Scheme 3B). The key reason of obtaining high enantioselectivities for the above reactions was attributed to the ability of the chiral tetraalkylammonium bromide phase-transfer catalyst to recognize the steric difference between the *ortho* substituents on the different anilides.

Asymmetric acyl transfer reaction is a powerful synthetic approach, whereby the addition of a nucleophilic catalyst to an acyl donor *in situ* generates the chiral adduct intermediate, that transfers the acyl group to the eventual nucleophilic substrate to yield the

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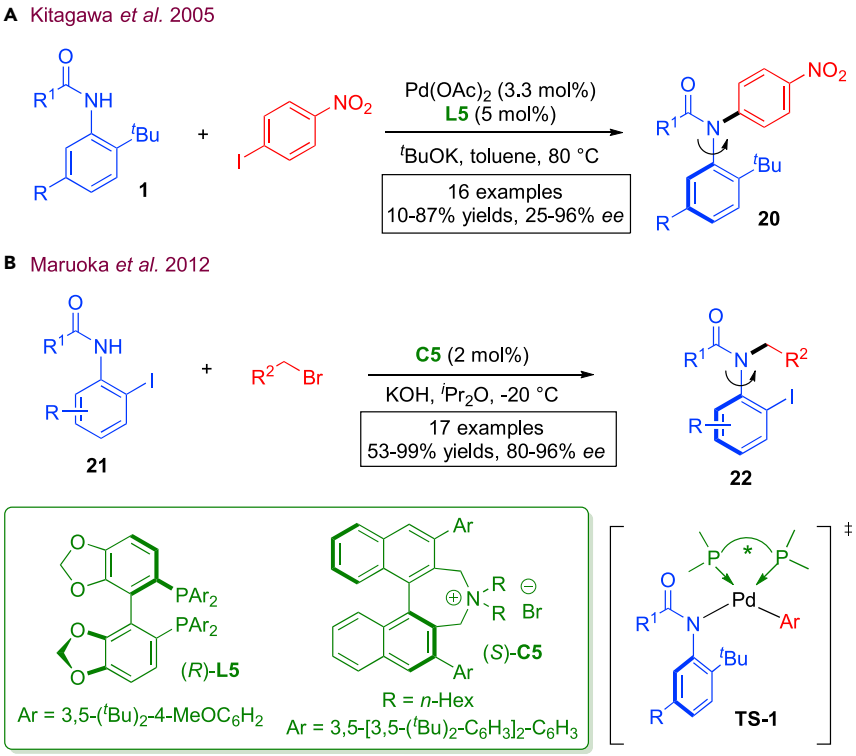

Scheme 3. Catalytic asymmetric *N*-arylation and *N*-alkylation
(A) Kitagawa *et al.* 2005.
(B) Maruoka *et al.* 2012.

final acylation product. In 2020, Dong and coworkers reported[36] an isothiourea-catalyzed atroposelective *N*-acylation of sulfonamides with α,β-unsaturated carbonic anhydrides (Scheme 4A). Almost at the same time, Lu, Zhao, and coworkers described[37] another isothiurea-catalyzed atroposelective *N*-acylation of sulfonamides, through reaction with anhydrides (Scheme 4B). More recently, Li et al. disclosed a palladium-catalyzed atroposelective synthesis of amides via carbonylation reaction.[38] By reacting with carbon monoxide (CO) and aryl iodides, a good range of cyclic and acyclic axially chiral amides were prepared in good yields with high enantioselectivities (Scheme 4C).

Catalytic asymmetric desymmetrization

Catalytic asymmetric desymmetrization of prochiral precursors is an attractive strategy for the preparation of enantiomerically enriched molecules.[39] When atroposelective synthesis is concerned, desymmetrization of compounds containing a prochiral C–N axis appears to be promising approach. Maleimides contain an electron-poor double bond, which react readily with a variety of nucleophiles at the prochiral stereogenic site, generating corresponding chiral products (Figure 4A). Among all the maleimides, *N*-aryl maleimides are structurally very unique; the presence of an electron-poor carbon–carbon double bond and a C–N axis makes them ideal precursors for the simultaneous creation of both central stereogenic center and axially chiral axis (Figure 4B). In a more conventional construction of C–N axial chirality, e.g., N–H functionalization, the stereochemical determining event takes place in a position close to the aryl substituent (Figure 4C). However, catalytic asymmetric desymmetrization of *N*-aryl maleimides requires a remote stereochemical control; undoubtedly, it is more challenging to achieve excellent stereochemical controls of two chiral elements via the desymmetrization strategy (Figure 4D).

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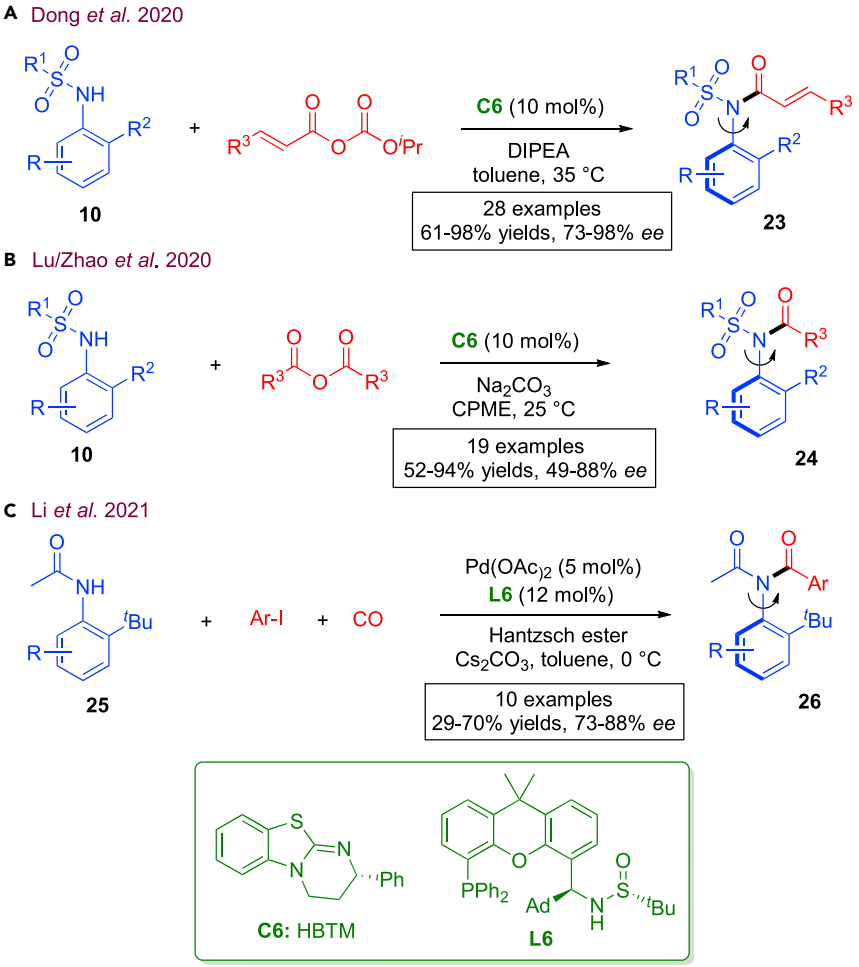

Scheme 4. Catalytic asymmetric *N*-acylation

(A) Dong *et al.* 2020.

(B) Lu/Zhao *et al.* 2020.

(C) Li *et al.* 2021.

The pioneering report on the asymmetric construction of C–N axes via desymmetrization of *N*-aryl maleimides were first disclosed by the Hayashi group in 2007.[40] Through a rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acids **28** to maleimides **27**, *N*-aryl succinimides **29** with a C–N axis were prepared in high yields with excellent stereoselectivities (Scheme 5A). Recently,[41] Xu and coworkers reported a palladium-catalyzed enantioselective hydrosilylation of maleimides, creating silyl succinimides containing a C–N axis in good yields with good-to-excellent diastereo- and enantioselectivities (Scheme 5B). More recently,[42] Li and coworkers developed a rhodium-catalyzed C–H alkylation of benzamides by utilizing *N*-arylmaleimides as the alkylating agent, *N*-aryl succinimides **35** bearing an axially chiral axis and a central chirality were constructed via a single stereo-determining step (Scheme 5C).

The first organocatalytic construction of axial chirality via the desymmetrization of *N*-aryl maleimides was reported by Bencivenni et al. in 2014.[43] The remote control of C–N axial chirality of atropisomeric succinimides **41** was realized via a catalytic vinylogous Michael addition. By employing cinchona alkaloid primary amine **C7**,

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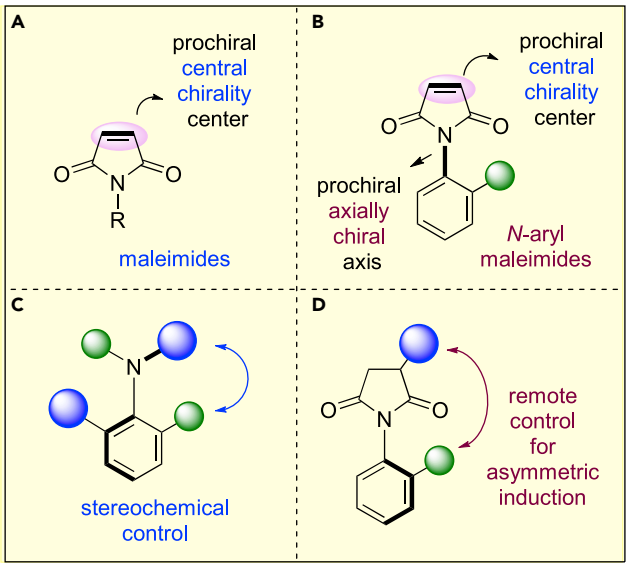


Figure 4. Challenges in desymmetrization of *N*-aryl maleimides

(A) Maleimides.

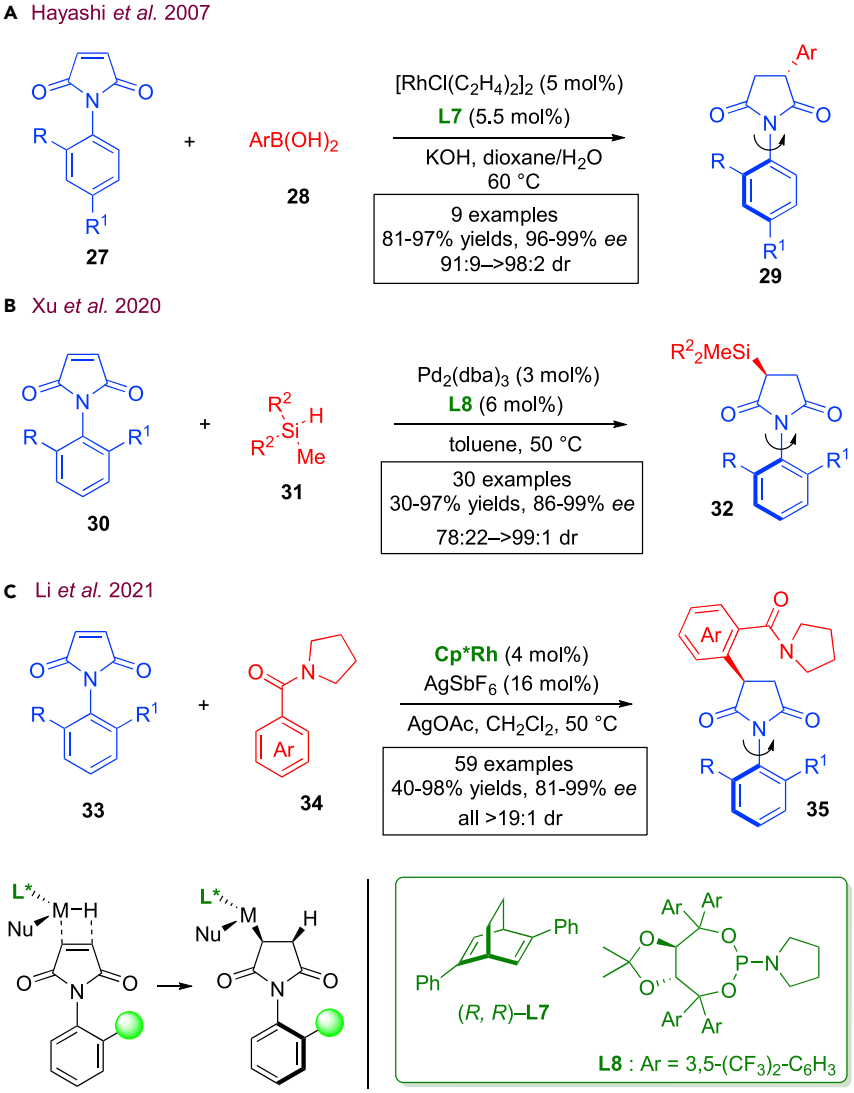
(B) *N*-aryl maleimides.

(C) Stereochemical control.

(D) Remote control for axial chirality.

simultaneous and exclusive remote control of the chiral axis and the newly formed stereocenters was achieved (Scheme 6A). Subsequently,[44] the same authors extended their organocatalytic atroposelective desymmetrization of *N*-aryl maleimides, by devising a formal Diels-Alder reaction with enones (Scheme 6B). Furthermore,[45] the Bencivenni group developed the Michael addition of a series of carbon nucleophiles **39** to *N*-aryl maleimides for the atroposelective synthesis of *N*-(e-*tert*-butylphenyl)succinimides **43**, achieving remote control of the chiral axis and the concurrent generation of adjacent quaternary and tertiary stereocenters (Scheme 6C). Using their chiral *N*,*N*′-dioxide-Sc(III) complex, Feng and coworkers accomplished catalytic asymmetric desymmetrization of *N*-aryl maleimides with unprotected 3-substituted-2-oxindoles, efficiently constructing both central chirality centers and axial axes.[46] Very recently, Jindal, Mukherjee, Biju, and coworkers described an *N*-heterocyclic carbene (NHC)-catalyzed atroposelective desymmetrization of *N*-aryl maleimides.[47] The reaction process involves an intermolecular Stetter-aldol cascade of dialdehydes **40** with prochiral *N*-aryl maleimides, followed by oxidation, affording C–N axially chiral *N*-aryl succinimides **44** in good yields and *ee* values (Scheme 6D).

