Review

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

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SUMMARY

Atropisomers bearing X-Y axis serve as an important addition to the repertoire of axially chiral compounds, and have received increasing attentions from various disciplines of chemical science. 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 challenging due to the relatively lower rotational barriers. However, the intrinsic shorter bond length and electron-repelling effect lead to a congested hetero X-Y axis, which result in stable and novel axially chiral frameworks. Recent years have witnessed rapid progresses in this emerging domain. A number of catalytic atroposelective approaches have been established for accessing these synthetically challenging skeletons. The practicability of these strategy is highlighted by the ease of these X-Y axially chiral compounds to be converted into new ligands or catalysts, which could in turn contribute to the discovery of new types of atropisomers.

Keywords: atropisomerism, N–N axial chirality, asymmetric N-allylic alkylation, 1-aminopyrrole, 3-aminoquinazolinone

INTRODUCTION

Atropisomerism, stereoisomerism arising from an axially restricted rotation, constitute one fundamentally important chirality element in the course of nature.[1] Since the first report in 1922,[2] atropisomers have greatly expanded in catalyst design, drug discovery, material sciences and natural products synthesis. Among them, C–C atropisomers, e.g., axially chiral biaryls, aryl alkenes and aryl amides, are most well-represented frameworks (Figure 1), where research in these areas have been intensively pursued in the past decades.[1, 3-6] For instance, axially chiral biaryls have proven to be privileged motifs for enantio-control. BINOL-derived chiral ligands and catalysts have been made readily available and are routinely screened in current asymmetric catalysis.[7] On the other hand, atropisomers featuring an X–Y axis beyond the C–C bond, e.g., C–N, C–O, C–B and even N–N bond, have been largely overlooked until recently. The lack of studies is mainly due to the complications that arise from the reduced rotation barriers induced by the deplanarization of the heteroatom-containing plane.[8] Nevertheless, any forces (including electronic, steric, H-bonding, and π-stacking effect) imposing an energy barrier of > 23 kcal mol^{-1} to rotation may create a stereogenic axis.[9] In this context, while introducing heteroatom(s) into the axis could portray higher structural variability, atropisomers around an X–Y bond could evolve with an appropriate nonplanar arrangement of four substituent groups in pairs (Figure 1).

The bigger picture

As a type of stereoisomerism, atropisomerism constitute one fundamentally important chirality element in the course of nature. Atropisomers not only could vary significantly in their biological activities and functions, but also show potential in chiral ligand and catalyst developments. While C–C atropisomers, e.g., axially chiral biaryls, have been intensively pursued in the past decades, atropisomers featuring an X–Y axis beyond the C–C bond, e.g., C–N, C–O, C–B and even N–N bond, have been largely overlooked until recently. The lack of studies is mainly due to the complications that arise from the reduced rotation barriers induced by the deplanarization of the heteroatom-containing plane. This review summarizes the state-of-the-art catalytic asymmetric approaches to atropisomers around an X–Y axis, including N–H functionalization, desymmetrization, C–X bond formation, Ar *de novo* construction and functionalization, as well as kinetic resolution.

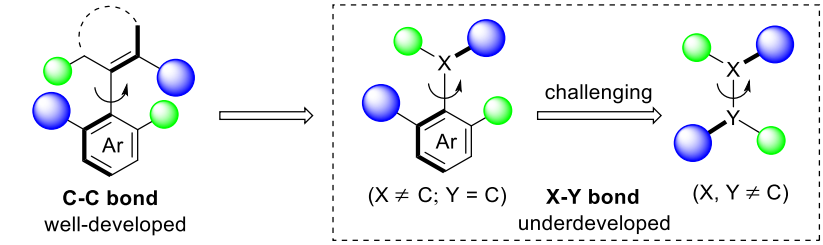
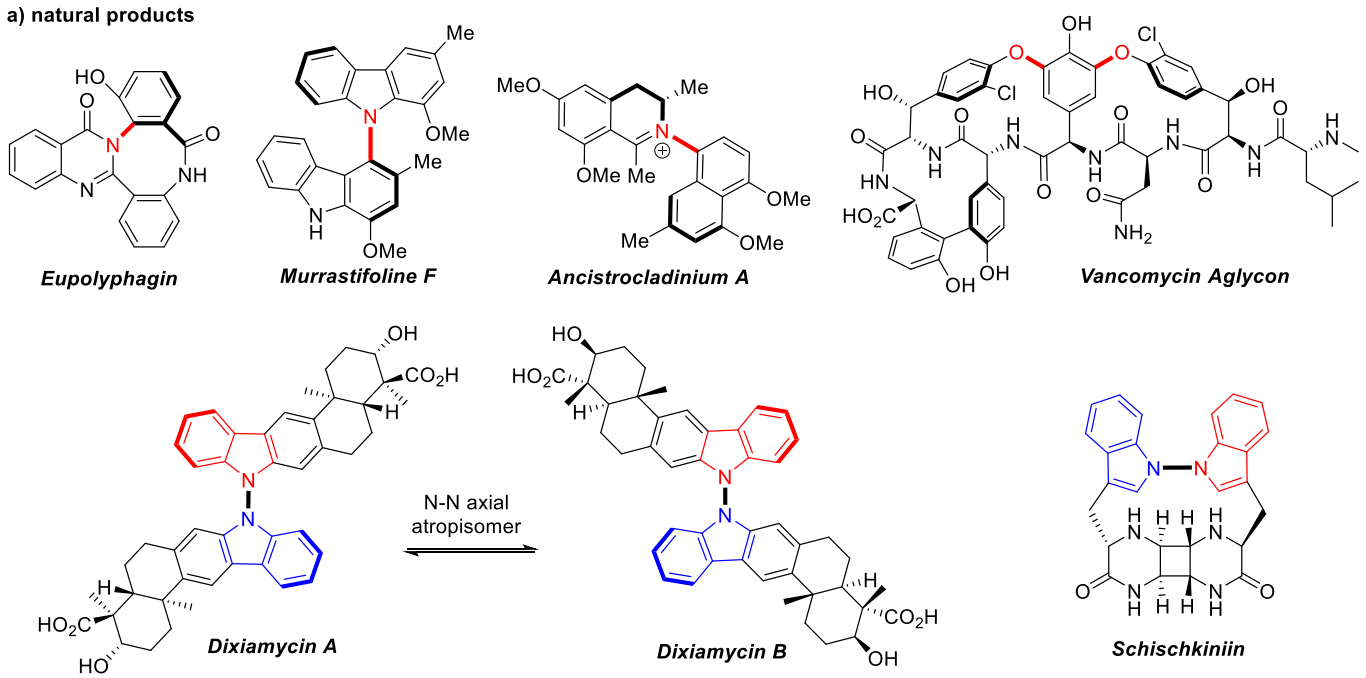
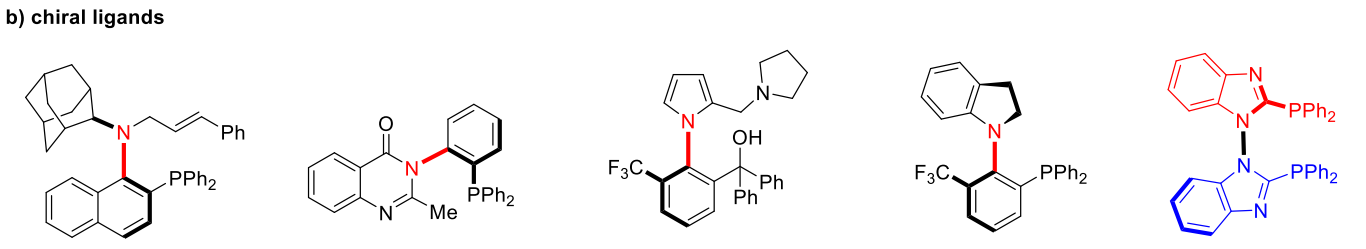


Figure 1. The profile of catalytic asymmetric synthesis of atropisomers.





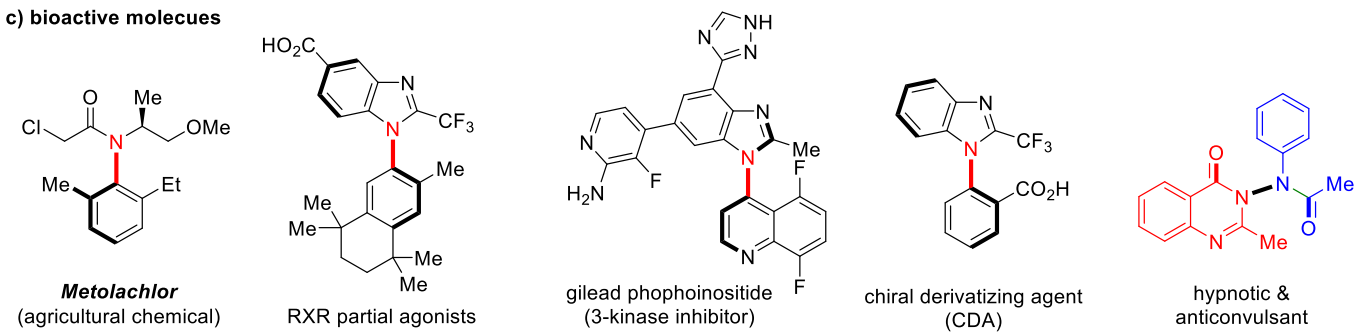


Figure 2. Representative atropisomeric molecules around an X-Y bond.

Although the scientific community has also been aware of atropisomers around a X–Y bond for a long time, early attentions were restricted to the research of their physical characteristics such as rotational energy barrier, racemization, conformational analysis, and photoelectric property.[10-12] With their presence in natural products, chiral ligands, and bioactive molecules, as illustrated in Figure 2, neglect of the significance of X–Y axial chirality in catalytic asymmetric synthesis changed drastically. The first attempt came from the Kitagawa/Taguchi[13] and Curran[14] groups. They independently achieved the asymmetric syntheses of C–N axial anilides through a Pd-catalyzed *N*-allylation of achiral N–H anilides, albeit with unsatisfied enantioselectivities. From then on, catalytic asymmetric approaches involving both metal- and organo-catalysis for accessing these synthetically challenging X–Y atropisomeric molecules have been springing up.[15-17]

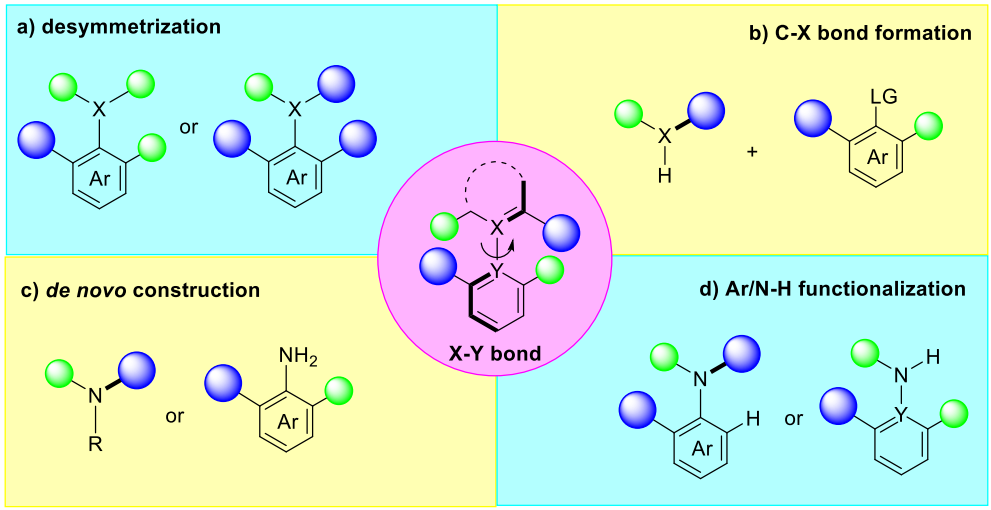
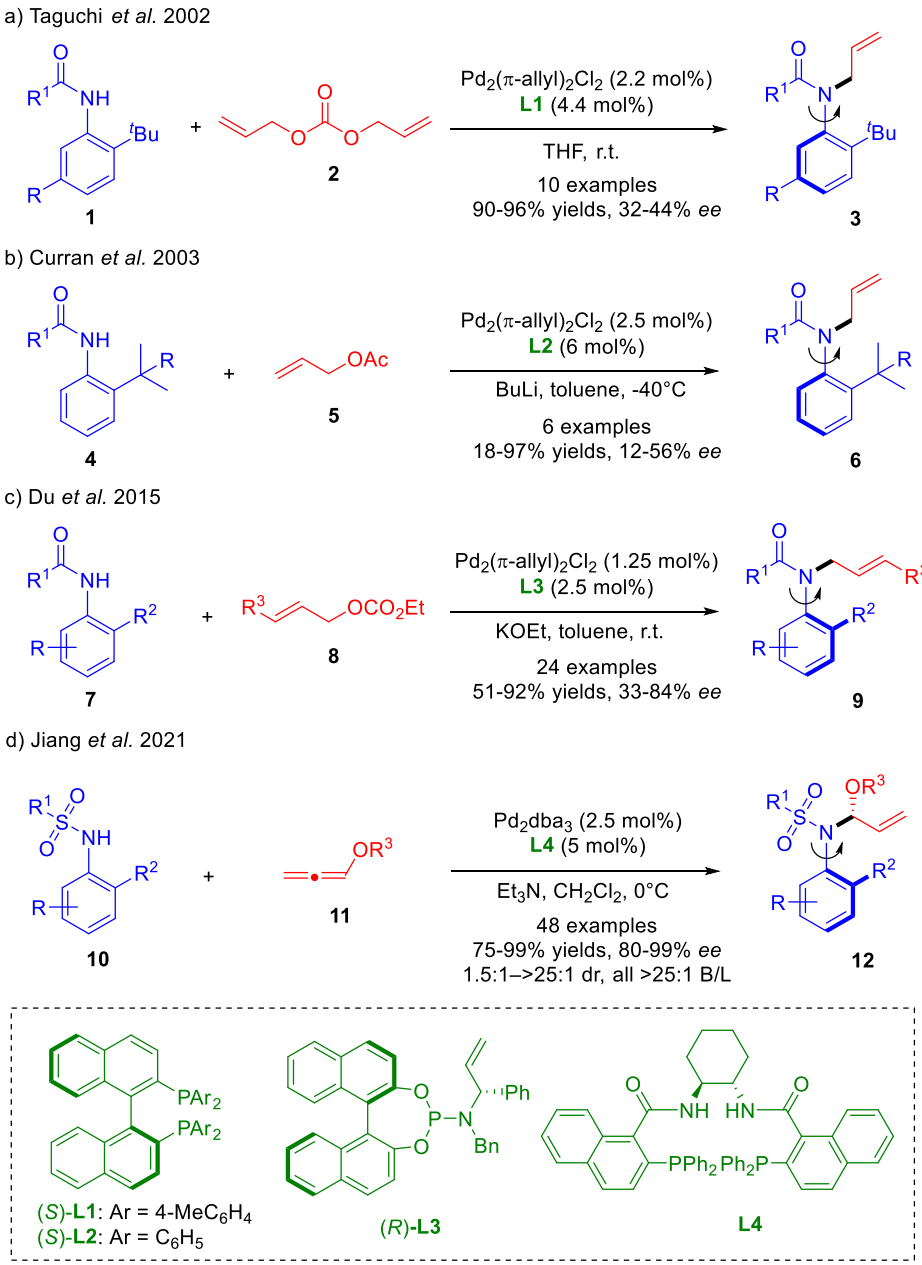