The *N*-arylmaleimide analogs have also been employed as substrates in the asymmetric desymmetrization strategy for the construction of C–N axial chirality. In 2016, the Tan group documented an organocatalytic asymmetric tyrosine click-like reaction,[48] which was applied successfully to the atroposelective synthesis of *N*-arylurazoles via a desymmetrization reaction of triazolediones **45**. The reaction was applicable to 2-naphthols and 2-substituted indoles, under the catalysis of bifunctional thiourea-tertiary amine catalyst **C10** and chiral phosphoric acid (CPA) **C11**, respectively. Excellent remote enantiomeric control arising from the efficient discrimination of the two reactive sites in triazoledione and the transfer of stereochemical information into the prochiral axis far from the reaction site was achieved (Scheme 7A). Shortly after, the same group devised an asymmetric three-component reaction to construct chiral spirooxindole-urazoles



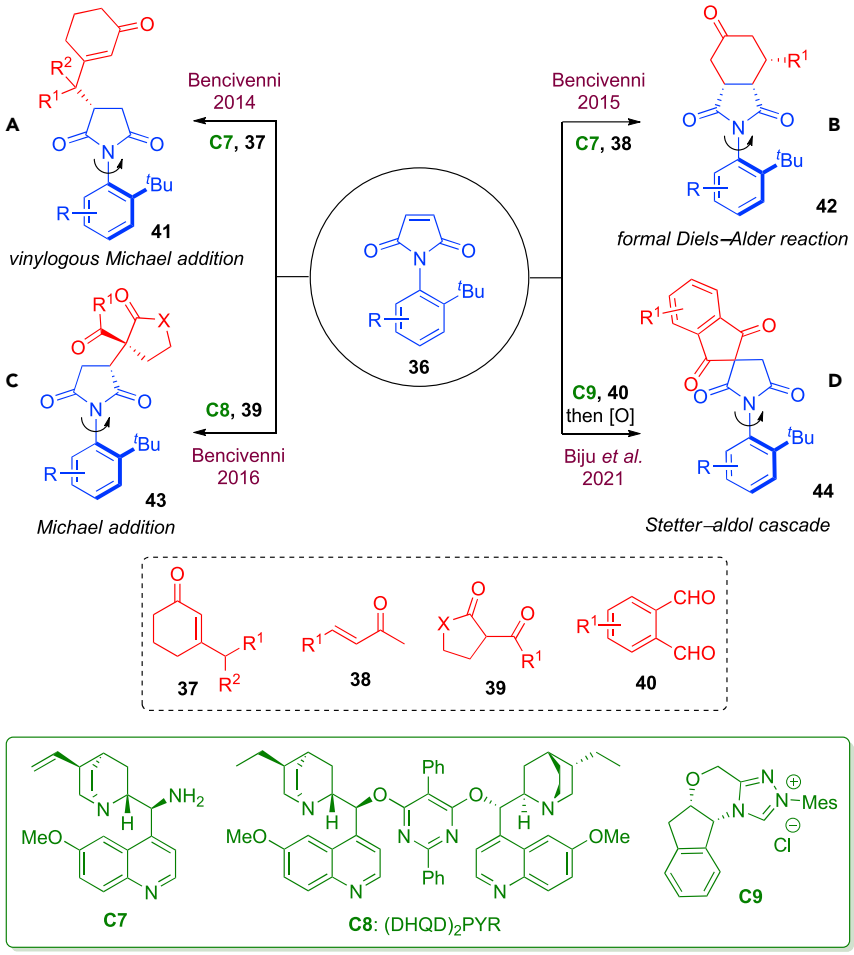
Scheme 5. Transition-metal-catalyzed asymmetric desymmetrization

(A) Hayashi *et al.* 2007.

(B) Xu *et al.* 2020.

(C) Li *et al.* 2021.

containing a C–N axial axis through a similar desymmetrization strategy.[49] The NHC-catalyzed desymmetrization of prochiral urazoles **48** was developed by the Chi group for an atroposelective synthesis of C–N axially chiral urazoles **49**.[50] Stereoselective addition of a nitrogen atom of prochiral *N*-arylurazoles **48** to an ynal-derived acetylenic acylazolium intermediate was the key step, and *N*-arylurazoles **49** bearing a chiral C–N axis were obtained in excellent yields and with good optical purities (Scheme 7B). Very recently, Cheng, Fang, and coworkers disclosed a nickel-catalyzed hydrocyanative desymmetrization of *N*-aryl 5-norbornene-endocis-2,3-dicarboximides **50**, allowing for the creation of five contiguous stereogenic carbon centers and one remote C–N axial axis.[51] By performing theoretical studies, the authors concluded that the rigid structure of cyclic imide is essential for enantiomerical control, and it was believed that the presence of the imide carbonyl group is essential for this reaction process (Scheme 7C).



Scheme 6. Organocatalytic desymmetrization of *N*-aryl maleimides

(A) Bencivenni *et al*. 2014.

(B) Bencivenni *et al*. 2015.

(C) Bencivenni *et al*. 2016.

(D) Biju *et al*. 2021.

Although many catalytic asymmetric desymmetrization strategies employ *N*-arylmaleimides for the atroposelective construction of C–N axes, there are also a limited number of examples that other prochiral C–N axial compounds are utilized as substrates. In 2016, Kitagawa *et al*. described a palladium-catalyzed reductive asymmetric desymmetrization of quinazolinones **53** for the direct enantioselective synthesis of mebroqualone derivatives **54** around a C–N axis.[52] The reaction process contains an enantioselective monohydrodebromination, followed by KR of the resulting monobromophenyl products (Scheme 8A). In 2019, the Tan group reported a CPA-catalyzed atroposelective desymmetrization of *N*-arylpyrroles **55**.[53] As opposed to the common dual activation mode of CPA, a monofunctional activation mode was proposed by the authors. The hydrogen-bonding interaction between ketomalonate and CPA was believed to be crucial for the asymmetric induction (Scheme 8B).

Although less common, intramolecular desymmetrization strategy has also been used for the catalytic asymmetric synthesis of C–N axially chiral compounds. In

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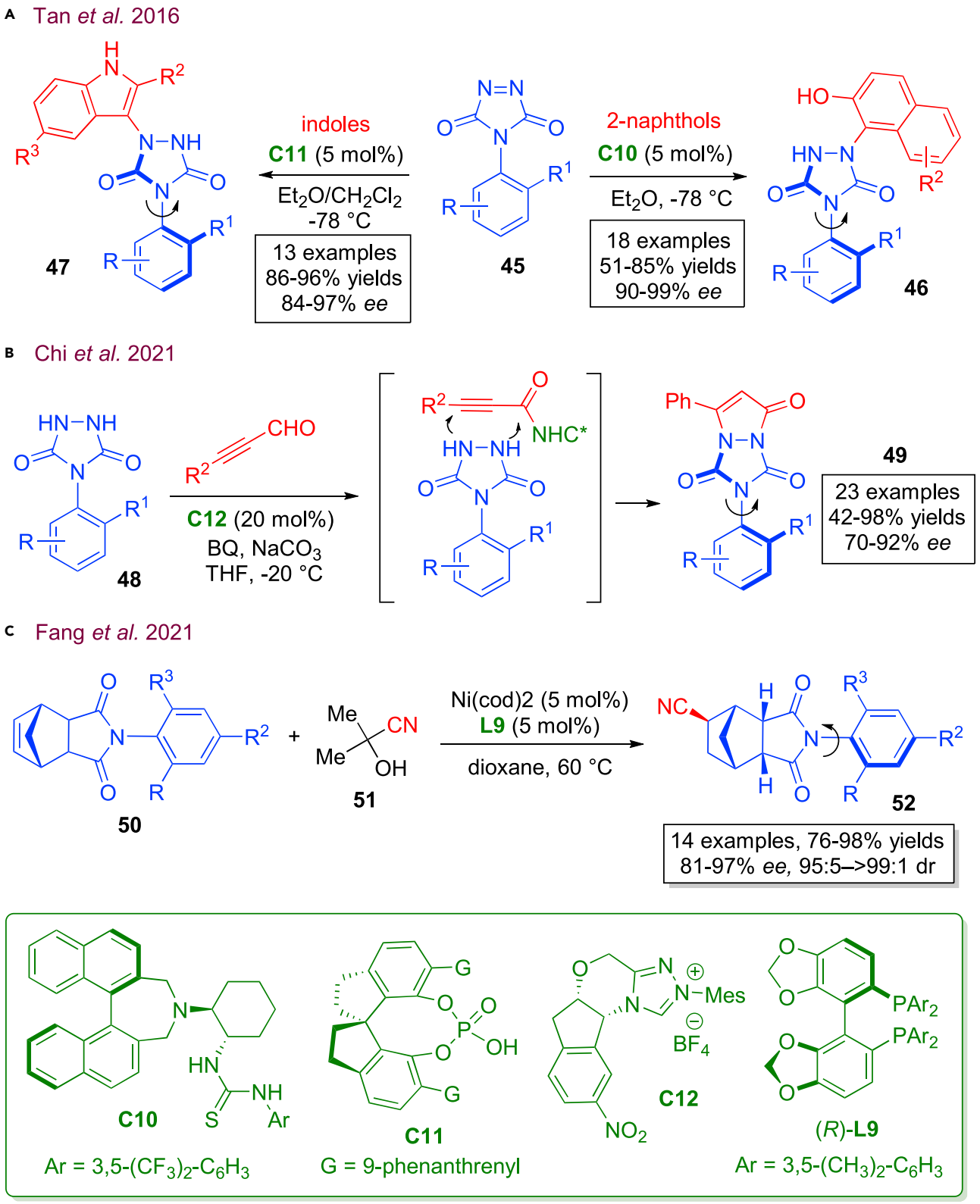
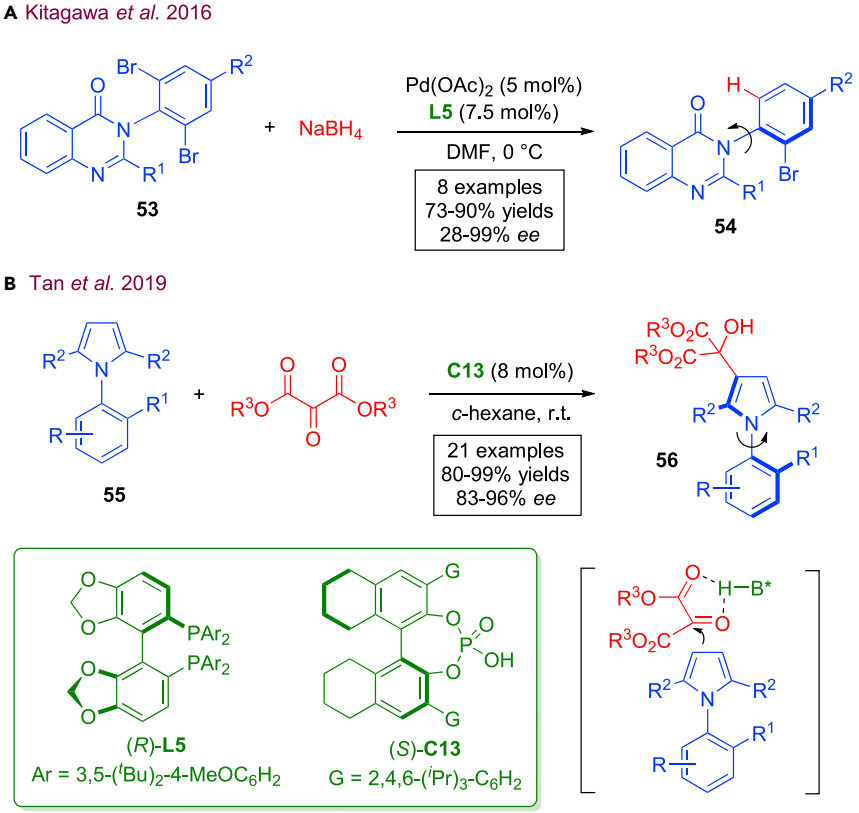


Scheme 7. Catalytic asymmetric desymmetrization of *N*-arylmaleimide analogs

(A) Tan *et al.* 2016.

(B) Chi *et al.* 2021.

(C) Fang *et al.* 2021.



Scheme 8. Catalytic asymmetric desymmetrization of other prochiral C–N axes

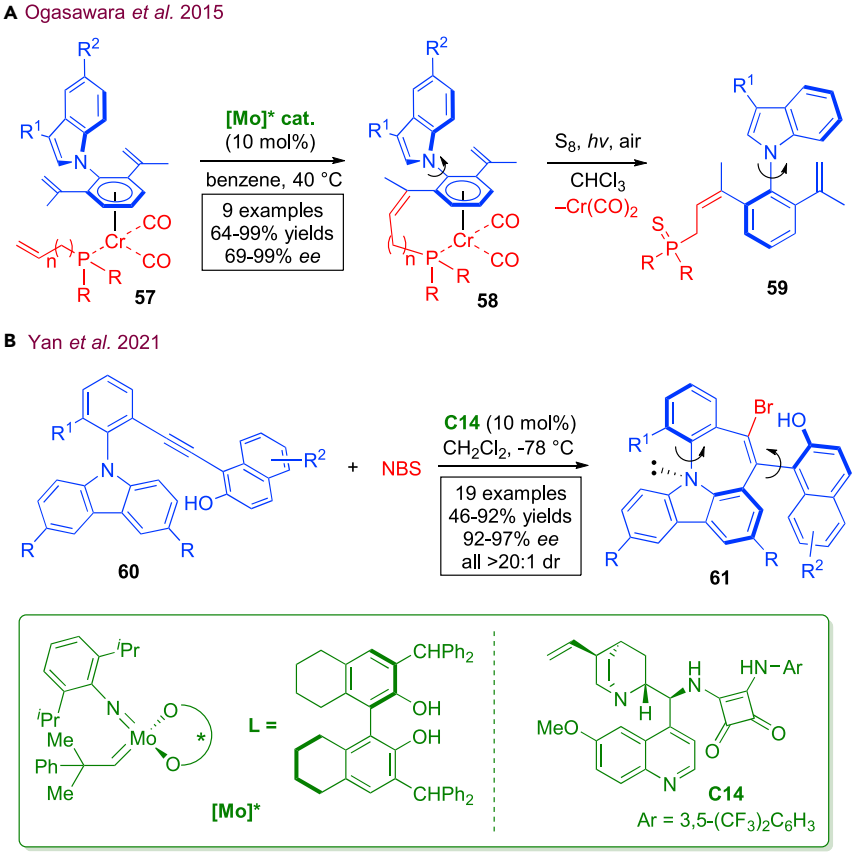
(A) Kitagawa *et al.* 2016.

(B) Tan *et al.* 2019.

2015, Ogasawara et al. developed a molybdenum-catalyzed asymmetric ring-closing metathesis (RCM) of prochiral (π-arene)-chromium complexes **57**.[54] Both C–N axial chirality and π-arene-based planar chirality were simultaneously induced, furnishing the corresponding bridged (π-arene)chromium complexes **58** in excellent yields and *ee* values. Subsequent removal of the dicarbonylchromium fragment led to the C–N axially chiral N-arylindoles **59** with complete retention of the enantiopurity (Scheme 9A). Very recently, Yan and coworkers disclosed an organocatalytic enantioselective synthesis of chiral azepine skeleton bearing multiple-stereogenic elements via an intramolecular desymmetrization process.[55] Through a bromination/intramolecular electrophilic aromatic substitution sequence, under the catalysis of cinchona alkaloid-based squaramide, various configurationally defined azepine heterocycles with four types of fully controlled stereogenic elements, i.e., C–N chirality, C–C chirality, nitrogen chiral center, and saddle-shaped conformation, were obtained with excellent diastereo- and enantioselectivities (Scheme 9B).

Catalytic asymmetric C–N bond formation

As opposed to the various desymmetrization strategies that are based on the structural elaborations of the existing prochiral C–N molecules, direct asymmetric construction of C–N axis is a more straightforward approach. In this context, azodicarboxylates have been employed in the asymmetric electrophilic amination reactions of various aryls. The pioneering studies were first disclosed by the Jørgensen group, whereby they reported that Brønsted base catalyzed asymmetric electrophilic aminations of 8-amino-2-naphthols **62** with azodicarboxylates.[56,57] It is



Scheme 9. Intramolecular desymmetrization strategy
(A) Ogasawara *et al.* 2015.
(B) Yan *et al.* 2021.

interesting to note that a new class of quinoline-core amination-based cinchona alkaloids, e.g., **C15**, were crucial for excellent asymmetric induction (**TS-2**). This method is unfortunately limited in scope as the amino group at C8 position played an indispensable role to stabilize the C–N axial chirality (Scheme 10A). In 2014, the Gong group reported an asymmetric synthesis of heteroaryl atropisomers.[58] In the presence of gold complex, a catalytic cycloisomerization-amination cascade of 2-(alkynyl)phenyl boronic acids **65** with azodicarboxylates led to the asymmetric creation of boron-containing C–N atropisomers **66**. Mechanistically, it was proposed that the *in situ*-generated chiral vinylgold intermediate stereoselectively attacks the azodicarboxylates that is coordinated by another chiral gold complex to form the desired products (**TS-3**) (Scheme 10B). Recently, the Zhang group described an atroposelective amination of *N*-aryl 2-naphthylamines **67** with azodicarboxylates.[59] The reaction took place readily via a concerted control strategy involving π–π interaction and dual H-bond (**TS-4**). Notably, this type of naphthalene-1,2-diamines **69** was reported to have a good C–N axial stability, due to the intramolecular hydrogen-bonding interaction (Scheme 10C). Shortly after, a CPA-catalyzed amination reaction of 1,3-benzenediamines **70** was reported by Yang and coworkers.[60] The corresponding C–N atropisomeric products were obtained with high configurational stabilities and have potential of being used as organocatalysts (Scheme 10D).

Transition-metal-catalyzed *N*-arylation reactions, including Buchwald-Hartwig and Ullmann couplings, are widely used synthetic tools for the direct formation of C–N bonds.

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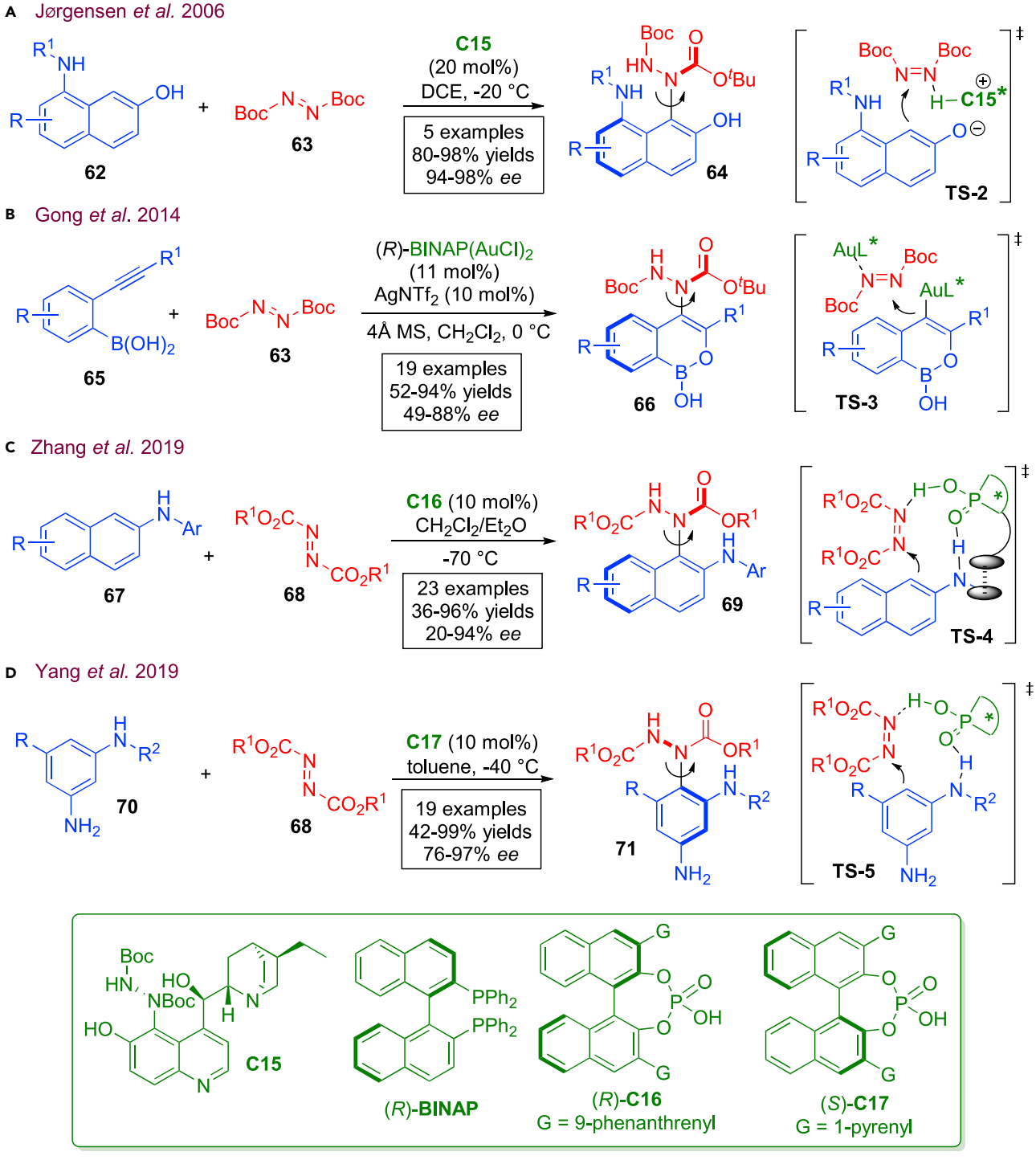

Scheme 10. Catalytic asymmetric aminations with azodicarboxylates

(A) Jørgensen *et al.* 2006.

(B) Gong *et al.* 2014.

(C) Zhang *et al.* 2019.

(D) Yang *et al.* 2019.

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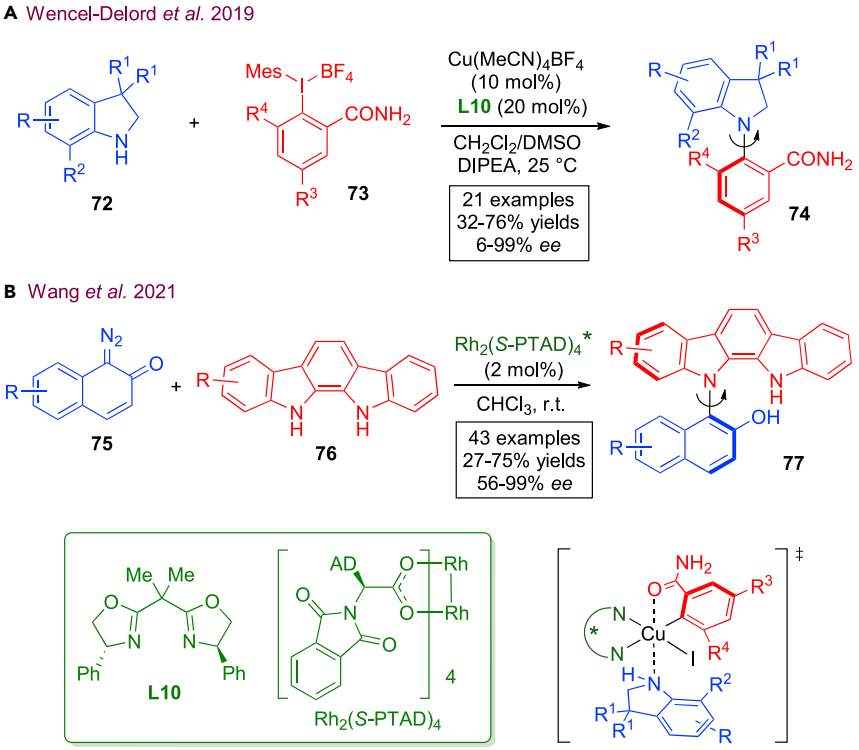
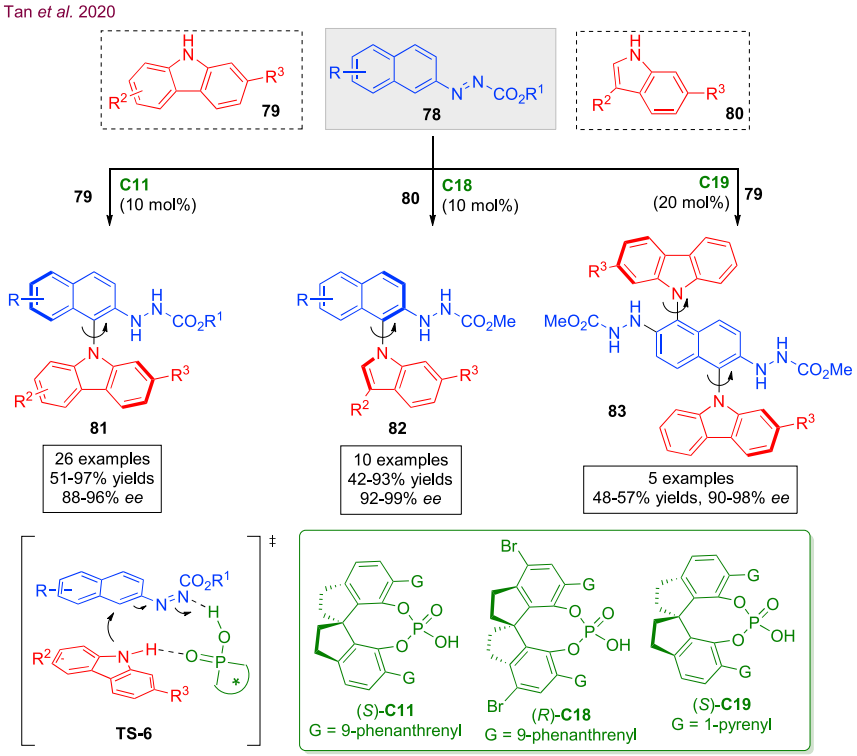


Scheme 11. Transition-metal-catalyzed C–N coupling reactions
(A) Wencel-Delord *et al.* 2019.
(B) Wang *et al.* 2021.

However, such coupling reactions are often sensitive to the steric bulkiness of the coupling partners, and high reaction temperatures are usually required, making the atroposelective synthesis of C–N axial compounds a challenging task. In 2019, Wencel-Delord and coworkers reported the first metal-catalyzed atroposelective *N*-arylation reaction.[61] The key to their success was the employment of a highly active hypervalent iodine reagent **73**, which allows the occurrence of copper-catalyzed atroposelective Ullmann-type *N*-arylation at room temperature, thus affording a broad range of C–N axially chiral compounds **74** with excellent enantiomeric excesses (Scheme 11A). Very recently, Wang and coworkers reported a Rh(II)-catalyzed asymmetric C–N coupling reaction between diazonaphthoquinones **75** and carbazoles **76** via carbene N–H insertion.[62] Enantiomerically enriched *N*-arylindolocarbazole **77** around the C–N axis were obtained in moderate to good yields and with high enantioselectivities. The synthetic value of this protocol was well illustrated by late-stage functionalization of natural products and bioactive molecules, construction of polyaromatic ring, and synthesis of *N*-arylindolocarbazole-derived CPA (Scheme 11B).

In 2020, Tan and coworkers reported an organocatalytic enantioselective C–N coupling reaction.[63] Prior to their report, such organic catalyst-promoted C–N coupling reactions were unknown. The employment of an azo-group at the C2 position of naphthalenes was key to the success of this strategy, which makes the C1 position of naphthalene electrophilic, rather than being nucleophilic. In the presence of CPA catalysts, *N*-nucleophilic carbazoles directly attacked the azonaphthalenes **78**, and the dual hydrogen-bond activation of powerful CPA catalyst ensured excellent enantiomeric control (**TS-6**). This reaction is broad in scope, both carbazoles **79** and indoles **80** were found to be suitable reaction partner. Interestingly, the reported



Scheme 12. Organocatalytic C–N coupling reactions
Tan *et al.* 2020.

reaction was applied to enantioselective synthesis of 1,5-dicarbazole naphthalene derivative **83** possessing two chiral C–N axes, which has great potential in OLED (Organic Light-Emitting Diode) materials (Scheme 12).

Catalytic asymmetric *de novo* construction

The power of modern synthetic organic chemistry has enabled the assembly of structurally diverse C–N atropisomers via *de novo* construction of the (hetero-)aromatic ring, which has emerged as an important strategy for the construction of C–N axially chiral compounds. In 2006, Tanaka et al. reported an enantioselective synthesis of axially chiral anilides **86** via *de novo* construction.[64] The reaction involves a [2+2+2] cycloaddition of ynamides **85** with 1,6-diynes **84** via a possible mode of activations illustrated in **TS-7** under the catalysis of rhodium(I)/BINAP complex. This seminal documentation represents an early example in which C–N axially chiral molecules could be constructed from simple building blocks with excellent stereochemical control (Scheme 13A). Almost at the same time,[65] Hsung and coworkers reported a rhodium(I)-catalyzed asymmetric [2+2+2] cycloaddition of 1,6-diynes **84** with ynamides **87**, forming enantiomerically enriched biaryls **88** containing both the C–C and C–N axial chiralities (Scheme 13B).