Figure 3. The profile of catalytic asymmetric synthesis of X-Y axially chiral compounds.

This review highlights creative and practicable catalytic asymmetric protocols and is categorized according to the strategy applied for building up a stereogenic X–Y axis (Figure 3). Out of those strategies listed, catalytic enantioselective desymmetrization of prochiral substrates represents a direct strategy for C–X axial chirality (Figure 3a). Either the aromatic ring or heteroatom-containing plane could serve as the reaction site for desymmetrization. On the same note, asymmetric coupling reactions have emerged as effective means to construct atropisomeric C–X bonds (Figure 3b). In addition, C–N atropisomers can be assembled via catalytic asymmetric *de novo* construction of the aromatic ring or nitrogen-containing plane (Figure 3c). Besides that, atroposelective N–H functionalization, including *N*-arylation, *N*-alkylation, *N*-allylation, and *N*-acylation reactions, has been generally employed to guarantee excellent enantioselectivities. Recently, enantioselective C–H bond functionalization has been developed as a powerful approach for the construction of C–N axes (Figure 3d). In view of the vast advancement achieved in the catalytic asymmetric synthesis of C–N atropisomers, the main section of this review will focus on synthetic strategies for stereogenic axes that arise due to restricted rotation about the C–N bonds, and representative examples are illustrated. Approaches to more challenging axially chiral C–O, C–B and even N–N bonds will be discussed separately in the last section. Strategies employing either enantiopure starting materials or multi-step reactions are excluded.[18-19] This timely review aims to provide an overview to readers in related fields and beyond, facilitating their findings in axial chirality, asymmetric catalysis, natural product synthesis, and drug discovery.

ATROPISOMERS AROUND C-N BOND

Catalytic asymmetric N-H functionalization

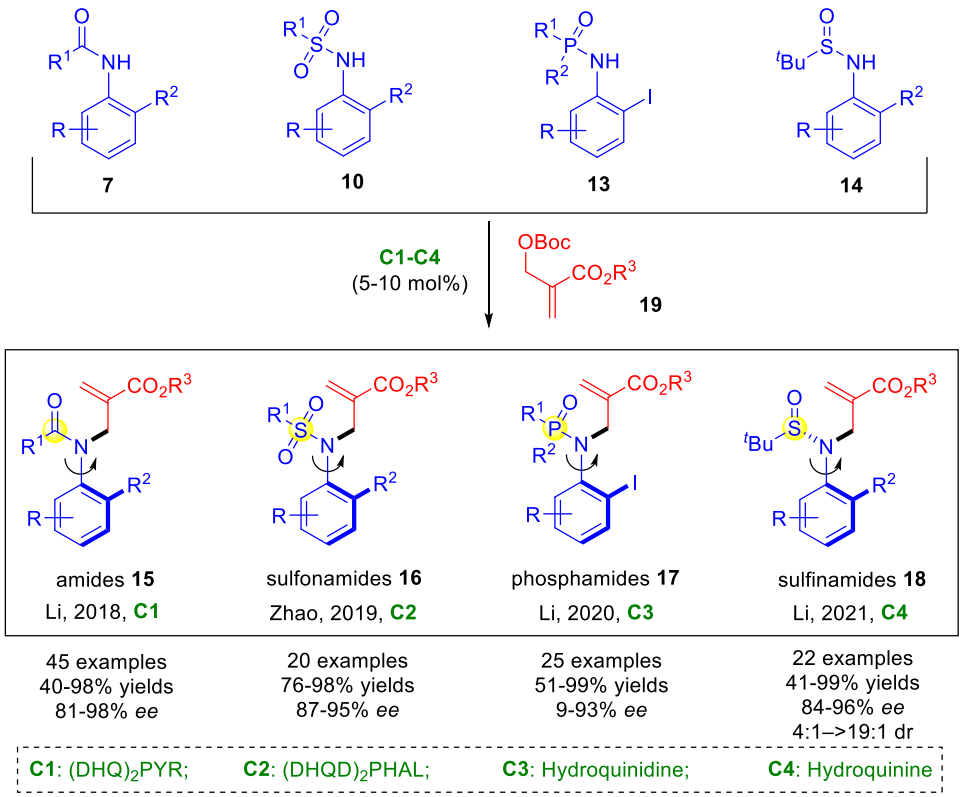


Scheme 1. Pd-catalyzed asymmetric *N*-allylation.

The seminal works came from the Kitagawa/Taguchi and Curran groups (Scheme 1a & 1b).[13-14] They independently achieved the catalytic enantioselective synthesis of axially chiral anilides around the C–N bond via a Pd-catalyzed Tsuji–Trost allylation. The BINAP-Pd complex displayed a high catalytic efficiency for axially chiral anilides **3** and **6** in terms of yield. In spite of the low enantioselectivity, these two works represent the first catalytic asymmetric synthesis of C–N axially chiral compounds. In 2015, Du *et al.* further developed this Pd-catalyzed asymmetric allylic amination (Scheme 1c).[20] By using a phosphorus amidite–olefin ligand **L3**, the *ee* value was increased to a moderate level. It was reasoned that a high enantio-control of the C–N axial chirality of the anilides by using π-allyl palladium chemistry could be challenging, owing to the attack of anilide anion to *π*-allyl carbon from the opposite side of the Pd atom.[15, 21] Trost ligand enabled hydroamination of alkoxyallenes with N–H nucleophiles has emerged as a powerful tool to construct chiral *N,O*-acetals. Very recently, Jiang and co-workers have successfully accomplished the efficient and rapid construction of a family of C–N axially chiral sulfonamides **12** via Pd-catalyzed atroposelective hydroamination process (Scheme 1d).[22] The projected reaction was featured

by a wide functional group tolerance, good to excellent yields, enantio-, and diastereoselectivities, as well as excellent branched/linear (B/L) selectivities. Additionally, elaborations of the products were readily carried out to create valuable C–N axially chiral compounds, such as atropoisomeric non-natural amino acid and eight-membered cyclic sulfonamide. Lastly, DFT calculations involving the thermodynamically stable *syn*-Pd(π-allyl) intermediate were performed for the origin of chiral induction in terms of both stereogenic center and axis.

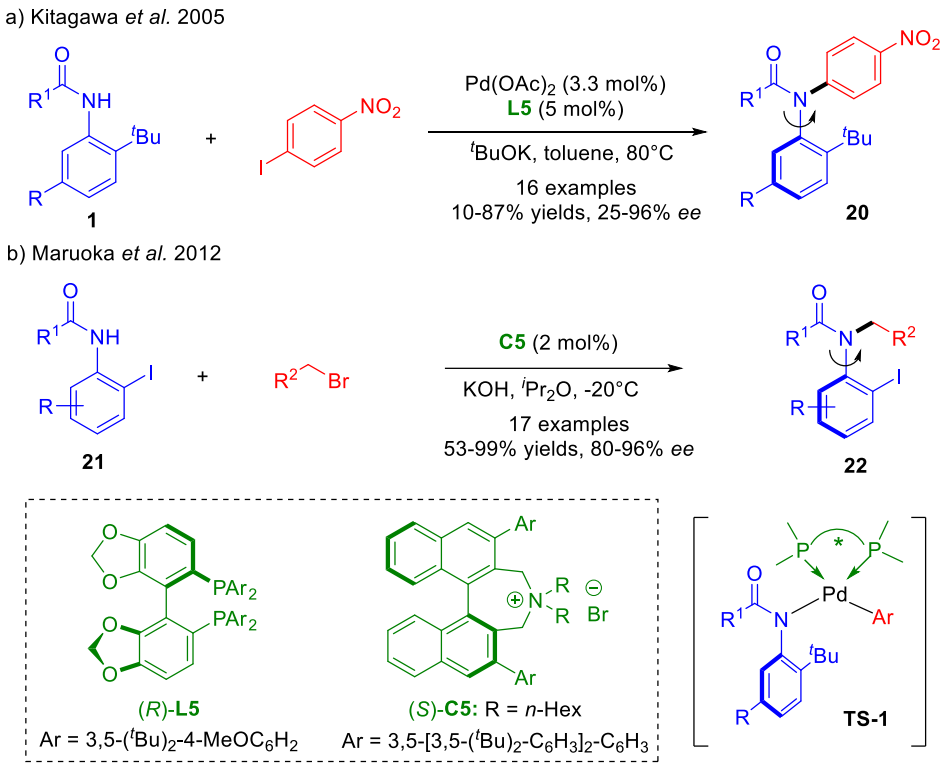
Organocatalytic asymmetric allylic alkylation (AAA) reaction of modified Morita–Baylis–Hillman (MBH) adducts has been developed as one of the most useful bond-forming reactions.[23-24] Enantioselective substitutions of racemic MBH adducts greatly benefit the synthesis of centrally chiral compounds. However, such a process for achiral MBH adducts is usually considered to be challenging, likely because of the lack of chirality at the bonding site and the required remote enantio-control for catalyst.[25] In 2018, Li *et al.* pioneered the organocatalytic atroposelective *N*-allylic alkylation reaction of anilides **7** with achiral MBH adducts **19** (Scheme 2).[26] By using the biscinchona alkaloid **C1** as catalyst, a broad range of C–N axially chiral anilide products **15** were accessed with good to excellent yields and enantioselectivities. Later, this elegant protocol has successfully been extended to constructions of C–N axially chiral sulfonamides **16**,[27] phosphamides **17**,[28] and sulfinamides **18**[29] by the same group and the Zhao group. In addition, the synthesized C–N axially chiral *ortho*-iodine substituted phosphamides **17** could be utilized as efficient chiral hypervalent iodine(III) catalysts for the asymmetric oxidative dearomatization of phenols. Notably, sulfinamides **18** compatibly contain both S-stereogenic center and C–N axial chirality.



Scheme 2. Organocatalytic asymmetric N-allylic alkylation.

In 2005, the Kitagawa/Taguchi group developed an elegant atroposelective *N*-arylation reaction of anilides, which represented the first highly enantioselective and practical catalytic synthesis of C–N axially chiral compounds (Scheme 3a).[30-31] 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). Additionally, the present reaction could be extended to intramolecular version by employing delicately designed substrates. The

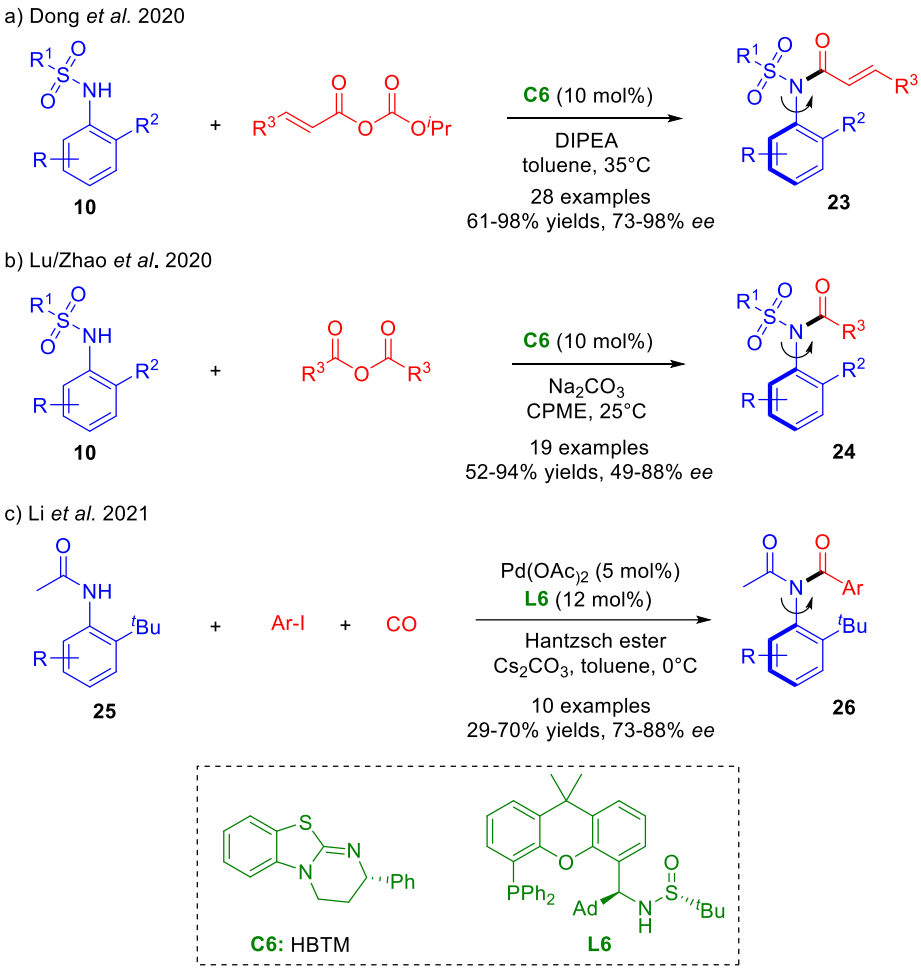
observed excellent enantioselectivities could be accounted by a reductive elimination process of Pd-amide intermediate (**TS-1**), wherein the C–N bond formation occurred near the chiral phosphine ligand.



Scheme 3. Catalytic asymmetric *N*-arylation and *N*-alkylation.

The substitution of alkyl halides has been recognized as a direct protocol to manipulate N–H compounds. In 2012, the Maruoka group developed a highly enantioselective synthesis of C–N axially chiral 2-iodoanilides **22** via the asymmetric *N*-alkylation process (Scheme 3b).[32] In the presence of Maruoka catalyst **C5**, a chiral phase-transfer catalyst, 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, the substrate scope had been broadened beyond 2-iodoanilides, such as *o*-*tert*-butyl and *o*-bromoanilide.[33] The excellent enantio-control was attributed to the good recognition capability of phase-transfer catalyst for the steric difference between the *ortho* substituents on anilides.

Enantioselective acyl transfer reaction has been extensively investigated as a powerful tool in asymmetric catalysis, wherein the *in situ* generated chiral adduct intermediate from acyl donor and nucleophilic chiral catalyst, could transfer the acyl group to nucleophilic substrate in an enantioselective manner. In 2020, isothiourea-catalyzed atroposelective *N*-acylation of sulfonamides has been established by the Dong group (Scheme 4a)[34] and the Lu/Zhao group (Scheme 4b)[35] independently. A variety of acylated C–N axially chiral anilides **23** and **24** were afforded in good to excellent enantiopurity. Very recently, Li *et al.* described an unprecedented palladium-catalyzed asymmetric carbonylation of ArI with amides, inlaying the carbonyl group in the axially chiral amides via a carbonylative reaction (Scheme 4c).[36] *N*-acetyl-*N*-phenyl anilides **26** were prepared atroposelectively, albeit with moderate yields and enantioselectivities.



Scheme 4. Catalytic asymmetric *N*-acylation.

Catalytic asymmetric desymmetrization

Catalytic asymmetric desymmetrization of prochiral precursors is a promising and attractive strategy to prepare enantio-enriched stereogenic compounds, which avoids bond-formation at the target position.[37] In this context, enantioselective synthesis of atropisomers could capitalize on the desymmetrization of prochiral compounds with a preformed C–N axis motif. Maleimides are a kind of good acceptors with a prochiral stereogenic center. In particular, *N*-aryl succinimides are regarded as significant precursors for C–N atropisomeric succinimides as it merges the prochiral stereogenic center and axis into one moiety (Figure 4b). In contrast to the conventional chiral control mode, catalytic asymmetric desymmetrization of *N*-aryl succinimides requires a remote control for the C–N axial chirality (Figure 4d). Owing to their remote relation, neither central chirality nor axial chirality can be induced by each other. In this regard, simultaneous control of two chiral elements via desymmetrization strategy is challenging.

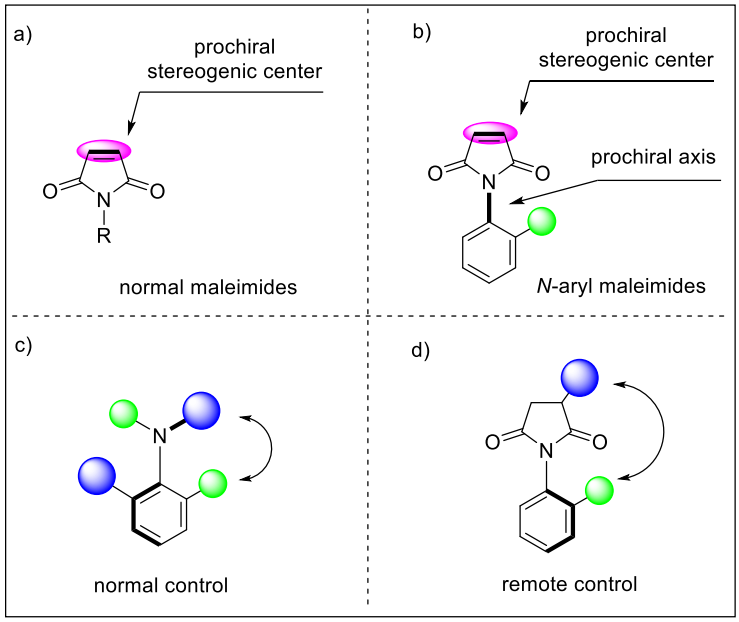
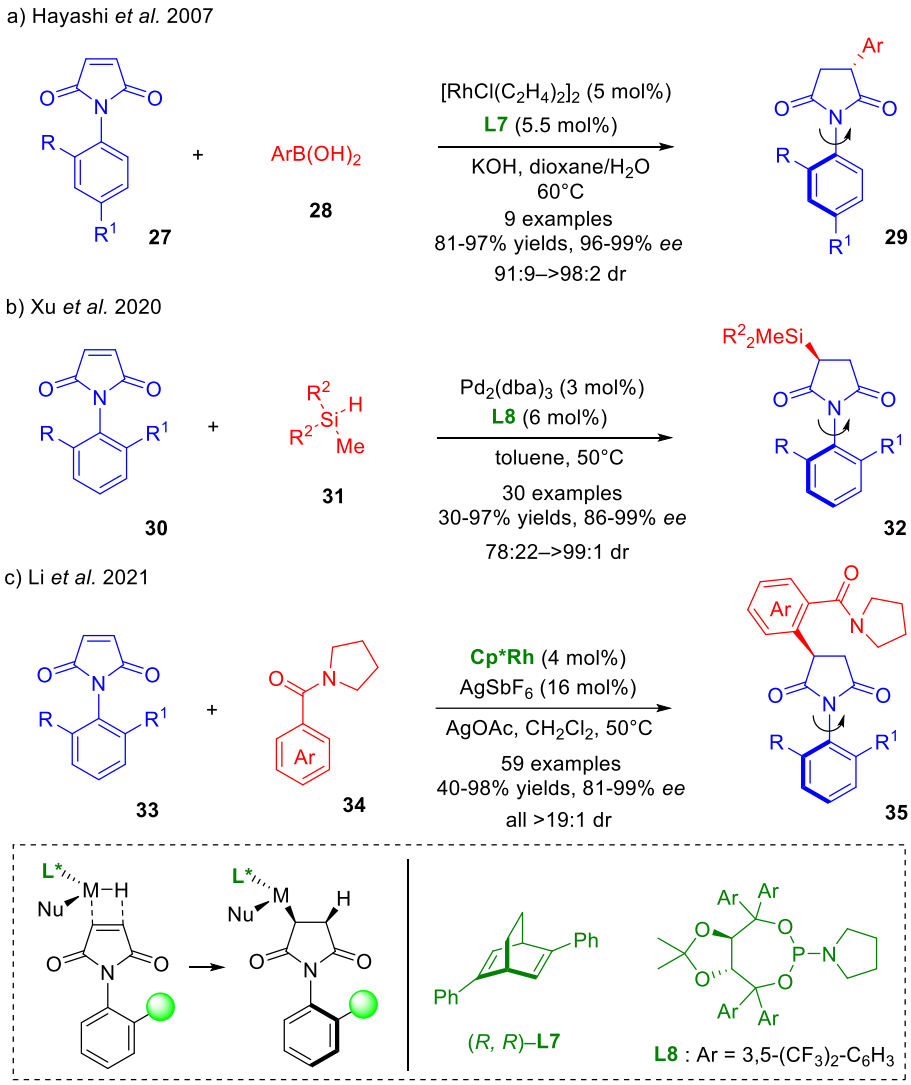


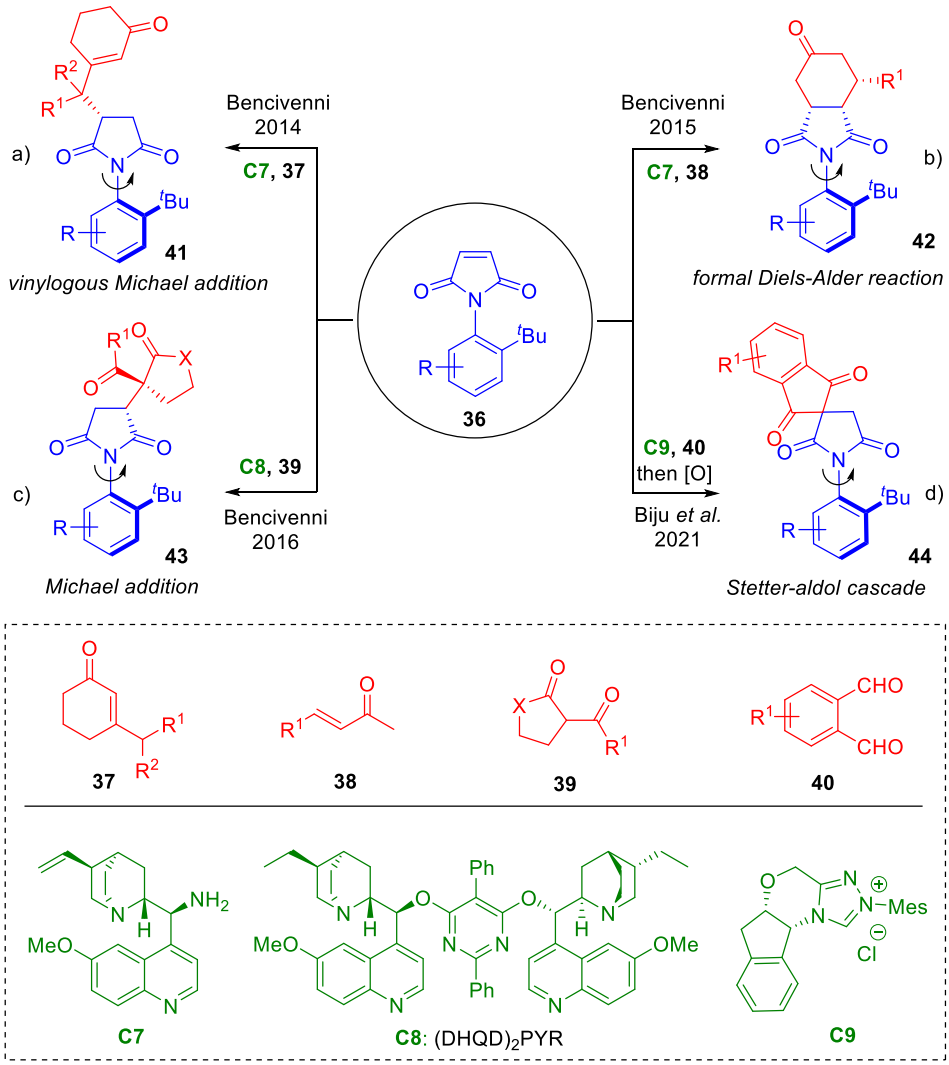
Figure 4. Challenges in desymmetrization of *N*-aryl maleimides.