Chiral *N*-arylindole skeletons bearing C–N axial chirality exist widely in natural products, and they are also useful chiral ligands in asymmetric catalysis; however, their catalytic asymmetric synthesis is quite limited. In 2010, the Kitagawa group reported the first catalytic atroposelective synthesis of axially chiral *N*-arylindoles via the *de novo* construction of the indole ring.[66] In the presence of chiral ligand **L12** SEGPHOS, palladium-catalyzed intramolecular *endo*-hydroaminocyclization of

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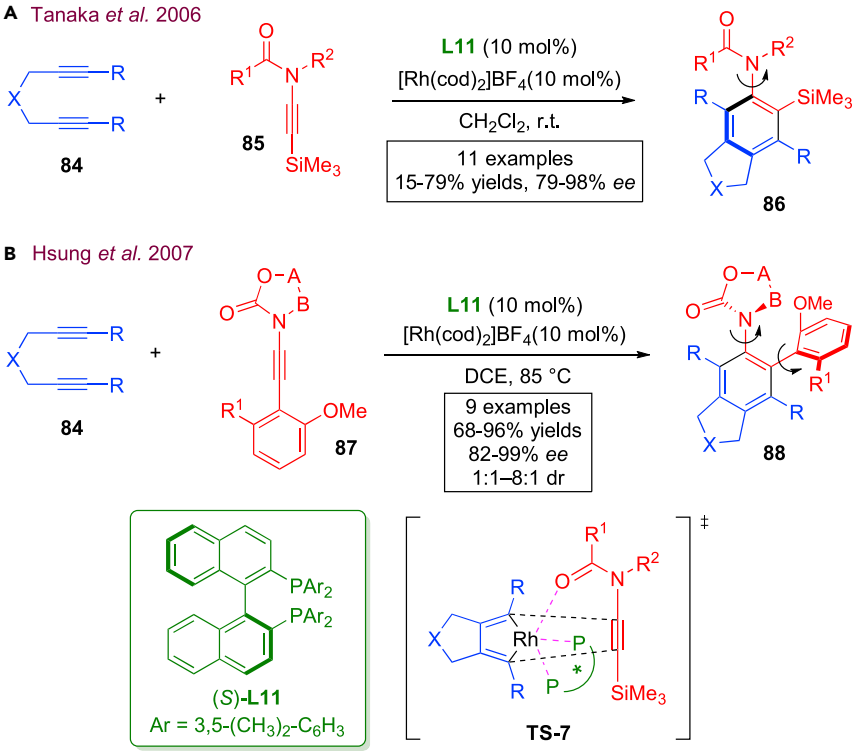

Scheme 13. Rhodium-catalyzed [2+2+2] annulation for the construction of C–N axially chiral compounds

(A) Tanaka *et al.* 2006.

(B) Hsung *et al.* 2007.

ortho-alkynylaniline **89** led to the formation of *N*-arylindoles **90** in high yields with moderate to good enantioselectivities (Scheme 14A). Almost a decade later, Lin and coworkers reported an organocatalytic *de novo* construction of *N*-arylindoles.[67] In the presence of chiral spirocyclic phosphoric acid **C20**, a three-component cascade reaction of aromatic amines **91**, 2,3-diketoesters **92**, and 1,3-cyclhexanediones **93** led to atroposelective synthesis of axially chiral *N*-arylindoles **94** with excellent enantiomeric excesses (Scheme 14B).

With the presence of an *ortho*-substituent, *N*-aryl-phenanthridin-6-one derivatives are able to maintain a stable C–N axially chiral structure. Riding on their earlier success of atroposelective synthesis of *N*-(2-tert-butylphenyl)-3,4-dihydroquinolin-2-one[33] and by employing biphenyl amide substrates **95**, Kitagawa and coworkers achieved an asymmetric synthesis of C–N axially chiral phenanthridin-6-one derivatives **96**, through a (*R*)-DTBM-SEGPHOS-Pd(OAc)$_2$-catalyzed intramolecular Buchwald-Hartwig amination reaction.[68] However, as the authors noticed, the enantioselectivity of the reaction strongly depended on solvents, bases, temperatures, and the bulkiness of the *ortho* substituents (Scheme 15A). Recently, Gu and coworkers reported an atroposelective synthesis of anilides via a copper-catalyzed enantioselective intramolecular Ullmann-type amination reaction.[69] Using a readily prepared ligand *N*,*N*′-(cyclohexane-1,2-diyl)dipicolinamide **L13** and running the reaction at a relative low temperature, the C–N axially chiral arylphenanthridin-6-ones **98** were prepared in high yields with nearly perfect *ee* values (Scheme 15B). Very recently, Hong, Zhou, and coworkers reported an efficient synthesis of C–N axially chiral phenanthridin-6-one derivatives from readily available simple starting materials.[70,71] The authors elegantly made use of palladium/chiral NBE*

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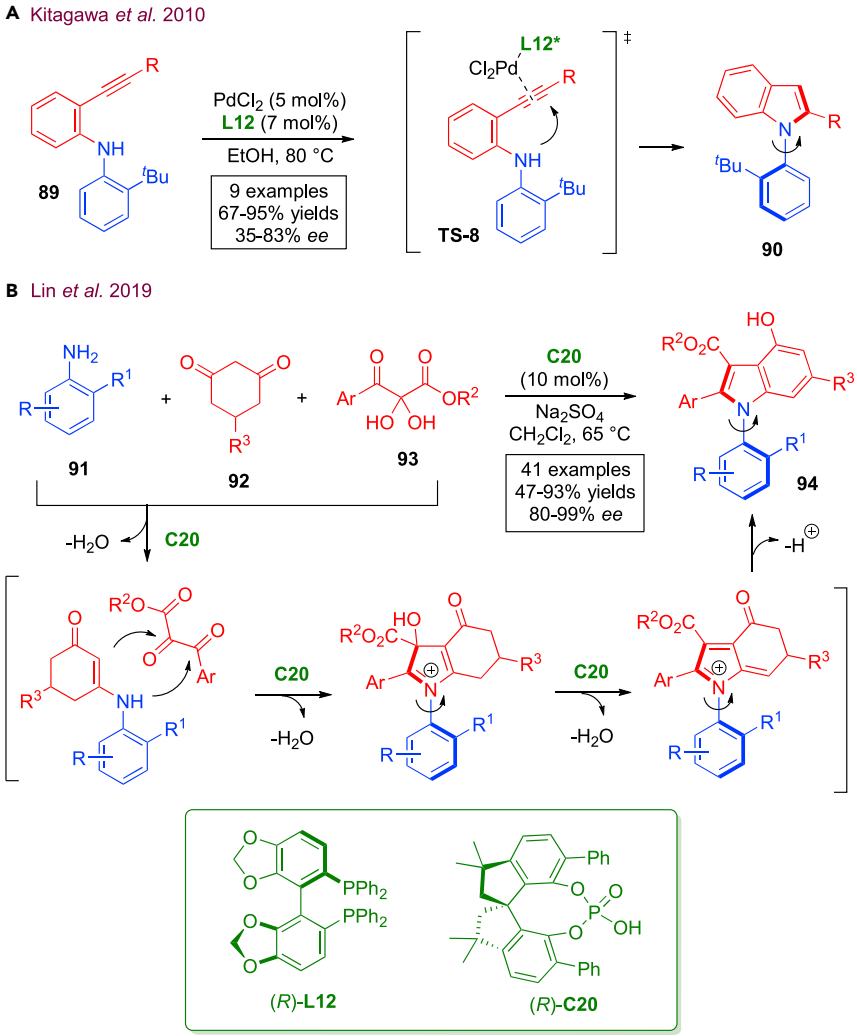
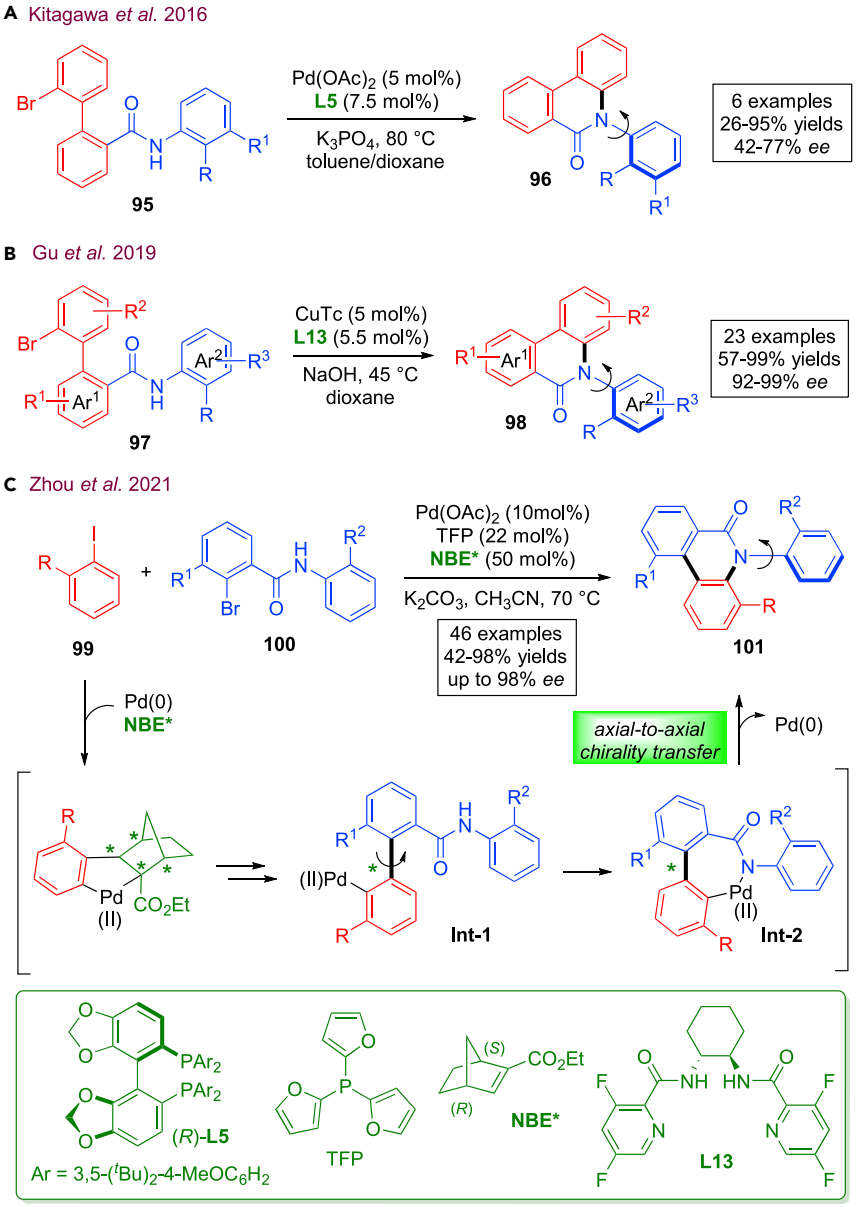


Scheme 14. Catalytic atroposelective synthesis of *N*-arylindoles
(A) Kitagawa *et al.* 2010.
(B) Lin *et al.* 2019.

(norbornene) cooperative catalysis (Catellani reaction) and sequence of C–H activation, oxidative addition, and reductive elimination to form the key axially chiral palladium (II) intermediate **Int-1**. Following an intramolecular amidation (**Int-2**), the crucial axial-to-axial chirality transfer took place with high fidelity, eventually producing C–N axially chiral phenanthridinones **101**. The proposed mechanistic pathways were well supported by the DFT calculations performed (Scheme 15C).

Benzimidazoles are structural motifs that are widely present in bioactive compounds and medicinally useful agents, and considerable efforts have been devoted to their efficient synthesis. The Miller group reported the first atroposelective synthesis of *N*-arylbenzimidazoles via a CPA-catalyzed intramolecular cyclodehydration reaction.[72] Subsequently, Miller, Sigman, Toste, and coworkers examined disparate catalytic scaffolds for the atropisomer-selective cyclodehydration: C_2-symmetric CPAs and phosphothreonine (pThr)-embedded peptidic phosphoric acids.[73] Both types of phosphoric acids were effective in promoting intramolecular cyclodehydration



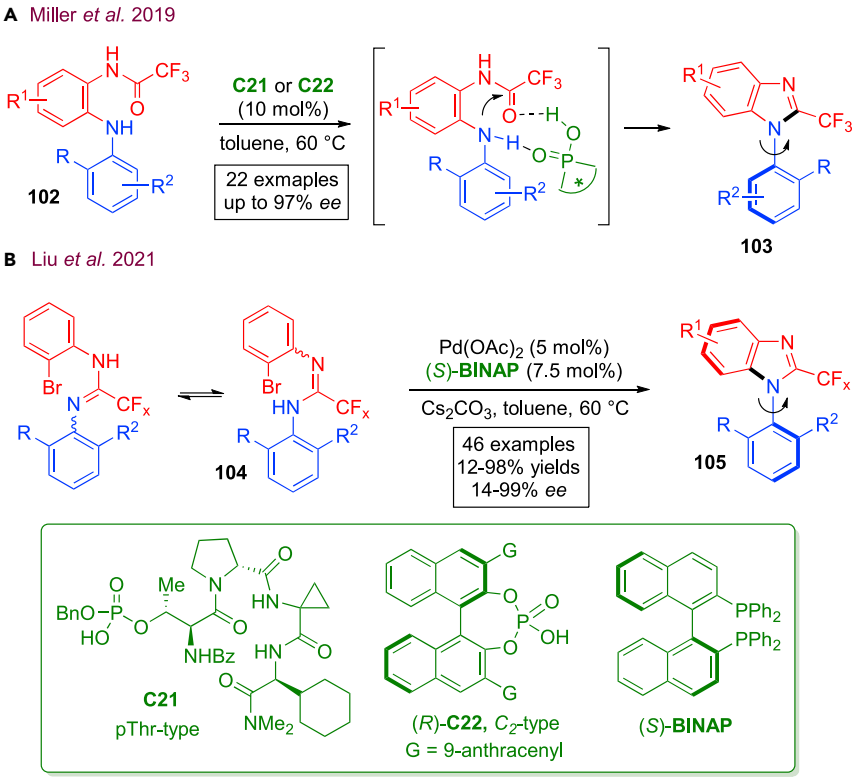
Scheme 15. Catalytic atroposelective synthesis of *N*-arylphenanthridin-6-ones

(A) Kitagawa *et al.* 2016.

(B) Gu *et al.* 2019.