The pioneering desymmetrization of *N*-aryl maleimides was reported by the Hayashi group in 2007 (Scheme 5a).[38] The protocol was well-established by a rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acids **28** to *N*-aryl maleimides **27**. The products *N*-aryl succinimides **29** with a C–N axis were obtained with excellent stereoselectivities and yields. The efficient chiral induction was enabled by the addition of chiral Rh complex generated *in situ* to olefin unit, in which the facial discrimination of prochiral C–N bond was controlled due to the steric hindrance effect between chiral ligand and substituent groups of *N*-aryl maleimides. Very recently, excellent enantio-control of C–N axial chirality had been achieved via desymmetrization of *N*-aryl maleimides, in a palladium-catalyzed hydrosilylation by Xu (Scheme 5b),[39] and a rhodium-catalyzed C–H alkylation by Li (Scheme 5c).[40] Both approaches feature mild reaction conditions, broad substrate scope, and excellent enantio- and diastereoselectivity.



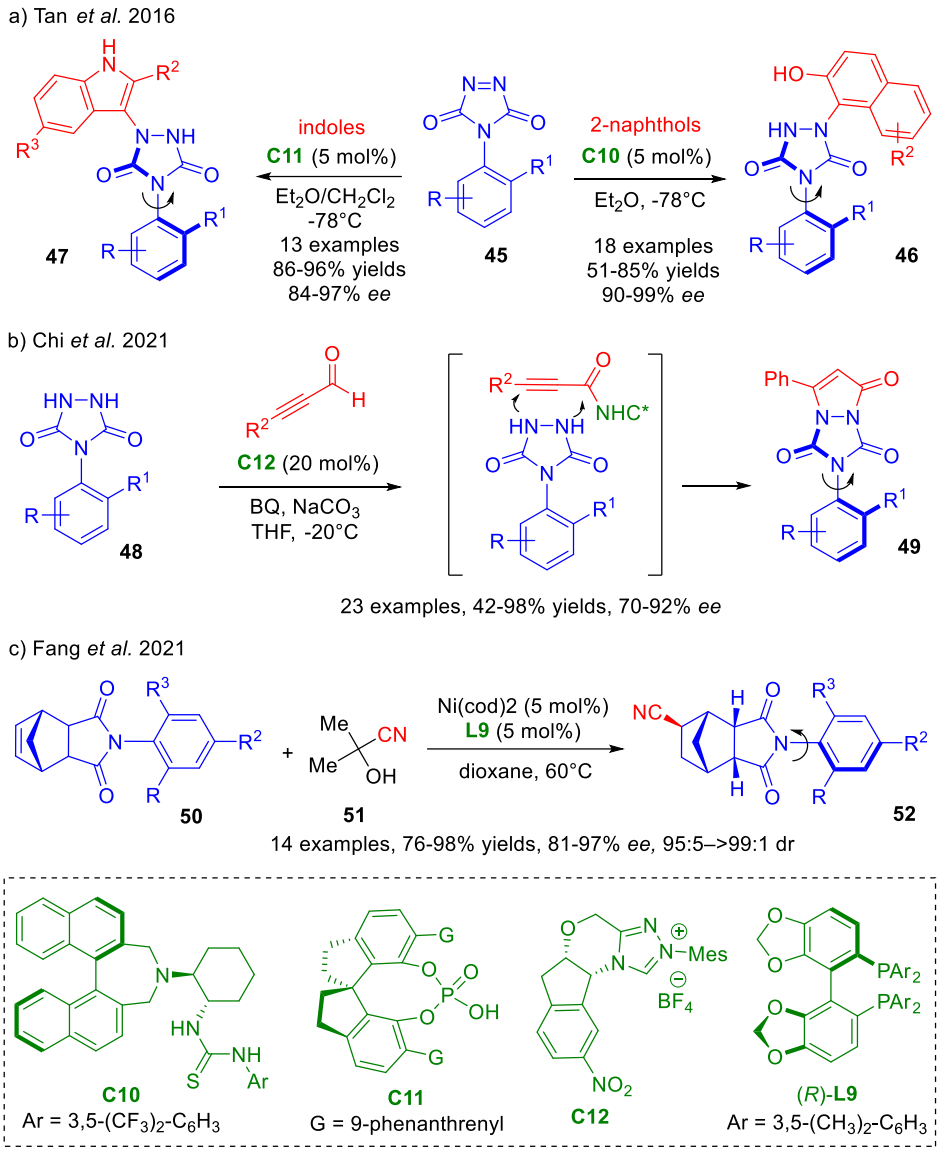
Scheme 5. Transition-metal-catalyzed asymmetric desymmetrization.

Organo-catalyzed asymmetric desymmetrization of *N*-aryl maleimides was initiated by Bencivenni *et al.* in 2014 (Scheme 6a).[41] They found that the remote control of C–N axial chirality of atropisomeric succinimides **41** could be realized via a catalytic vinylogous Michael addition/desymmetrization sequence. Under the catalysis of cinchona alkaloid primary amine **C7**, the following two simultaneous stereochemical events were guaranteed: the formation of remote two contiguous stereocenters through a conjugated π-system and the more distant control of an axial chirality far from the reaction site. The projected reaction proceeded smoothly with excellent *ee* values, in spite of the observed moderate diastereoselectivity. In their following studies, this organocatalytic atroposelective desymmetrization strategy for *N*-aryl maleimides could be further extended to formal Diels–Alder reaction with enones (Scheme 6b),[42] and Michael addition reaction with α-acylbutyrolactones and 2-cyano-2-phenylacetates (Scheme 6c).[43] In a similar work by Feng *et al.*, the catalytic asymmetric Michael addition/desymmetrization reaction of *N*-aryl maleimides with unprotected 3-substituted-2-oxindoles was successfully accomplished by using their developed chiral *N,N'*-dioxide-Sc(III) complex.[44] Very recently, Biju *et al.* described an elegant *N*-heterocyclic carbene (NHC)-catalyzed atroposelective desymmetrization of *N*-aryl maleimides (Scheme 6d).[45] This approach involves intermolecular Stetter-aldol cascade of dialdehydes **40** with prochiral *N*-aryl maleimides followed by oxidation, affording various C–N axially chiral *N*-aryl succinimides **44** in good yields and *ee* values.



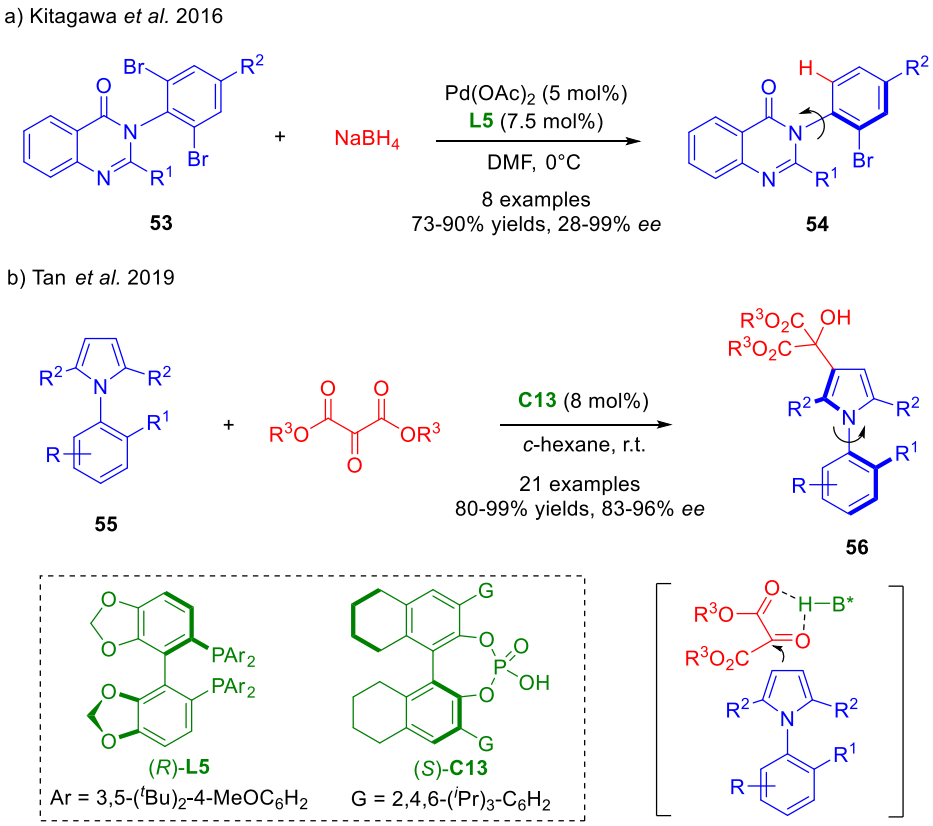
Scheme 6. Organo-catalyzed asymmetric desymmetrization.

The catalytic asymmetric desymmetrization of *N*-arylmaleimide analogues has also been pursued for construction of C–N axial chirality. In 2016, the Tan group documented that the organocatalytic asymmetric tyrosine click-like reaction could be applied successfully to the desymmetrization of triazolediones **45** (Scheme 7a).[46] Excellent remote enantiocontrol, that arises 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 using bifunctional thiourea-tertiary amine catalyst **C10** for 2-naphthols and chiral phosphoric acid (CPA) **C11** for 2-substituted indoles. The resulting C–N axially chiral urazoles possess potential application as effective chiral organocatalysts/ligands. Later, the synthesis of C–N axial chirality containing spirooxindole–urazoles had been achieved by the same group via a similar desymmetrization strategy.[47] Early this year, Chi *et al.* reported a facile synthesis of C–N axially chiral urazoles **49** via NHC-catalyzed desymmetrization of prochiral urazoles **48** (Scheme 7b).[48] Atroposelective addition of a nitrogen atom of prochiral urazole **48** to an ynal-derived acetylenic acylazolium intermediate was the key step for enantio-control. The final annulation product urazoles **49** bearing a chiral C–N axis were obtained with excellent yields and optical purities. Besides, Fang *et al.* developed a nickel-catalyzed hydrocyanative desymmetrization of norbornene-fused *N*-arylmaleimides **50**, allowing for quick construction of compounds containing both five continuous stereogenic carbon centers and one remote N–C axial chirality (Scheme 7c).[49] It was reported that rigid structure and resident carbonyl group of cyclic imide were essential to control the enantioselectivity, as determined from the control experiments and DFT calculations.



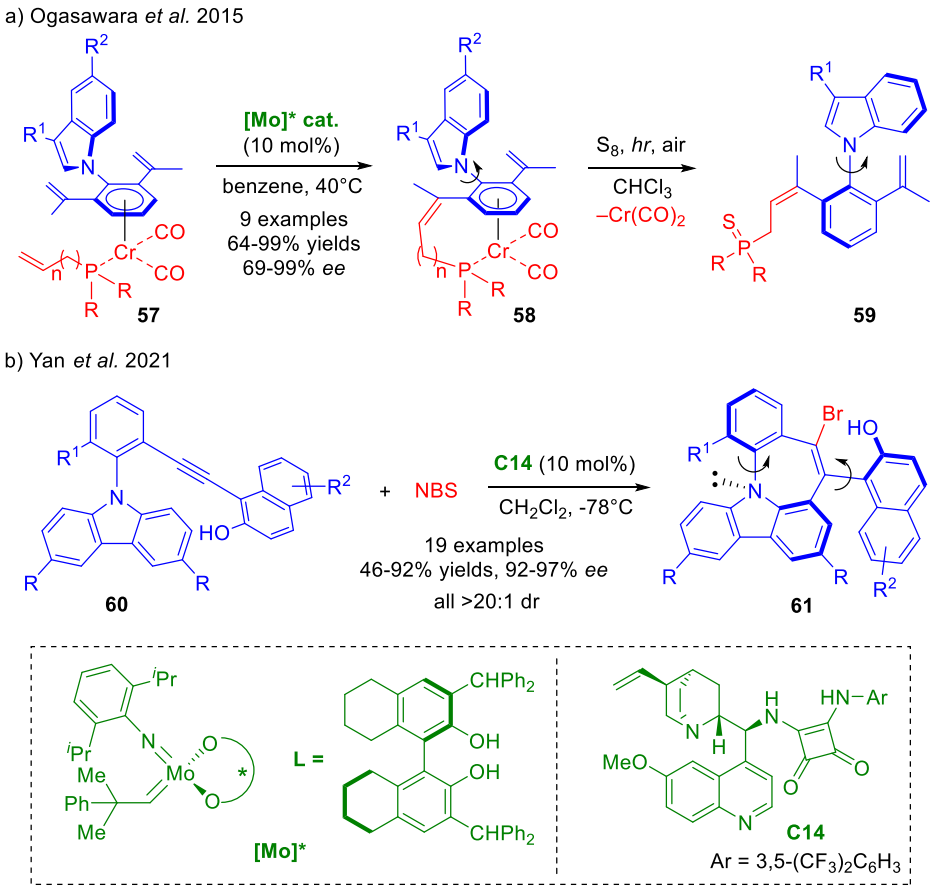
Scheme 7. Catalytic asymmetric desymmetrization of *N*-arylmaleimide analogues.

In addition to the abovementioned *N*-arylmaleimides and their analogues that require a remote enantio-control, there are other prochiral C–N axes that have been successfully utilized in catalytic asymmetric desymmetrization to access optically C–N chiral compounds. For instance, Kitagawa *et al.* developed a palladium-catalyzed reductive asymmetric desymmetrization of quinazolinones **53** for direct enantioselective synthesis of mebroqualone derivatives **54** around a C–N axis (Scheme 8a).[50] The good to excellent *ee* values were attributed to a sequence of asymmetric mono-hydrodebromination and over reduction via kinetic resolution. However, this methodology is sensitive to substituent (R^2) at the C_4'-position, amount of $NaBH_4$, and reaction temperature. In 2019, a CPA-catalyzed atroposelective desymmetrization of *N*-arylpyrroles **55** was achieved by the Tan group (Scheme 8b).[51] As opposite to the well-reported dual activation mode, CPA bonded precisely to the ketomalonates and transferred its stereo-information to the distant C–N axis. The resulting axially chiral arylpyrroles with high structural diversity and excellent enantiocontrol served as chiral building blocks for rapid transformations to functionalized pyrroles with potential bioactivity and ligands for asymmetric catalytic reactions.



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

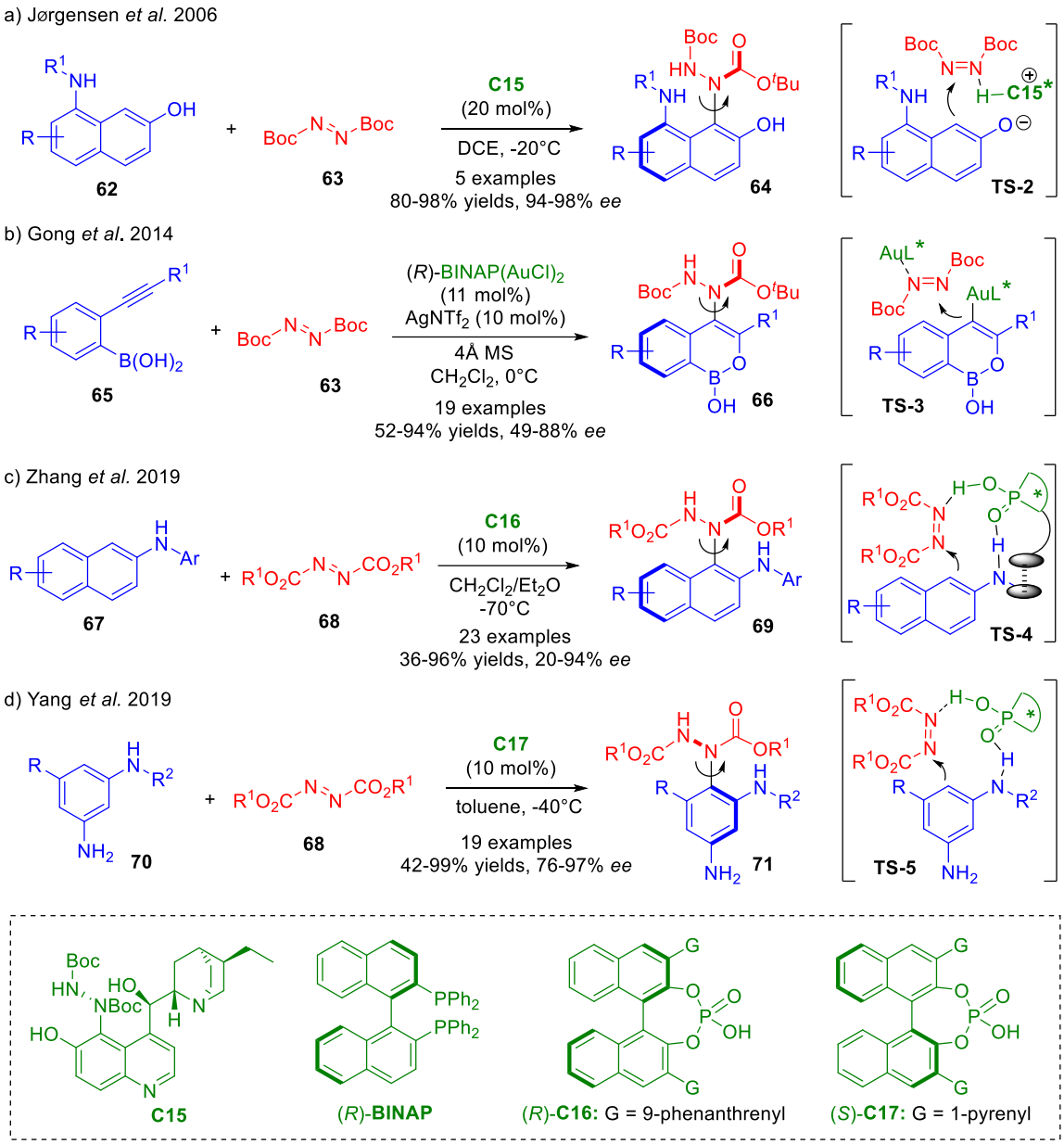
Furthermore, the catalytic asymmetric construction of C–N axial chirality via desymmetrization strategy could proceed via intramolecular reaction. In 2015, Ogasawara *et al.* developed a molybdenum-catalyzed asymmetric ring-closing metathesis (RCM) of prochiral (π-arene)-chromium substrates **57** (Scheme 9a).[52] Both C–N axial chirality and π-arene-based planar chirality were simultaneously induced, providing 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. Very recently, in an organocatalytic enantioselective synthesis of chiral azepine skeleton bearing multiple-stereogenic elements by Yan et *al.*, the C–N chirality was constructed via an intramolecular desymmetrization process (Scheme 9b).[53] By using this robust method involving *ortho*-quinone methide (VQM), various configurationally defined azepine heterocycles with four types of fully controlled stereogenic elements, including C–N chirality, C–C chirality, nitrogen chiral center, and saddle-shaped conformation, were obtained with a wide range of substrate scope, and excellent diastereo- and enantio-selectivity.



Scheme 9. Intramolecular desymmetrization strategy.

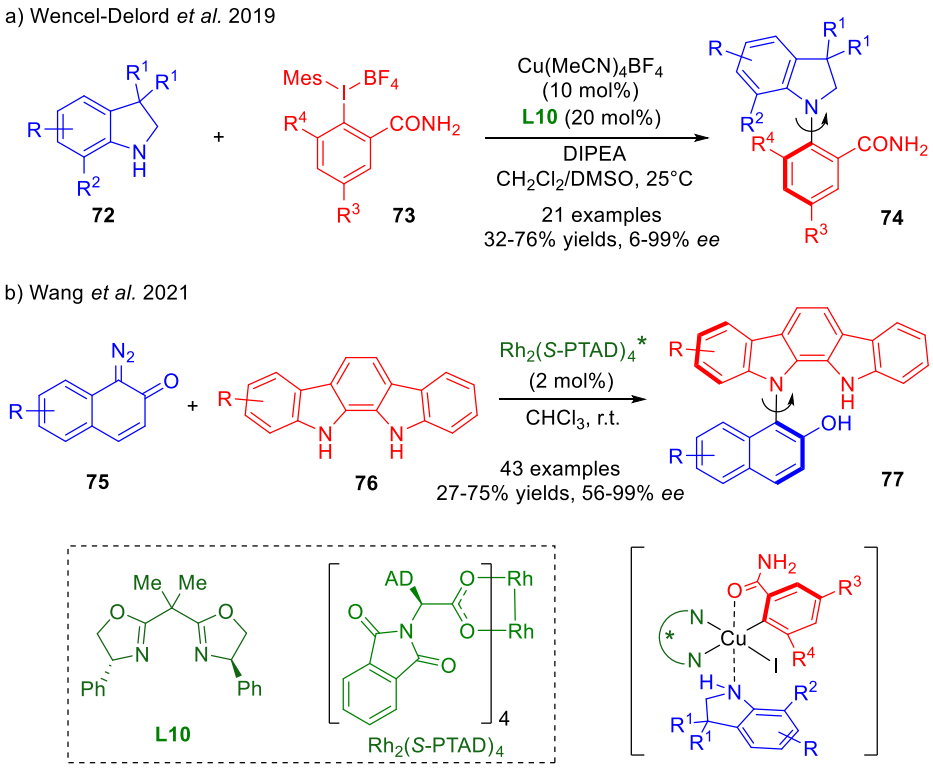
Catalytic asymmetric C-N bond formation

Unlike the modifications of the existing pro- or achiral C–N bonds, construction of the C–N axis while introducing chiral information is regarded as the more straightforward method. In this context, the asymmetric electrophilic aminations of electron-rich aromatic rings with azodicarboxylates have been well employed. The landmark work had been made by the Jørgensen group in Brønsted base catalyzed asymmetric electrophilic aminations of 8-amino-2-naphthols **62** with azodicarboxylates (Scheme 10a).[54-55] The use of new aminated cinchona alkaloid **C15** was crucial for the excellent enantioselectivity (**TS-2**). However, this protocol was limited by substrate, since the amino group at C8 position played an indispensable role to stabilize the C–N axial chirality. In 2014, the Gong group reported a chiral Au-complex catalyzed cycloisomerization–amination cascade of 2-(alkynyl)phenyl boronic acids with azodicarboxylates for the construction of boron-containing C–N atropisomers **66** (Scheme 10b).[56] Chiral vinylgold intermediate, proposed to be generated *in situ*, stereoselectively attacked the azodicarboxylates coordinated by another chiral Au-complex (**TS-3**). Additionally, CPA-catalyzed atroposelective amination of *N*-aryl 2-naphthylamines with azodicarboxylates was disclosed by the Zhang group (Scheme 10c),[57] which readily occurred via a concerted control strategy involving π–π interaction and dual H-bond (**TS-4**). Notably, this type of atroposelective naphthalene-1,2-diamines **69** was reported to possess good C–N axial stability, due to the intramolecular hydrogen-bonding interaction. Later, Yang *et al.* further developed this CPA-catalyzed amination protocol by employing 1,3-benzenediamines **70** as suitable substrates (Scheme 10d).[58] The corresponding C–N atropisomeric products were obtained with high configurational stabilities, and could be modified as novel chiral organocatalyst.



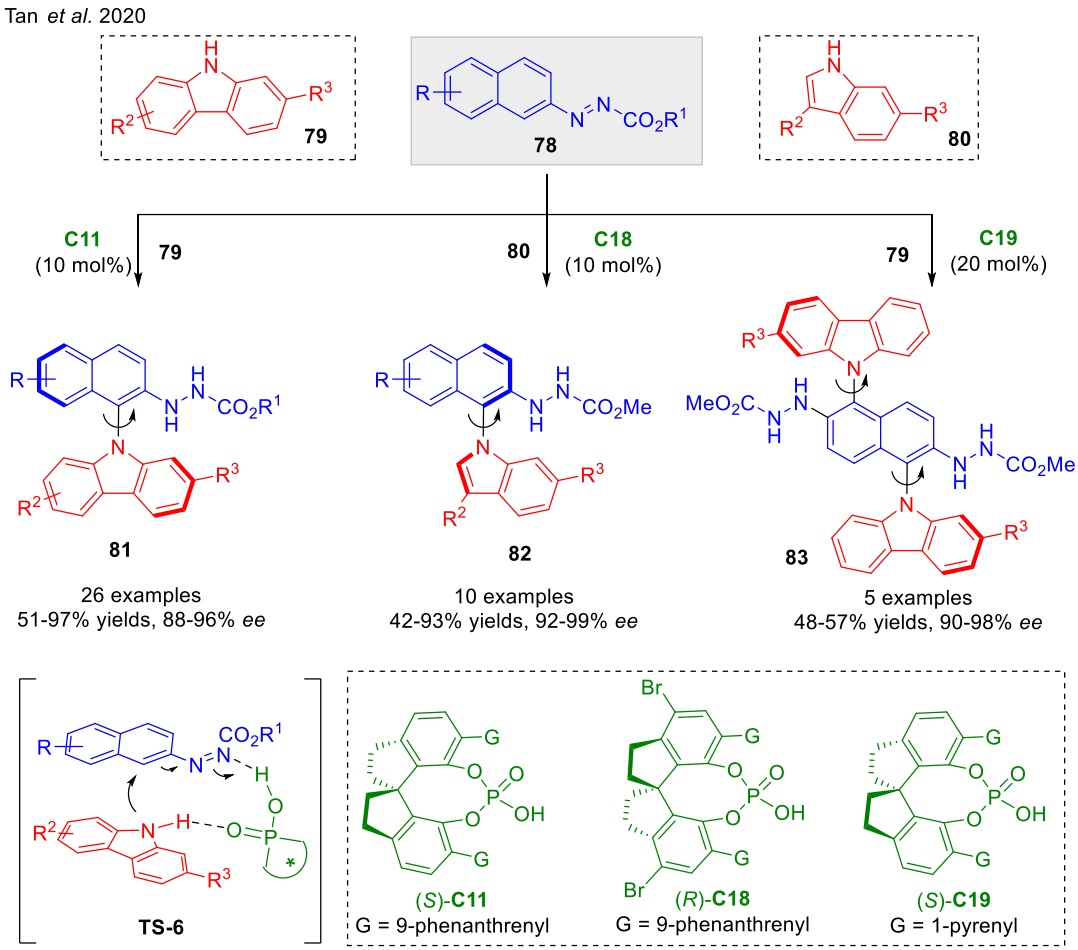
Scheme 10. Catalytic asymmetric aminations with azodicarboxylates.