(C) Zhou *et al.* 2021.

reaction, *de novo* forming benzimidazoles with a C–N axis atroposelectively. Mechanistically, the authors performed a substrate profiling, which provided insight into the origin of asymmetric induction. Although the steric effects from large groups on the catalyst and substrate dictate enantioselectivity for the C_2-type CPA-catalyzed reactions, conformational adaptation seems to limit repulsive interactions for the reactions promoted by the pThr-type CPAs (Scheme 16A). More recently, Lu, Liu, and coworkers described a palladium-catalyzed intramolecular Buchwald-Hartwig amination for the highly enantioselective synthesis of C–N axially chiral *N*-arylbenzimidazoles **105**.[74] As the authors noted, potential coordination of amidines to transition metals, the tautomerization process, as well as E/Z isomerization



Scheme 16. Intramolecular catalytic atroposelective synthesis of *N*-arylbenzimidazoles
(A) Miller *et al.* 2019.
(B) Liu *et al.* 2021.

make the control of enantioselectivity for this cross-coupling reaction challenging (Scheme 16B).

The C–N axially chiral N-aryl-benzimidazoles were also constructed in an intermolecular fashion. Utilizing an earlier method developed by Zhou et al. on phosphorus acid-catalyzed synthesis of benzimidazoles through condensation of benzene-1,2-diamines with β-ketoesters,[75] Fu and coworkers recently accomplished an atroposelective preparation of axially chiral *N*-aryl benzimidazoles.[76] In the presence of a CPA catalyst **C23**, the target products **108** bearing a C–N axis were prepared in high yields with excellent enantioselectivities (Scheme 17A). Very recently, Zhong, Tan, and coworkers disclosed a nitrosobenzene-enabled enantioselective construction of atropisomeric *N*-arylbenzimidazoles.[77] In this elegant domino reaction sequence, the nitroso group played a unique role, serving as an electrophilic site and a nucleophilic site at different stages of the reaction. In the presence of CPAs, the nucleophilic addition of naphthylamine to nitrosobenzne forms **Int-3**. Subsequent dehydration and [1,5]-H shift furnishes benzyl imine **int-4**. A CPA-catalyzed intramolecular enantioselective addition of amine to imine gives rise to the formation of annulated **Int-5**, which undergoes oxidative aromatization to form *N*-aryl-benzimidazoles **112** (Scheme 17B). Interestingly, the authors discovered two sets of conditions to access *N*-aryl-benzimidazoles in opposite configuration by using a CPA catalyst with the same absolute configuration.

Isoindolinones are important pharmacophores, and they are also widely present in a range of natural products. However, catalytic atroposelective synthesis of C–N

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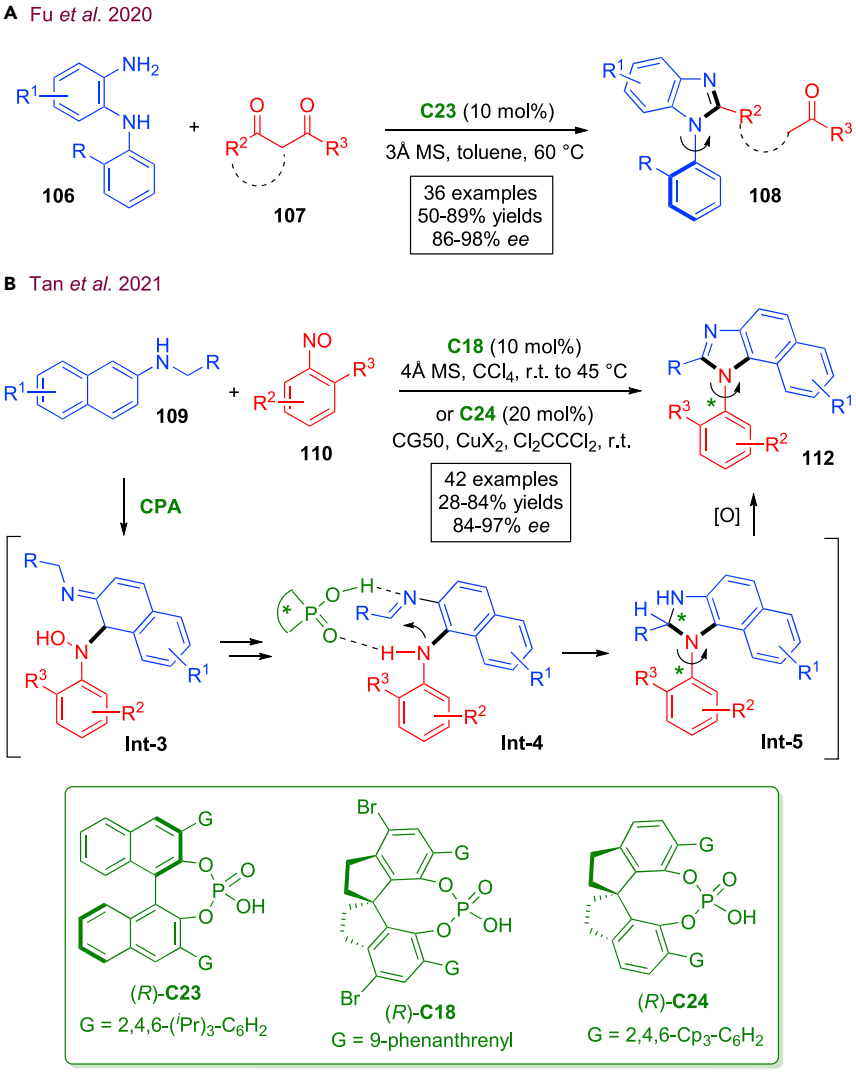
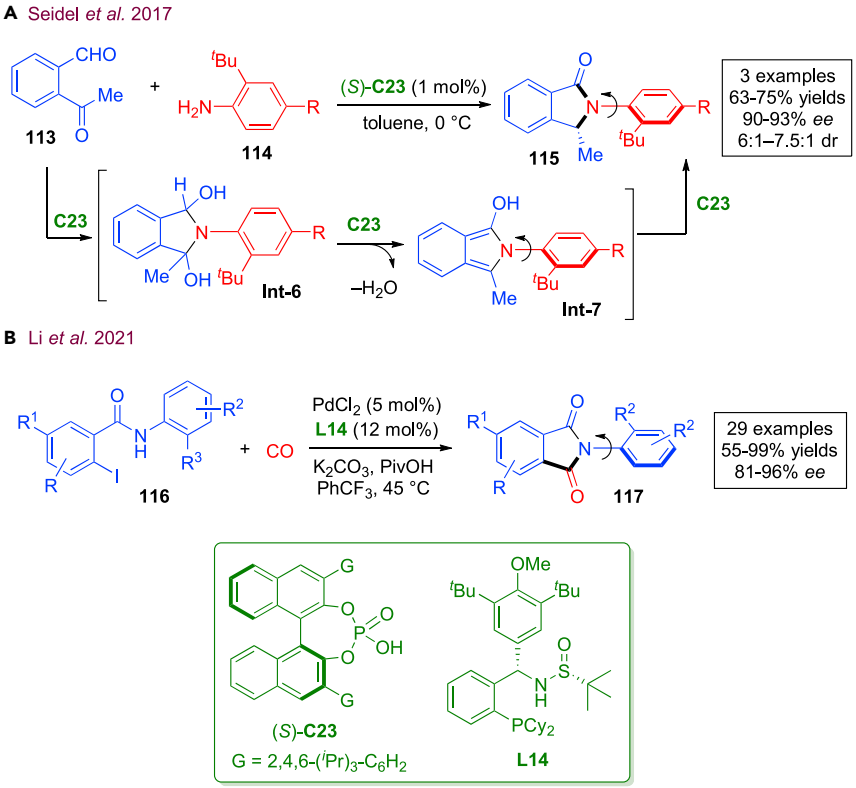


Scheme 17. Intermolecular catalytic atroposelective synthesis of *N*-arylbenzimidazoles

(A) Fu *et al.* 2020.

(B) Tan *et al.* 2021.

axially chiral *N*-aryl-isoindolinones remain unexplored until very recently. In 2017, Seidel and coworkers reported a catalytic atroposelective preparation of isoindolinones.[78] In the presence of CPA **C23**, a highly enantioselective biomimetic condensation between 2-acylbenzaldehydes **113** and anilines **114** led to the formation of *N*-aryl-isoindolinones **115** bearing both a central chirality and a chiral C–N axis. It is proposed that the reaction proceeds through the formation of cyclic bishemiaminal **Int-6**, followed by sequential dehydration and tautomerization. Moreover, the method was successfully applied to the first synthesis of mariline A (Scheme 18A). Very recently,[38] Sun, Li, and coworkers described an atroposelective carbonylation of aryl iodides with amides for the synthesis of enantiomerically enriched *N*-aryl-isoindolindiones **117** containing a C–N axial chiral element. With the employment of Sadphos ligand **L14**, palladium-catalyzed carbonylative cycloamidation proceeded smoothly and with high enantiomeric control (Scheme 18B).

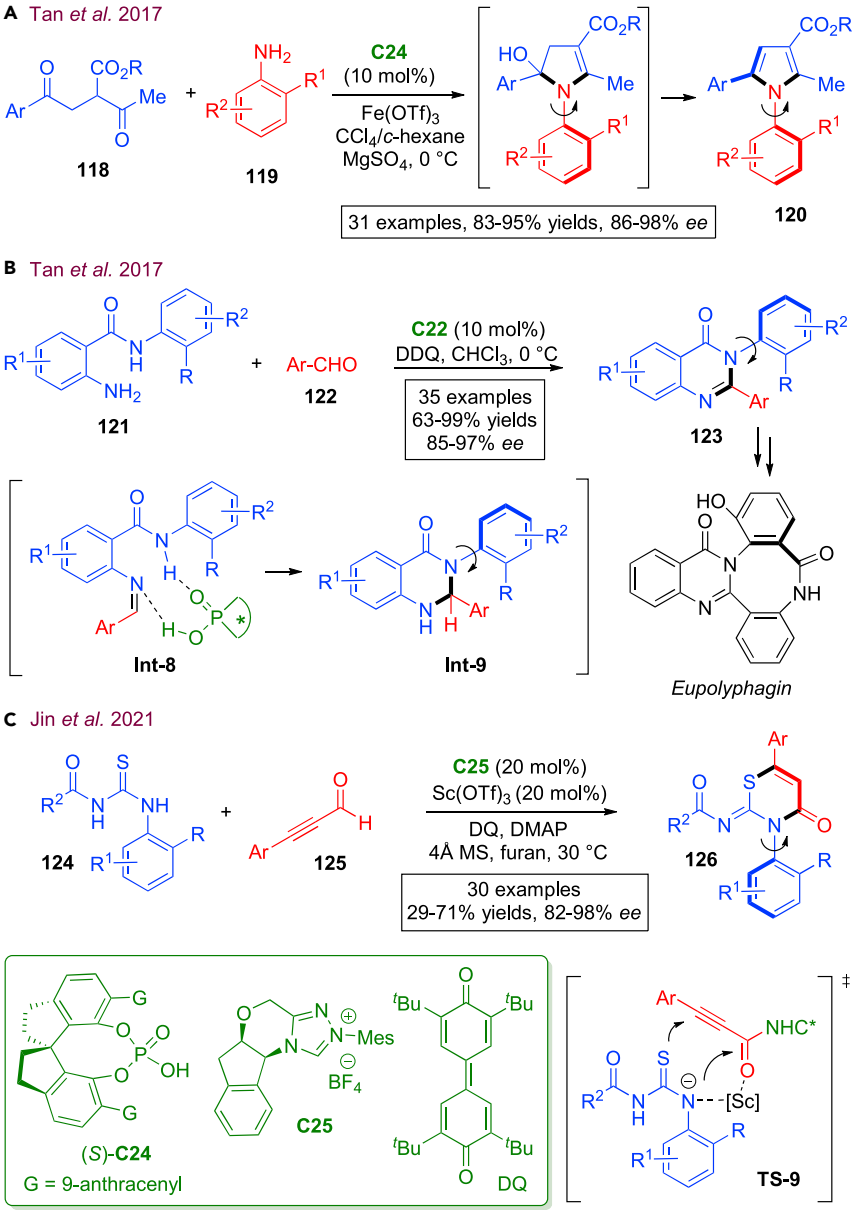


Scheme 18. Catalytic atroposelective synthesis of *N*-arylisoindoli(di)nones

(A) Seidel *et al.* 2017.

(B) Li *et al.* 2021.

Pyrroles are key structural scaffolds that are widely present in bioactive molecules and natural products, and they also find broad applications in materials science. When the synthesis of pyrroles is concerned, the Paal-Knorr reaction represents a classical method that is powerful for their preparation. The first catalytic asymmetric Paal-Knorr reaction was developed by Tan and coworkers, when they reported a highly atroposelective synthesis of arylpyrroles in 2017.[79] In the presence of CPA catalyst **C24** and Lewis acid $Fe(OTf)_3$, the condensation between diketones **118** and anilines **119** proceeded smoothly, furnishing a good range of axially chiral *N*-arylpyrroles **120** around the C–N bond in high yields with good-to-excellent enantioselectivities. An interesting observation in this study is the solvent-dependent enantioselectivity. Simply changing the solvent system led to the formation of opposite enantiomer even when a chiral catalyst with the same configuration was employed (Scheme 19A). Another structural motif that is often found in natural products and bioactive compounds is quinazolinone. Through *de novo* construction, the Tan group disclosed the first catalytic enantioselective synthesis of *N*-arylquinazolinones bearing a C–N axis.[80] The reported one-pot procedure is initiated by a CPA-facilitated hemiaminal formation, followed by the oxidative dehydrogenation, to generate a variety of C–N axially chiral aryl-quinazolinones **123**. With the employment of 4-methoxypentenone as a condensation partner and more acidic *N*-triflylphosphoramides at 60°C, the authors also developed a carbon–carbon bond cleavage strategy. Moreover, the practical use of this method was shown in the facile asymmetric total synthesis of eupolyphagin (Scheme 19B). Thiazines are an important class of heterocyclic compounds that are often found in medicinally useful agents and agrochemicals. Very recently, Jin and coworkers reported



Scheme 19. Catalytic atroposelective *de novo* synthesis of other *N*-aryl heterocyclic ring systems

(A) Tan *et al.* 2017.

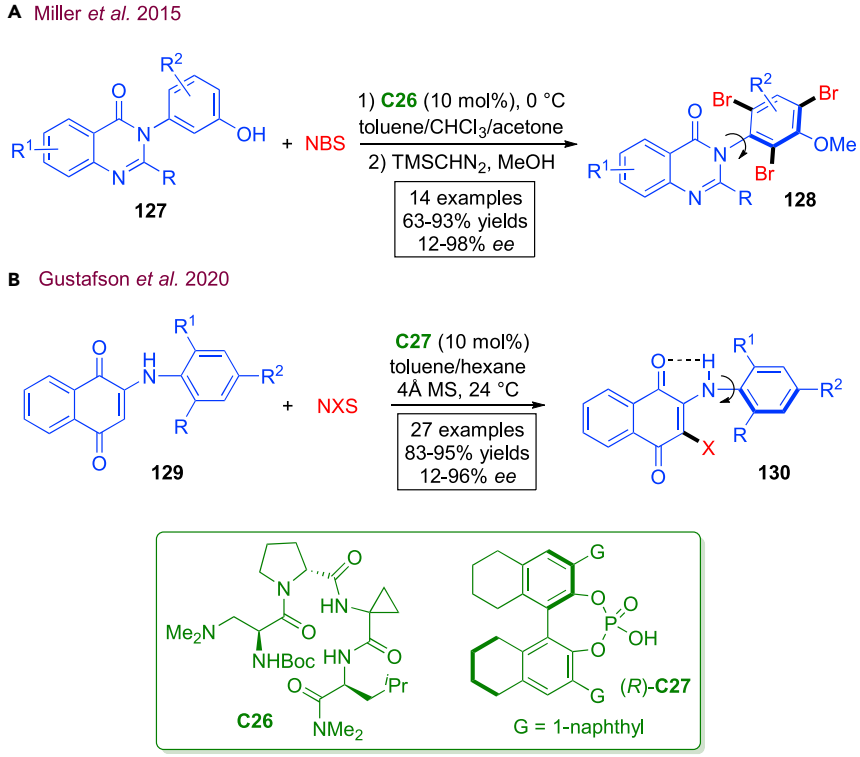
(B) Tan *et al.* 2017.

(C) Jin *et al.* 2021.

an atroposelective annulation for the synthesis of thiazine derivatives with C–N axial chirality.[81] The key steps of the reaction include a NHC-catalyzed addition of thiourea to ynal-derived acetylenic acylazolium intermediate, followed by an intramolecular lactamation, to form atropisomeric thiazines **126** with excellent enantioselectivities. The use of $Sc(OTf)_3$ was found to be important, improving the reaction yield with retention of the optical purity (Scheme 19C).

Catalytic asymmetric aryl functionalization

Asymmetric aryl functionalization of C–N-bearing prochiral substrates represents an important strategy to atroposelectively synthesize an axially chiral C–N bond. When



Scheme 20. Catalytic atroposelective electrophilic halogenation
(A) Miller *et al.* 2015.
(B) Gustafson *et al.* 2020.

such an aryl functionalization is concerned, the designated reaction process needs to (1) make good use of existing structural motifs, (2) effectively create the structural complexity of the final products, and (3) introduce the C–N axial chirality efficiently. In 2015, Miller and coworkers reported a pioneering study on the enantioselective synthesis of 3-arylquinazolin-4(3*H*)-ones using an atroposelective bromination strategy.[82] In the presence of tertiary amine-containing β-turn peptide catalyst **C26**, tribromination of quinazolinones **127** containing a pre-existing C–N bond led to a highly enantioselective production of C–N axially chiral 3-arylquinazolinones **128**. Recognizing the monobrominated products are stereoisomerically stable, the authors performed further elaborations on the products, e.g., a dehalogenative Suzuki-Miyaura cross-coupling sequence and a regioselective Buchwald-Hartwig amination (Scheme 20A). More recently, Gustafson and coworkers reported a catalytic atroposelective synthesis of *N*-aryl quinoids.[83] Under the catalysis of CPA, electrophilic halogenation took place smoothly, yielding a range of stereochemically stable *N*-aryl-quinoids **130** around the C–N axis (Scheme 20B). Diarylamines are useful molecular scaffolds in drug discovery; however, their enantioselective synthesis is a formidable task as diarylamines can potentially possess two chiral axes, and the stabilities of such axes are lower. Notably, the *N*-aryl quinoids can be regarded as diarylamine surrogate, and it is proposed that the strong intramolecular N–H–O hydrogen bonding makes the quinoid nitrogen exists in a planar confirmation, thus simplifying the two-axis system.

The pyrrole and indole substructures are commonly present in C–N axially chiral molecules. From a synthetic viewpoint, their functionalization at the C2 position represents one of the most straightforward approaches to introduce C–N axial chirality.

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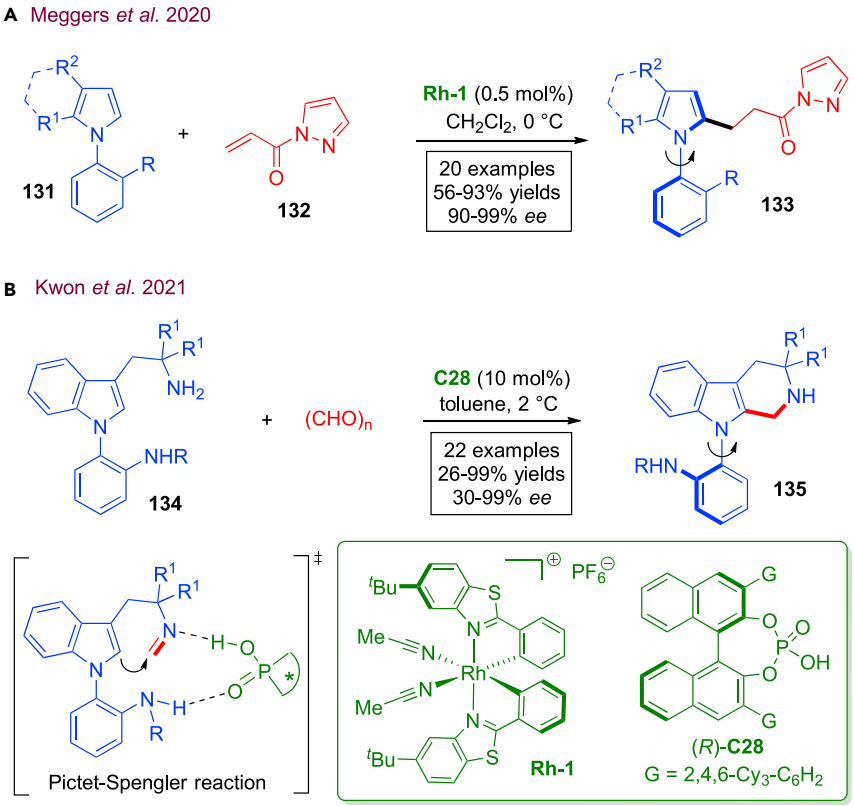
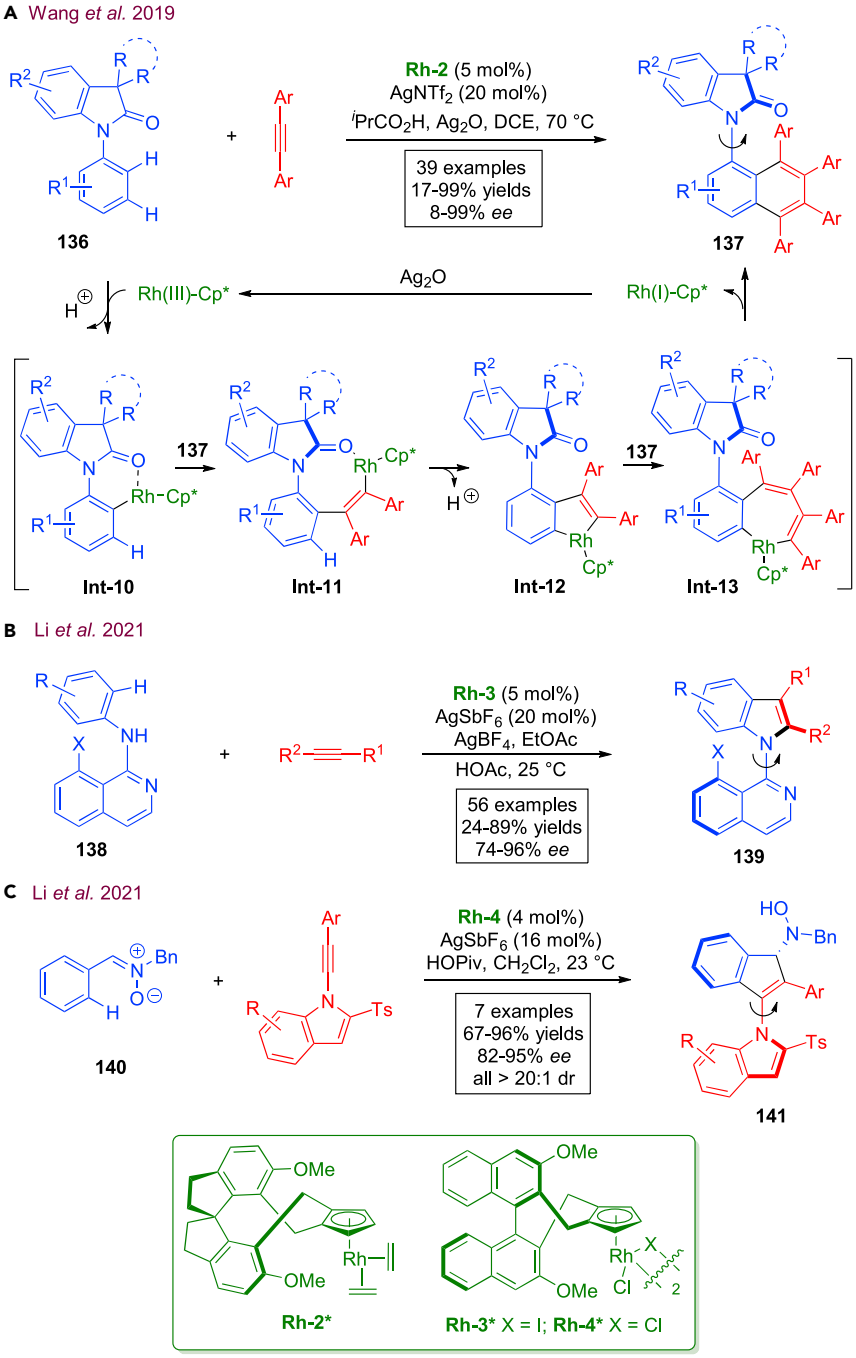


Scheme 21. Catalytic atroposelective C2-functionalization of *N*-arylpyrroles and *N*-arylindoles
(A) Meggers *et al*. 2020.
(B) Kwon *et al*. 2021.

In a recent report,[84] Meggers and coworkers accomplished a highly atroposelective synthesis of axially chiral *N*-arylpyrroles. The chiral-at-metal rhodium catalyst (**Rh-1**) promoted electrophilic aromatic substitution of configurationally labile substrates **131**, delivering alkylated *N*-arylpyrrole products **133** with C–N axial chirality in good yields with excellent enantioselectivities (Scheme 21A). The C2-functionalization of *N*-arylindoles was recently demonstrated by the Kwon group, when they described a synthesis of C–N sterogenic axis in *N*-arylindoles.[85] The CPA catalyst **C28** promoted a Pictet-Spengler reaction of arylpyrroles **134**, through a dual hydrogen-bonding interaction, to furnish highly enantioenriched *N*-aryl-tetrahydro-*β*-carbolines **135** with C–N axial chirality in good yields with high enantioselectivities. When electron-withdrawing group-substituted benzaldehydes were employed, products with both central and axial chiralities were obtained. The authors also studied the antiproliferative activities of the C–N axial products, further demonstrating the value of current methodology (Scheme 21B).

In recent years, transition-metal-catalyzed enantioselective C–H functionalization has emerged as a powerful strategy for the synthesis of atropisomers.[4] In this context, the C–H functionalization of arenes represents a promising approach to access C–N axially chiral molecules. The first example of utilizing C–H activation strategy for the asymmetric synthesis of C–N axially chiral compounds was reported by Wang and coworkers in 2019.[86] Through an enantioselective Satoh-Miura-type process involving dual C–H activation, a variety of C–N axially chiral *N*-aryloxindoles **137** were prepared in high yields with excellent *ee* values. Mechanistically, the first C–H



Scheme 22. Rh-catalyzed atroposelective C–H functionalization

(A) Wang *et al.* 2019.

(B) Li *et al.* 2021.

(C) Li *et al.* 2021.

bond cleavage leads to a six-membered rhodacyclic intermediate (**Int-10**). The following alkyne insertion gives a C–N axially chiral **Int-11**; subsequently, another C–H activation, alkyne insertion, and the final reductive elimination form the naphthalene ring. Preliminary mechanistic studies indicated that the C–H activation step was not the turnover-determining step (Scheme 22A). Very recently, Wang,

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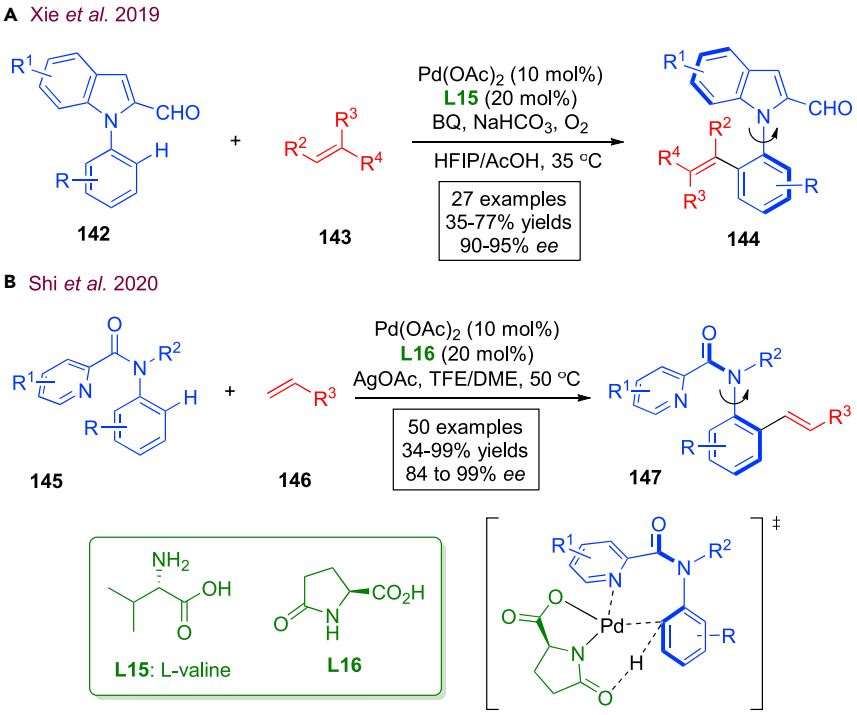

Scheme 23. Pd-catalyzed atroposelective C–H olefination

(A) Xie *et al.* 2019.

(B) Shi *et al.* 2020.