Transition-metal-catalyzed *N*-arylation reactions, including Buchwald–Hartwig and Ullmann couplings, have become practical tools for direct C–N bond formation. However, such a reaction is sensitive to the steric bulk of the coupling partners, and therefore requires high reaction temperatures. These limitations render their atroposelective applications difficult. In 2019, Wencel-Delord *et al.* disclosed a unique synthetic solution, by using a highly active hypervalent iodine reagent **73** (Scheme 11a).[59] This Cu-catalyzed asymmetric C–N coupling led to an unprecedented atroposelective Ullmann-type *N*-arylation under mild reaction conditions. A broad range of C–N axially chiral compounds **74** were yielded with moderate to excellent enantioselectivities. Alternatively, Wang *et al.* reported a Rh(II)-catalyzed asymmetric C–N coupling reaction between diazonaphthoquinones and carbazoles via carbene N–H insertion (Scheme 11b).[60] Enantio-enriched *N*-arylindolocarbazole atropisomers around the C–N axis were provided in moderate to good yields and 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 11. Transition-metal-catalyzed C-N coupling reactions.

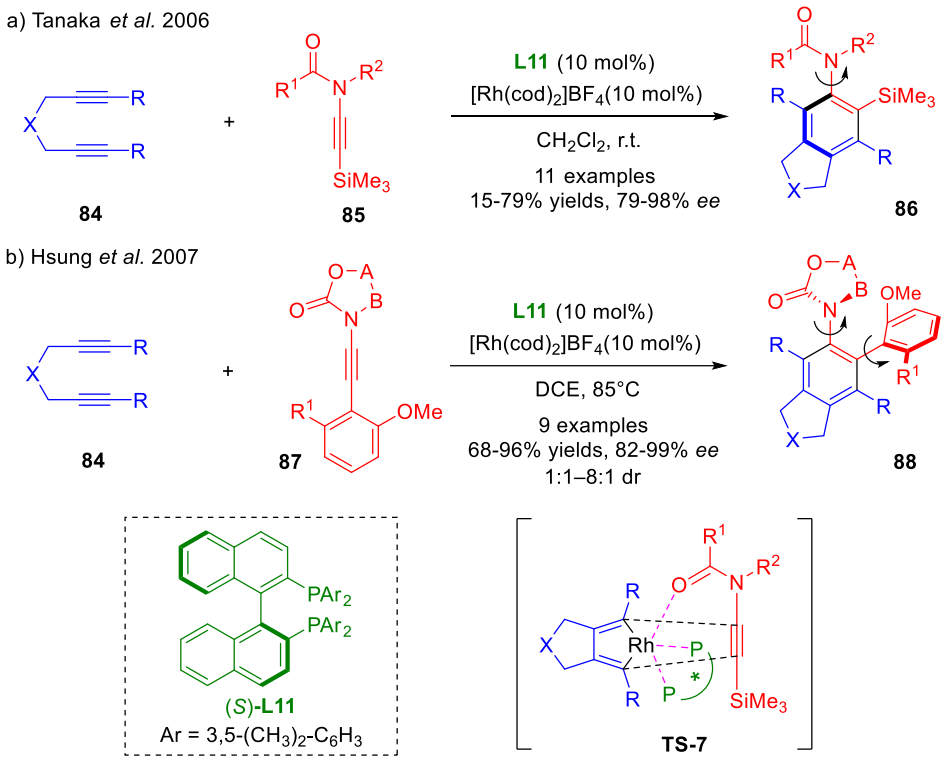
In 2020, Tan *et al.* reported the organo-catalyzed enantioselective C–N coupling reaction (Scheme 12).[61] Prior to that, such organo-catalyzed reactions were elusive. The employment of azonaphthalenes was key to the success of this strategy. With an azo-group at C2 position, the electrical property of the C1 position of naphthalene has been reversed from nucleophilic to electrophilic. In the presence of CPA catalyst, N nucleophilic carbazoles directly attacked the azonaphthalenes **78**, and the dual hydrogen-bond activation facilitated excellent enantio-control (**TS-6**). This reaction accommodated broad substrate scope, both carbazoles **79** and indoles **80** served as suitable nucleophiles. Various C–N atropisomeric *N*-arylcarbazoles and *N*-arylindoles were accessed in good yields with excellent *ee* values. Remarkably, the reported protocol had been successfully applied to the enantioselective synthesis of 1,5-dicarbazole naphthalene derivative **83** possessing two chiral C–N axes, which has significant potential in OLED materials.



Scheme 12. Organo-catalyzed C-N coupling reactions.

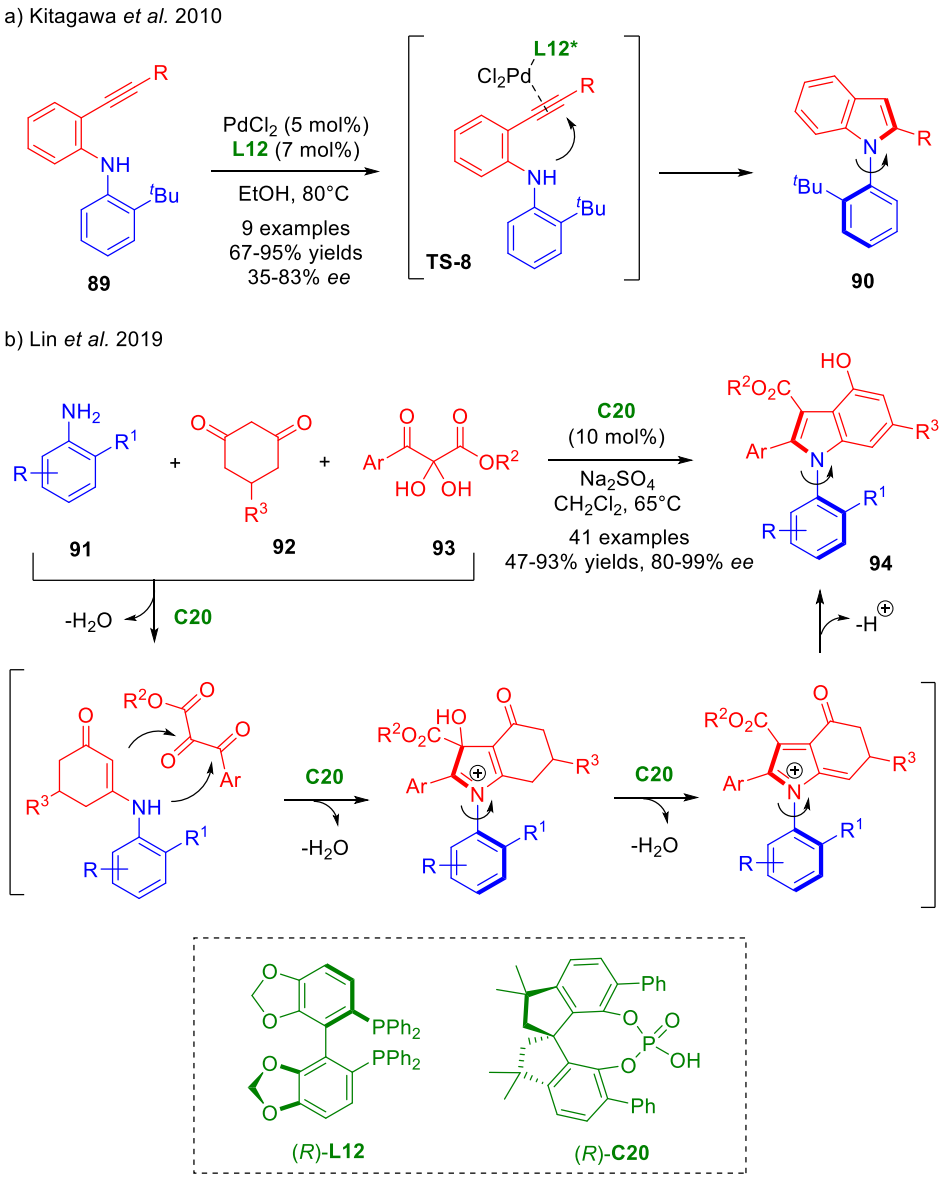
Catalytic asymmetric *de novo* construction

Given the synthetic diversity, assembling the C–N atropisomers via *de novo* construction of the (hetero-) aromatic ring has emerged as an effective mean. In 2006, Tanaka *et al.* disclosed their seminal work on asymmetric cycloadditions of ynamides **85** with 1,6-diynes **84** (Scheme 13a),[62] allowing the preparation of enantioenriched C–N axially chiral anilides **86**. The protocol was proceeded via a chemo- and stereo-selective [2 + 2 + 2] pathway (**TS-7**) under the catalysis of rhodium(I)/BINAP complex. This report is one of the early examples on construction of C–N axis with high enantioselectivity. Independently, the Hsung group reported a similar Rh(I)-catalyzed asymmetric [2 + 2 + 2] cycloaddition of ynamides **87** (Scheme 13b),[63] affording the corresponding products **88** containing both the C–C and C–N axial chirality with excellent *ee* values.



Scheme 13. Catalytic atroposelective synthesis of benzene rings.

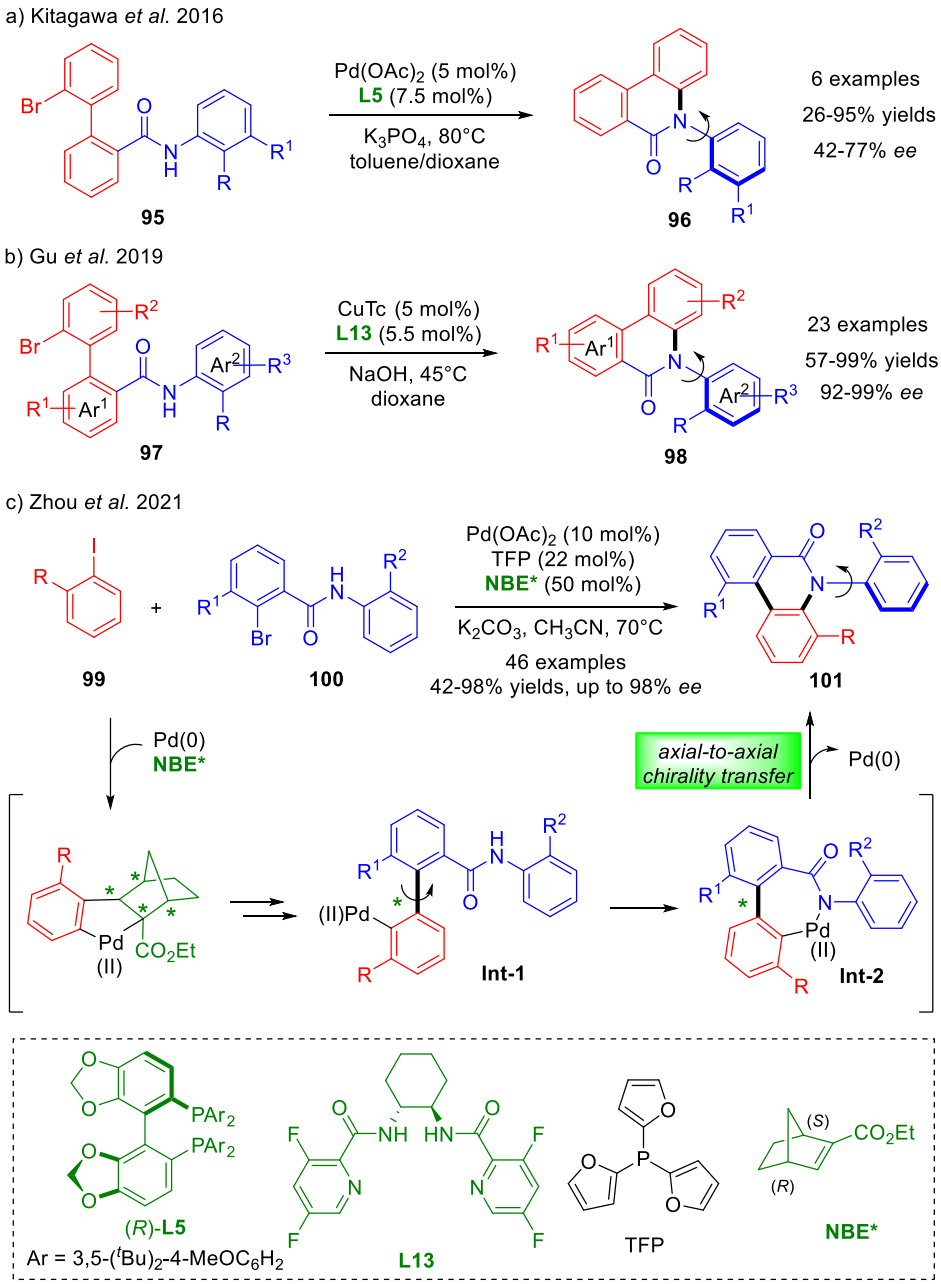
Although chiral *N*-arylindole skeletons with C–N axial chirality exist in natural products and chiral ligands for asymmetric catalysis, their catalytic asymmetric synthesis is rare. In 2010, the Kitagawa group reported the first catalytic asymmetric atroposelective synthesis of axially chiral *N*-arylindoles via the *de novo* construction of the indole ring (Scheme 14a).[64] Pd-catalyzed intramolecular *endo*-hydroaminocyclization of *ortho*-alkynylaniline **89** was performed in the presence of chiral ligand **L12** SEGPHOS. Generally high yields were achieved, albeit with moderate enantioselectivities. After nearly a decade of silence, in 2019, CPA-catalyzed *de novo* construction of *N*-arylindoles **94** around the C–N bond was accomplished by Lin *et al.* (Scheme 14b).[65] This creative method was enabled by an asymmetric three-component Doyle indole synthesis. By using their own developed chiral spirocyclic phosphoric acid **C20**, a variety of C–N axially chiral *N*-arylindoles were obtained in good yields with excellent *ee* values. In addition, further manipulation of the product led to a chiral monophosphorus ligand on the basis of C–N axial chirality.



Scheme 14. Catalytic atroposelective synthesis of indoles.

By bearing an *ortho*-substituent, *N*-aryl-phenanthridin-6-one derivatives could maintain a stable C–N axially chiral motif. With the success in atroposelective *N*-arylation reaction of anilides compounds (Scheme 3a),[30-31] Kitagawa et *al*. applied the asymmetric Buchwald-Hartwig amination reaction into the synthesis of C–N axially chiral phenanthridin-6-one derivatives (Scheme 15a).[66] However, the standard high reaction temperature did not fit well into this system, in terms of racemization of the product. This issue has been addressed by the Gu group, using a Cu-catalyzed enantioselective intramolecular Ullmann-type amination reaction (Scheme 15b).[67] It was reported that the readily prepared ligand *N,N'*-(cyclohexane-1,2-diyl)dipicolinamide **L14** displayed an excellent stereo-induction. The corresponding C–N axially chiral products **98** were prepared in high yields and with nearly perfect *ee* values, and could undergo further transformations without loss of enantiopurity. In addition to the abovementioned intramolecular strategies, Zhou et *al*. developed a unique and elegant intermolecular method for synthesizing optically active C–N axially chiral phenanthridin-6-one derivatives from simple substrates (Scheme 15c).[68] The presented reaction was benefited from the asymmetric Catellani reaction. In the presence of chiral norbornene ester (**NBE***) and Pd-TFP complex, a broad range of C–N axially chiral *N*-aryl-phenanthridin-6-one derivatives **101** were created with excellent enantioselectivity. A detailed DFT study implied

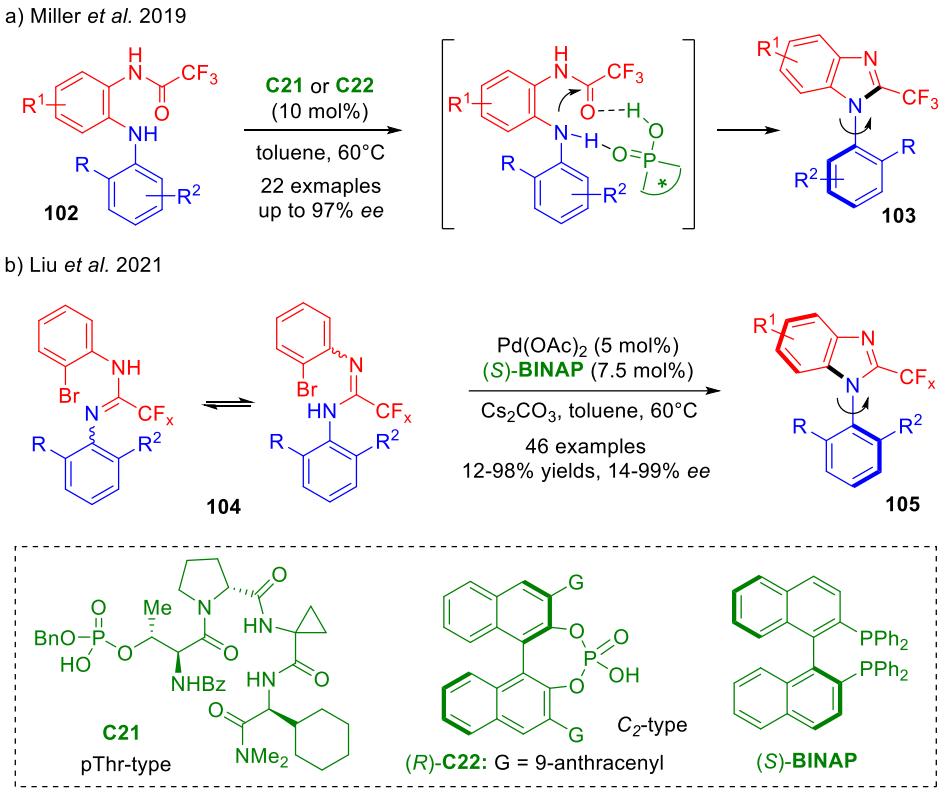
that the observed excellent chiral induction was brought about by an efficient axial-to-axial chirality transfer from an initially constructed C–C chiral axis to a C–N chiral axis.



Scheme 15. Catalytic atroposelective synthesis of phenanthridin-6-ones.

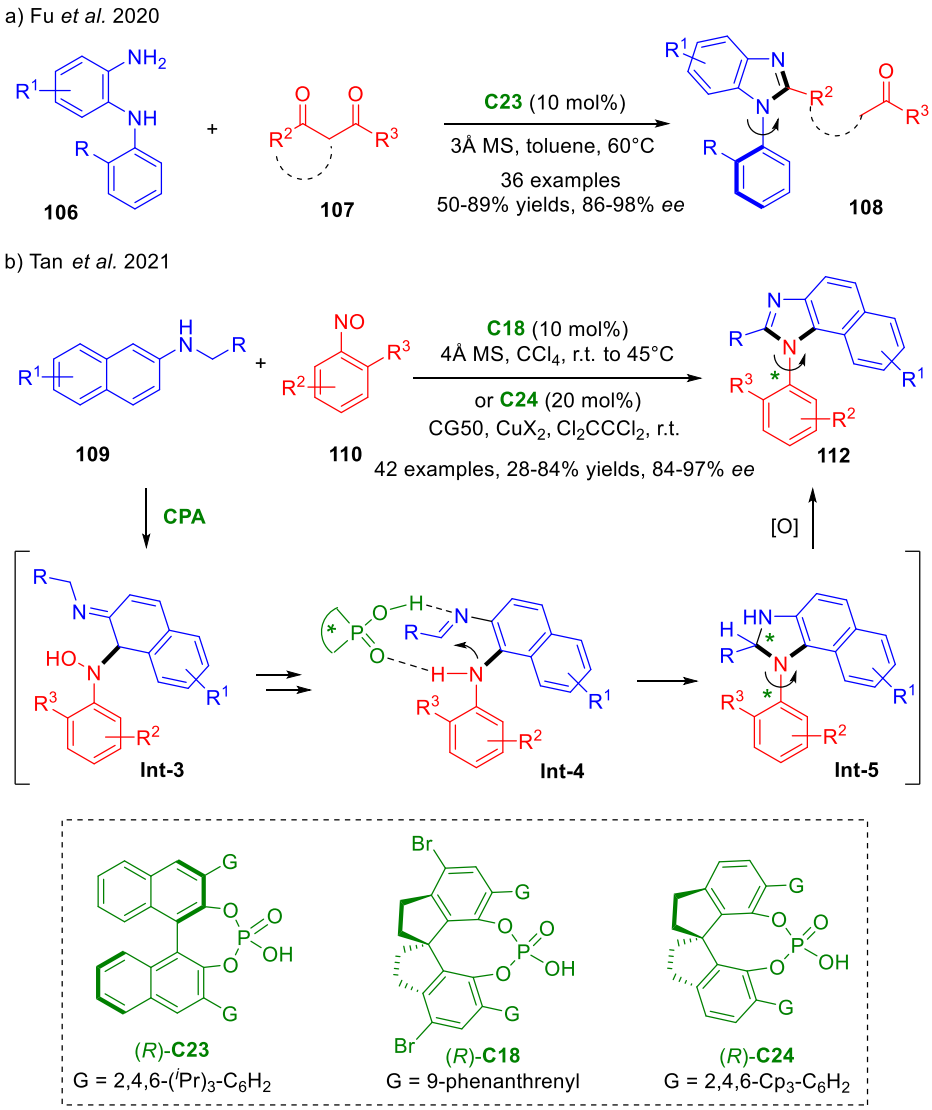
Benzimidazole structures are widely found in biologically active molecules, and therefore have received considerable attentions in the past decades. Their catalytic atroposelective synthesis was led by the Miller group (Scheme 16a).[69-70] The *de novo* formation of the benzimidazole ring was enabled by a CPA-catalyzed intramolecular cyclodehydration. Both phosphothreonine (pThr)-embedded peptidic and C_2-symmetric CPAs effectively promoted the generation of stereogenic C–N axes. Mechanistic studies revealed that steric effects appeared to dictate enantioselectivity for C_2-type CPA, while conformational adaptation seemed to be more important for pThr-type CPA. In 2021, Liu *et al.* described a Pd-catalyzed intramolecular Buchwald–Hartwig amination for the highly enantioselective synthesis of C–N axially chiral *N*-aryl-benzimidazoles **105** (Scheme 16b).[71] The authors highlighted that amidines can undergo tautomerization, E/Z isomerization and it has the potential to undergo

catalyst deactivation due to its strong coordination with transition metals. Collectively, these made the enantioselective induction of this cross-coupling reaction more challenging.



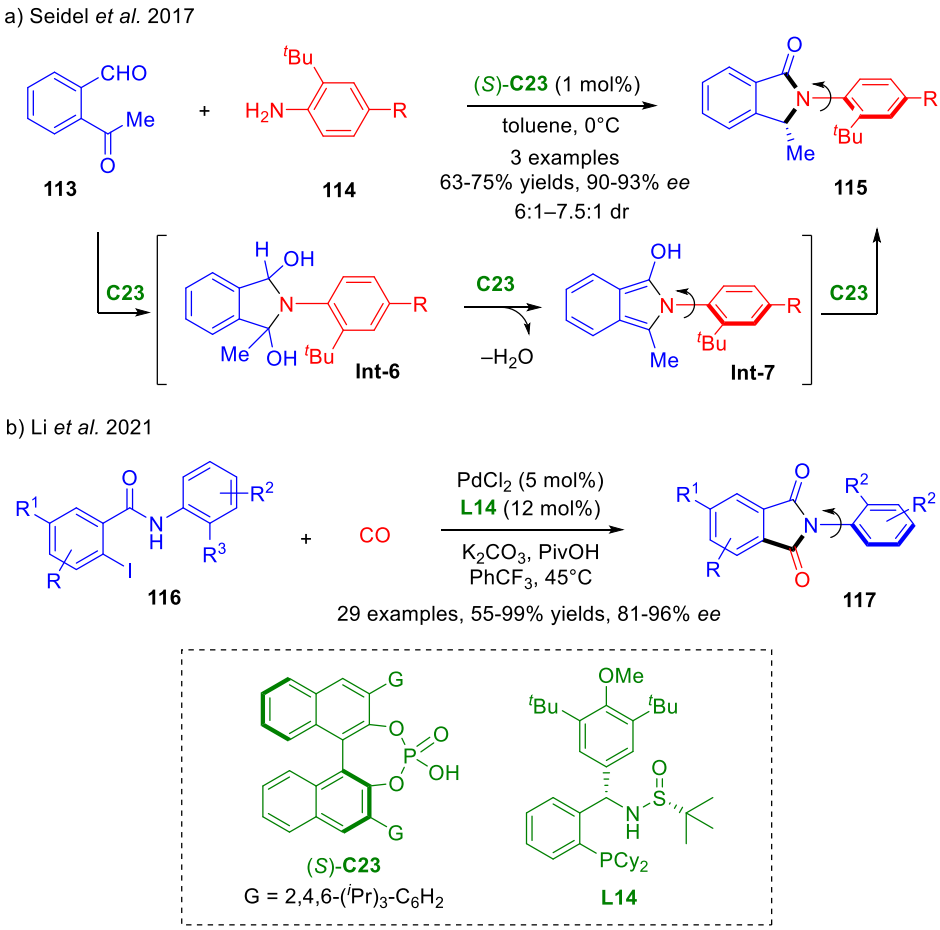
Scheme 16. Intramolecular catalytic atroposelective synthesis of benzimidazoles.

Furthermore, C–N axially chiral *N*-aryl-benzimidazoles could be prepared in an intermolecular manner. For example, the intermolecular cyclocondensation of substituted benzene-1,2-diamines and *β*-ketoesters via the selective C–C bond cleavage had emerged to give a facile access to benzimidazoles.[72] In 2020, Fu *et al.* accomplished the asymmetric version by using a CPA catalyst (Scheme 17a).[73] The target products **108** bearing a C–N axis were provided in high yields with excellent enantioselectivities. Just recently, Tan *et al.* described a nitrosobenzene-enabled enantioselective construction of C–N atropisomeric *N*-aryl-benzimidazoles **112** by means of CPA catalysis (Scheme 17b).[74] It was reported that the nitroso group played a unique role in this domino process. It acted as an electrophile in the initial C–N bond formation step, and functioned as a nucleophile to form the second C–N bond. Subsequent oxidative aromatization of stereoenriched **Int-5** afforded the desired axially chiral products with a wide range of substrate scope, high yields, and excellent *ee* values. Interestingly, two sets of conditions were adopted to access *N*-aryl-benzimidazoles **112** in opposite configuration while using CPAs of same absolute configuration.