Lan, Li, and coworkers documented a rhodium-catalyzed atroposelective construction of indoles via C–H activation.[87] The reported process is a rhodium(III)-catalyzed oxidative [3+2] annulation of anilines **138** bearing an *N*-isoqunolyl group and different types of internal alkynes. The authors also conducted preliminary mechanistic studies by performing DFT calculations, which suggested that the final C–N reductive elimination is the stereo-determining step in the whole reaction process (Scheme 22B). Shortly after, Li and coworkers accomplished an efficient construction of axially and centrally chiral indenes, also through the rhodium-catalyzed C–H activation strategy.[88] The chiral rhodium (III) complex (**Rh-4**) catalyzed [3+2] annulation of arylnitrones **140** with indolyl alkynes, in which nitrone acted as an electrophilic directing group. A broad range of products **141**, with both C–N axial and C-central chirality, were prepared with excellent enantio- and diastereo-selectivities under mild reaction conditions. Notably, the employment of different classes of alkynes offered flexible synthetic solutions to different classes of chiral indenes/indenones bearing C-central or C–C axial chirality (Scheme 22C).

Palladium-catalyzed reactions are among the most powerful organic transformations, thus are of pivotal importance in modern synthetic organic chemistry. In 2019, Zhang, Xie, and coworkers disclosed the first application of palladium-catalyzed C–H olefination for the atroposelective construction of C–N axial chirality.[89] The use of palladium/amino acid cooperative catalysis is crucial, and the amino acid cocatalyst is believed to play important roles in regio- and stereochemical controls (Scheme 23A). In 2020, Hong, Shi, and coworkers described an enantioselective synthesis of atropisomeric anilides via a palladium (II)-catalyzed C–H olefination.[90] Using readily available L-pyroglutamic acid **L16** as an inexpensive chiral ligand, a wide range of C–N axially chiral anilides **147** were prepared in high yields and

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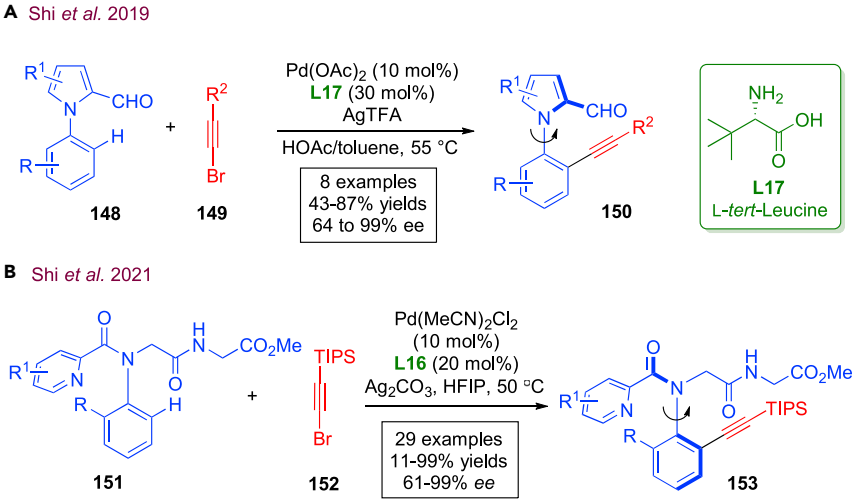


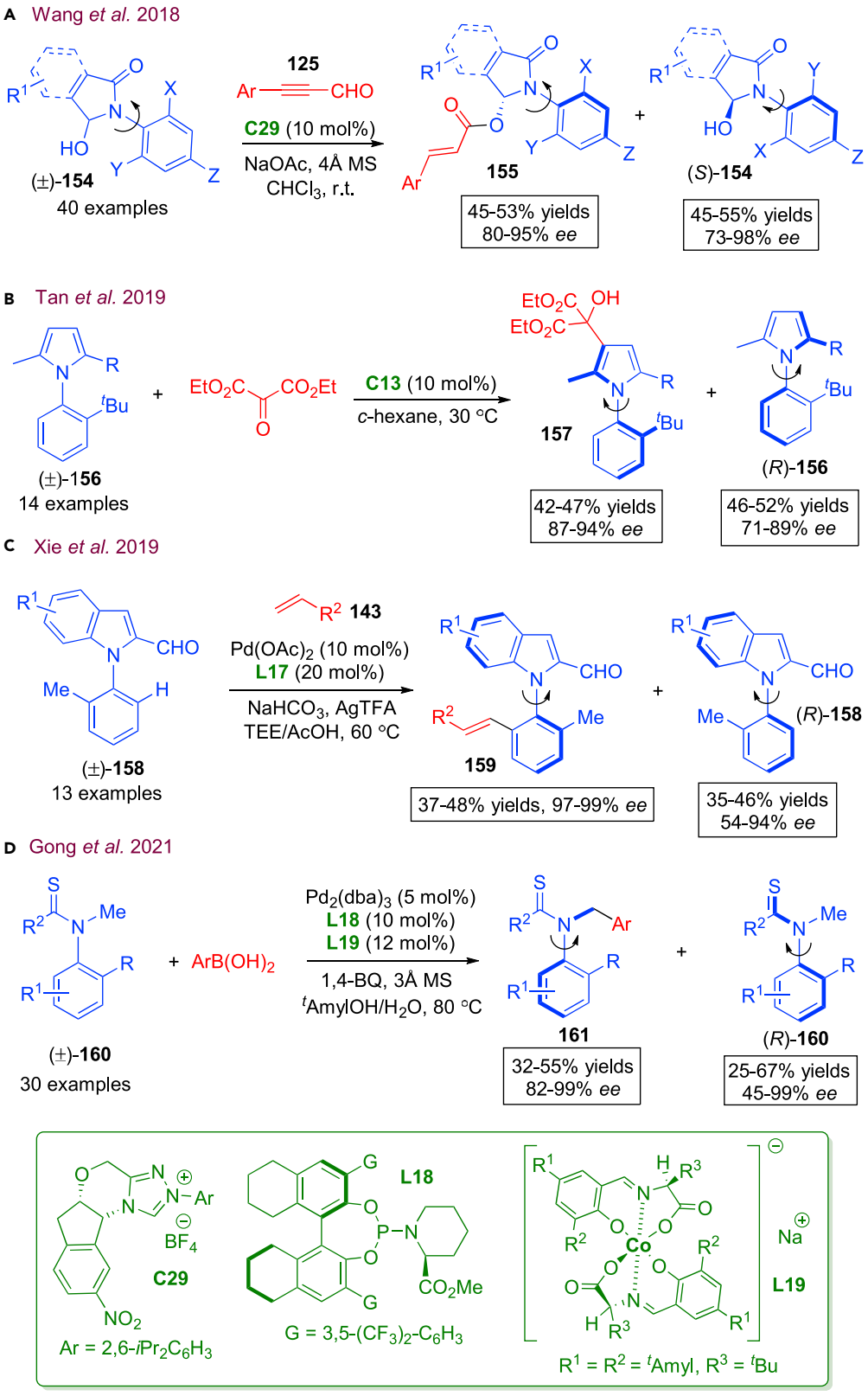
Scheme 24. Pd-catalyzed atroposelective C–H alkynylation
(A) Shi *et al.* 2019.
(B) Shi *et al.* 2021.

with excellent enantioselectivities under mild conditions. The racemization experiments were performed to study the atropostability of the products, and both steric and electronic effects were found to be important. Theoretical investigations carried out revealed that the amino acid ligand distortion accounts for the enantio-control in the C–H bond activation step (Scheme 23B).

Alkynation of prochiral substrates seems to be a simple and straightforward strategy to create C–N axial chirality. However, in practice, related examples are nevertheless quite rare, likely due to the linear structure of alkynes and thus inability to provide sufficient steric hindrance necessary to induce axial chirality. In a recent report, the Shi group employed a TIPS (triisopropylsilyl)-protected alkynyl substrates, which enabled the creation of C–N axial chirality via C–H activation.[91] Using *tert*-leucine **L17** as an efficient and transient chiral auxiliary and under the palladium catalysis, a range of *N*-arylpyrroles **150** with a bulky alkynyl moiety were atroposelectively formed in good yields (Scheme 24A). Very recently,[92] the same group reported an atroposelective synthesis of *N*-aryl peptoids by applying the same palladium-catalyzed asymmetric C–H alkynylation strategy. Notably, the structural modifications of peptoids are of great practical value, as the introduction of chirality in peptoids represents an important strategy for the determination of peptide secondary structures (Scheme 24B).

Kinetic resolution

KR is one of the most classic and fundamental processes in asymmetric catalysis and synthesis, in which racemic starting materials are resolved to provide enantiomerically pure chiral substances.[93] When the synthesis of C–N axially chiral compounds is concerned, there are a few catalytic reports that relied on KR to access C–N atropisomers. In 2018, Wang et al. developed an NHC-catalyzed enantioselective KR of anilides.[94] Racemic hemiaminals **154** were resolved through an NHC-catalyzed acylation, and the corresponding products with both C–N axial and central chirality were formed with excellent enantiomerical control (Scheme 25A). In 2019, Tan and coworkers constructed axially chiral *N*-arylpyrroles via the KR of racemic substrates.[53] Under the catalysis of phosphoric acid **C13** and through a remote stereochemical control, C–N axially chiral *N*-arylpyrroles **157** were prepared with good to high selectivity factors (Scheme 25B).


A Wang et al. 2018
(±)-154
40 examples
125
C29 (10 mol%)
NaOAc, 4Å MS
CHCl3, r.t.
155
45-53% yields
80-95% ee
(S)-154
45-55% yields
73-98% ee
B Tan et al. 2019
(±)-156
14 examples
C13 (10 mol%)
c-hexane, 30 °C
157
42-47% yields
87-94% ee
(R)-156
46-52% yields
71-89% ee
C Xie et al. 2019
(±)-158
13 examples
143
Pd(OAc)2 (10 mol%)
L17 (20 mol%)
NaHCO3, AgTFA
TEE/AcOH, 60 °C
159
37-48% yields, 97-99% ee
(R)-158
35-46% yields
54-94% ee
D Gong et al. 2021
(±)-160
30 examples
ArB(OH)2
Pd2(dba)3 (5 mol%)
L18 (10 mol%)
L19 (12 mol%)
1,4-BQ, 3Å MS
tAmylOH/H2O, 80 °C
161
32-55% yields
82-99% ee
(R)-160
25-67% yields
45-99% ee
C29
Ar = 2,6-iPr2C6H3
L18
G = 3,5-(CF3)2-C6H3
L19
R1 = R2 = tAmyl, R3 = tBu

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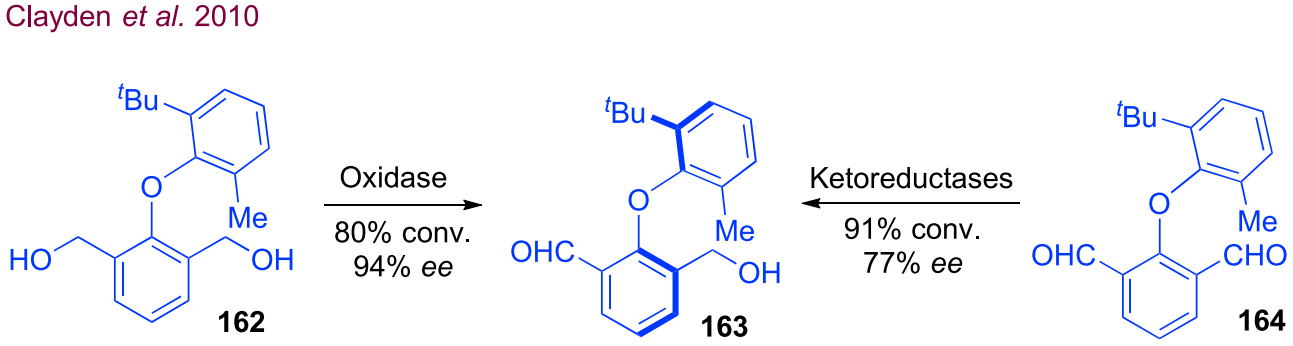
Scheme 25. Atroposelective kinetic resolution
(A) Wang *et al.* 2018.
(B) Tan *et al.* 2019.
(C) Xie *et al.* 2019.
(D) Gong *et al.* 2021.

Around the same time,[89] Xie and coworkers realized a KR of *N*-arylindoles via a palladium-catalyzed C–H olefination, enabled by the cooperative palladium/amino acid catalysis (Scheme 25C). In a similar approach, Ackermann et al. described a KR strategy via palladaelectro-catalyzed C–H olefination and allylation for C–N axial chirality construction.[95] Very recently, the Gong group disclosed an atroposelective C(sp^3)–H coupling for the KR of thioanilides.[96] Under the catalysis of a hybrid palladium catalyst containing an anionic chiral cobalt complex and a phosphoramidite ligand, the KR of atropisomeric thioanilides **160** produced both atropisomeric arylated thioanilides **161** and *N*-methyl atropisomeric thioanilides (*R*)-**160** with very high enantioselectivities (Scheme 25D).

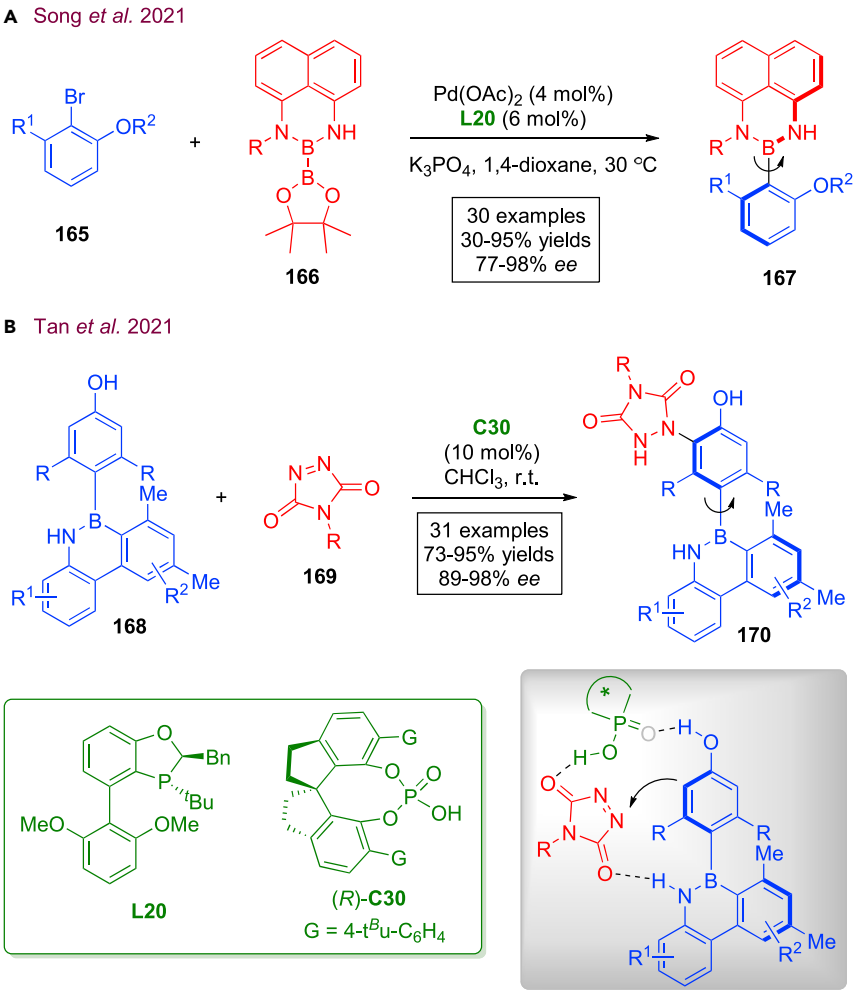
ATROPISOMERS AROUND OTHER BONDS

Although catalytic asymmetric synthesis of atropisomers around C–N axis has received much attention and has become a hot research area in the past few years, atropisomerism arising from restricted rotation about other bonds, such as C–O, C–B, and N–N, have been rarely explored. An early example on the enantioselective synthesis of C–O atropisomers was reported by Turner and Clayden more than a decade ago.[97] In this biocatalytic approach, a prochiral diol **162** or dialdehyde **164** was subjected to the desymmetrization reaction catalyzed by oxidase or ketoreductases, respectively, forming atropisomeric diaryl ethers **163**, a structural unit of vancomycin (Scheme 26). In 2018, Gustafson and coworkers described an organocatalytic synthesis of atropisomeric diaryl ethers through a C(sp^2)–H alkylation reaction with nitroalkanes. However, the results were less satisfactory; there were only a few examples reported, and the enantioselectivities were from poor to modest.[98]

Organoboron compounds are extremely useful synthetic intermediates, crucial for efficient asymmetric construction of chiral molecules. Although organoboron chemistry has made marvelous progress in the past decades, vast majority of the efforts are focused on the centrally chiral organoboron compounds. Axially chiral organoborons, i.e., C–B axially chiral molecules, remained unknown until very recently.[99] In comparison with stereoselective synthesis of atropisomers bearing a C–C or C–N axis, it is more challenging to synthesize C–B axially chiral molecules; the C–B bond is longer than the corresponding C–C and C–N bonds, which lowers the rotational barrier. In a very recent report, Song and coworkers documented the



Scheme 26. Catalytic asymmetric synthesis of atropisomer around the C–O bond: Clayden *et al.* 2010



Scheme 27. Catalytic asymmetric synthesis of atropisomers around the C–B bond

(A) Song *et al.* 2021.

(B) Tan *et al.* 2021.

construction of axially chiral arylborons via atroposelective Miyaura borylation.[100] The key to the success of this synthetic protocol was the development of a suitable unsymmetrical diboron reagent. In the presence of P-chiral monophosphorus ligand **L20**, palladium-catalyzed Miyaura borylation of bromoarenes **165** with unsymmetrical diboron **166** proceeded enantioselectively, forming a range of optically enriched atropsiomeric arylborons in generally good yields with high *ee* values (Scheme 27A). Around the same time, the Tan group described an enantioselective construction of C–B stereogenic axis through a desymmetrization strategy.[101] In Tan's approach, CPA **C30** effectively promoted the electrophilic aromatic substitution reaction of 3,5-disubstituted phenols **168** with diazodicarboxamides **169**, producing a class of axially chiral 4-azaborine-phenols **170** containing a stereogenic C–B bond under mild reaction conditions. Multiple hydrogen-bonding interactions of CPA with both substrates were believed to be crucial, setting the stereogenic B–C axis remotely (Scheme 27B).

The N–N bond containing motifs are widely present in natural products, pharmaceutical agents, and organic materials. Although there were studies toward the

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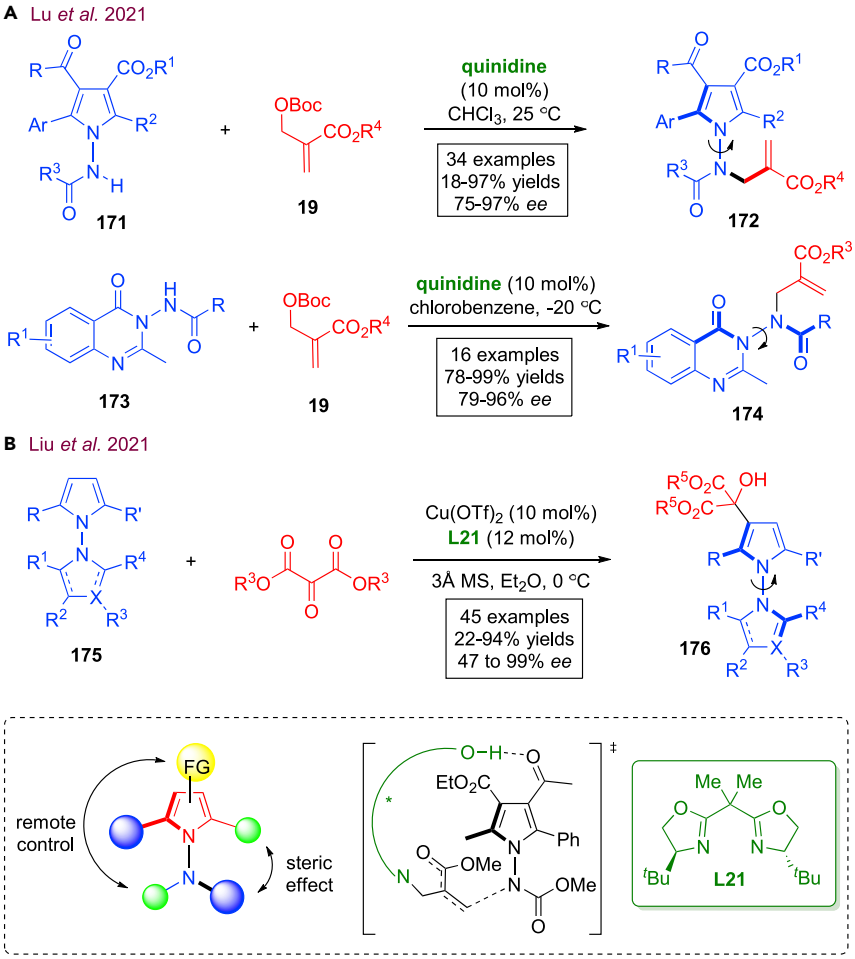

Scheme 28. Catalytic asymmetric synthesis of atropisomers around the N–N bond

(A) Lu *et al.* 2021.

(B) Liu *et al.* 2021.

synthesis of N–N containing structural motifs, the N–N atropisomerism phenomenon has been overlooked in the past few decades. Asymmetric synthesis of N–N axially chiral molecules is highly challenging because deplanarization of the two N-containing planes upon rotation leads to a low rotational barrier. On the other hand, the formation of such N–N axis could be favored, given the fact that the N–N bond is shorter. Additionally, the N–N axis is expected to be more crowded, due to the electronic barrier stemming from repulsive interaction between the lone pairs on the two nitrogen atoms. Atroposelective synthesis of N–N axially chiral compounds remained elusive until very recently, when Houk, Lu, and coworkers disclosed their finding.[102] The *N*-allylic alkylation reaction catalyzed by quinidine proceeded smoothly under mild conditions, forming a wide variety of N–N axially chiral 1-aminopyrroles **172** and 3-aminoquinazolinones **174** in high yields with excellent enantioselectivities. These N–N axially chiral frameworks are new addition to the families of axially chiral molecules. Notably, an interesting remote enantiomeric control phenomenon was uncovered, where the functional groups at C3- or C4-positions of the pyrrole ring, far away from the axis, can significantly affect enantiomeric induction (Scheme 28A). Around the same time, the Liu group reported an

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enantioselective synthesis of N–N biaryl atropisomers via a desymmetrization strategy.[103] Under copper-bisoxazoline catalysis, the Friedel-Crafts alkylation reaction of prochiral bipyrroles **175** with diethyl ketomalonate took place readily, giving rise to the formation of various axially chiral N–N bisazaheterocyclic compounds **176** in high yields with excellent enantioselectivities (Scheme 28B). When the publication of this manuscript was being finalized, a number of reports on the construction of N–N axial chirality appeared, including: Li et al.' preparation of N–N axially chiral 3-aminoquinazolinones via enantioselective *N*-alkylation/acylation[104,105]; independent reports from the Shi and Zhao groups on the synthesis of N–N axially chiral indole-pyrroles and pyrrole-pyrroles, respectively, both via CPA-catalyzed Paal-Knorr reactions.[106,107]

CONCLUSIONS AND OUTLOOK

In summary, atropisomers bearing a non-C–C axis are important additions to the repertoire of axially chiral molecules, and their asymmetric synthesis has attracted much attention, especially in recent few years. In comparison with conventional C–C axial chirality around biaryl and olefin axes, atropisomerism portrayed by C–N, C–O, C–B, or N–N bond have relatively lower rotational barriers, thus making it more challenging for their asymmetric synthesis. On the other hand, the shorter bond length and electron-repelling effect led to a congested hetero X–Y axis, resulting in stable axially chiral frameworks. The past decade has witnessed remarkable progress of this emerging research field. A wide variety of strategies have been developed for the asymmetric synthesis of the atropisomers containing an X–Y axis, from desymmetrization, C–X bond formation, to the *de novo* construction and aryl/N–H functionalizations. The practicality of methodologies developed were often demonstrated, through scaling-up experiments or via structural elaborations into new chiral ligands or catalysts.

Among the X–Y atropisomers, vast majority of examples are focused on the C–N atropisomerism. Such dominance can be attributed to a number of factors: the abundance of C–N atropisomers in nature, their relatively higher stability, and availability of synthetic tools for their efficient construction. However, undeniable fact is that other X–Y atropisomers have been largely overlooked for a prolonged period of time, and therefore, their asymmetric synthesis is at the infancy stage. The C–O axially chiral compounds, e.g., substituted biaryl ethers, are important structural motifs in natural products and bioactive molecules. The intrinsic bond nature of C–O makes it a real challenge for an efficient atroposelective construction of these molecular motifs, accounting for slow progress in this research area. Similarly, the C–B axially chiral chemistry was largely unexplored. Although the N–N bond containing motifs are widely present in nature, the catalytic atroposelective synthesis of N–N axially chiral molecules only appeared very recently. Viewed from a broader perspective, there are certainly many other possible X–Y atropisomers, for instance C–S,[108] C–P, N–P, and C(Sp^3)–N axes, among others, are worthy of future studies (Figure 5). Investigations on the atroposelective synthesis of these interesting and novel axially chiral entities will not only be of scientific curiosity and should also hold practical significance. Moving forward, we predict that more research efforts will be directed to the efficient atroposelective synthesis of currently less-studied chiral axes, as well as those presently unknown axially chiral molecules. To effectively construct the unknown X–Y atropisomers, the general strategies described earlier will certainly find applications. We also foresee that the combination of different approaches, for instance, *de novo* construction of an X–Y bond, may be advantageous for building certain target molecules. In addition to the powerful transition metal

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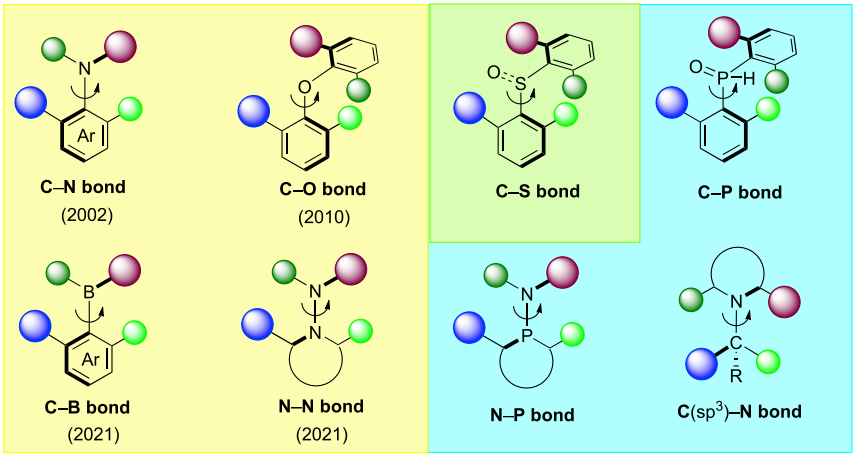

Figure 5. Atropisomerism portrayed by an X–Y bond

catalysis and organocatalysis, we anticipate extensive employment of radical processes,[109] photocyclizations,[110] biocatalysis,[97] and electrocatalysis[95] will be forthcoming.

In the course of advancing X–Y axial chirality, the moderate energy barriers associated with the projected structures pose a major challenge. Although one can certainly introduce more sterically demanding elements to restrict a bond rotation, such an approach is unable to generate broad structural diversity. In their elegant enantioselective synthesis of atropisomeric diaryl ether, Clayden and coworkers installed a chiral sulfoxide as a conformational auxiliary for a successful dynamic thermodynamic resolution.[111] In a two-axis system, by virtue of a low barrier to racemization for the four stereoisomers, Miller et al. achieved preferential bromination of one enantiomer via a peptide-catalyzed dynamic KR.[112] In light of these earlier pioneering studies, we believe enantioselective synthesis of X–Y atropisomers with multiple axes represents an intriguing direction.[113] The inclusion of another chiral element (axis) adds on to the molecular complexity. More importantly, the combination of steric and electronic effects and the potential interplay of kinetic and thermodynamics in such multiple-axis systems may lead to concerted rotations of axes in a gearing fashion,[114] offering a practical solution to the asymmetric synthesis of X–Y atropisomers of low energy barriers.

For the development of catalytic asymmetric methods to access axially chiral X–Y atropisomers, one needs to keep in mind the practical values of these molecules, i.e., their applications in asymmetric catalysis, pharmaceutical industry, and materials science. The next wave of the upcoming investigations on the X–Y axial chirality is expected to move this promising research field to a greater height, ultimately leading to the discovery of therapeutic agents and new generations of privileged chiral catalysts/ligands in asymmetric catalysis.

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AUTHOR CONTRIBUTIONS

Literature collection, G.-J.M. and C.-Y.G.; writing – original draft, writing – review & editing, G.-J.M., W.L.K., and Y.L.; conceptualization & project administration, G.-J.M. and Y.L.; supervision, Y.L.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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