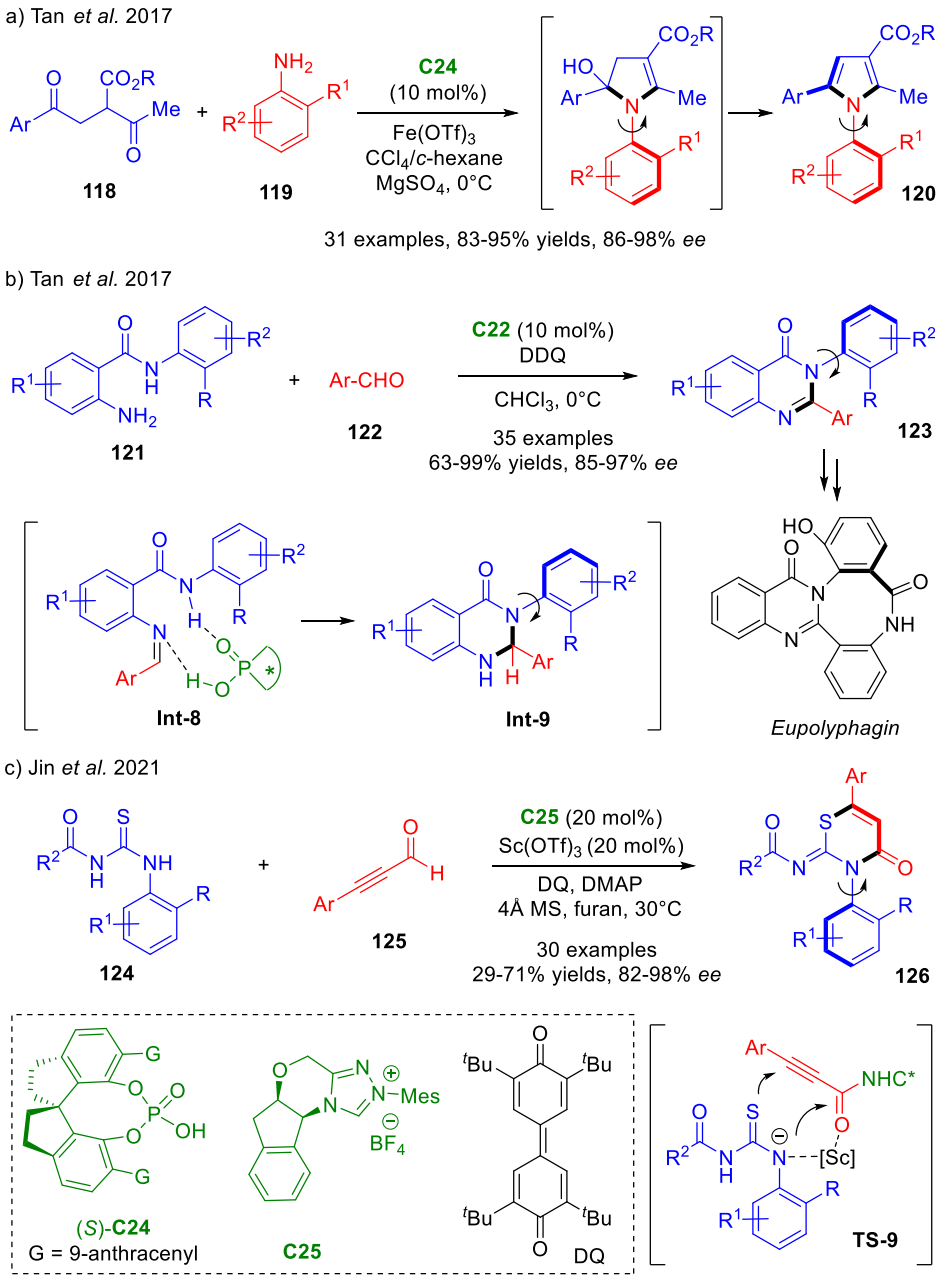
Scheme 17. Intermolecular catalytic atroposelective synthesis of benzimidazoles.

Catalytic enantioselective synthesis of isoindolinones has attracted a long-standing interest in synthetic chemistry due to their numerous biological activities. However, catalytic atroposelective construction of *N*-aryl-isoindolinones with C–N axial chirality remains underdeveloped. In this regard, Seidel *et al.* reported that their developed CPA-catalyzed biomimetic condensation reaction was applicable to the preparation of C–N axially chiral *N*-aryl-isoindolinones **115** (Scheme 18a).[75] The proposed mechanism involved the formation of cyclic bis-hemiaminal **Int-6** followed by dehydration, and CPA-catalyzed tautomerization of **Int-7** which was the key enantiodetermining step. The corresponding products bearing both central and C–N axial chirality were afforded with excellent *ee* values. Recently, Li *et al.* disclosed an unprecedented asymmetric carbonylation of ArI with carbon monoxide (CO) for C–N axially chiral *N*-aryl-isoindolindiones **117** (Scheme 18b).[36] By employing the Sadphos ligand **L14**, palladium-catalyzed carbonylative cycloamidation proceeded smoothly to produce cyclic amides with excellent efficiency. Significantly, a pair of enantiomorphous isomers of **117** can be easily obtained by simply changing the positions of substituents.



Scheme 18. Catalytic atroposelective synthesis of isoindolinones.

Pyrroles are prominent feedstocks, and their synthesis holds an important place in synthetic chemistry. In this context, the Paal–Knorr reaction has emerged as one of the most common approaches for pyrroles. However, it was not until 2017, that the first catalytic asymmetric Paal–Knorr reaction was developed by the Tan group (Scheme 19a).[76] The combination of CPA catalyst **C24** and Lewis acid $Fe(OTf)_3$ was the key to achieve effective enantiocontrol. A wide range of axially chiral *N*-arylpyrroles around the C–N bond were obtained in high yields with good to excellent enantioselectivities. Interestingly, the enantiocontrol was solvent-dependent. A change in the solvent system could lead to the opposite enantiomer even when using chiral catalyst with the same configuration. In the same year, catalytic asymmetric *de novo* construction of structurally privileged *N*-arylquinazolinones bearing a C–N axis was accomplished by the same group (Scheme 19b).[77] The reported approach involved a CPA-facilitated hemiaminal formation followed by the oxidative dehydrogenation. This one-pot protocol was applicable to a variety of C–N axially chiral aryl-quinazolinones **123**, and could be supplemented by the CPA-catalyzed carbon–carbon bond cleavage strategy. Remarkably, a facile asymmetric total synthesis of eupolyphagin bearing a C–N axial arylquinazolinone motif was enabled by the presented methodology. Recently, the elegant atroposelective synthesis of thiazine, an important heterocyclic structural motif, was achieved by Jin *et al.* (Scheme 19c).[78] Enantio-enriched thiazine derivatives with C–N axial chirality were readily constructed via an NHC-catalyzed atroposelective cycloaddition reaction. The utilization of additive $Sc(OTf)_3$ improved the reaction yield. The products **126** were rich in functionalities, and could be transformed to various functional molecules containing a chiral C–N axis without erosion of the optical purities.

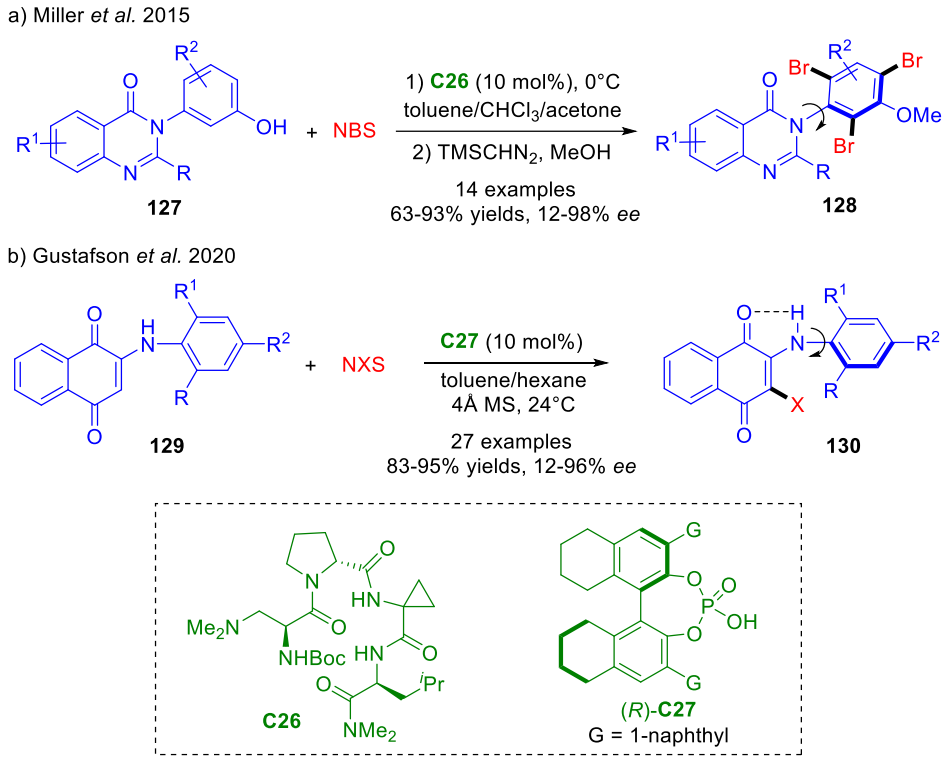


Scheme 19. Catalytic atroposelective synthesis of other rings.

Catalytic asymmetric Ar functionalization

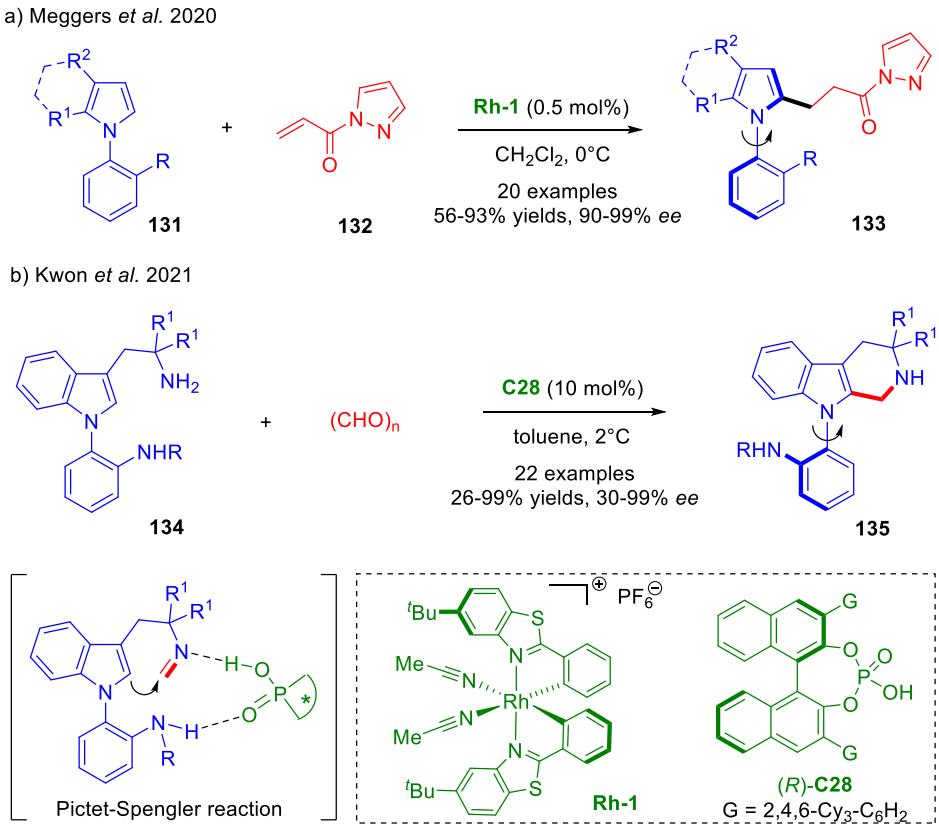
Nowadays, catalytic asymmetric functionalization of aromatic rings with a preexisting C–N bond, such as electrophilic halogenation and C–H bond activation, has become a reliable way to access C–N axial chirality. In 2015, the pioneering atroposelective bromination of quinazolinones **127** with a preformed C–N bond was developed by Miller *et al.* (Scheme 20a).[79] This tribromination was facilitated by a tertiary amine-containing *β*-turn peptide catalyst **C26**, in which the initial bromination event that yielded mono-*ortho*-substituted isomer was stereodetermining. Accordingly, the products via dehalogenation from C–N axially chiral **128** were stereoisomerically stable, and their further manipulations, including Suzuki–Miyaura cross-coupling and Buchwald–Hartwig amination, were actually feasible. Considering lower stereochemical stabilities caused by potential gearing mechanism, diarylamines and related scaffolds pose a challenge to chemists in terms of catalytic atroposelective synthesis. In 2020, an ingenious solution to this issue was reported by

Gustafson *et al.* (Scheme 20b).[80] They found that *N*-aryl-quinoids, diarylamine-like scaffolds, possessed a five-membered intramolecular N–H–O hydrogen bond, which fixed one of the axes into a planar conformation. CPA-catalyzed atroposelective electrophilic halogenation of this simplified system gave a large range of stereochemically stable *N*-aryl-quinoids **130** around the C–N axis in excellent efficiency.



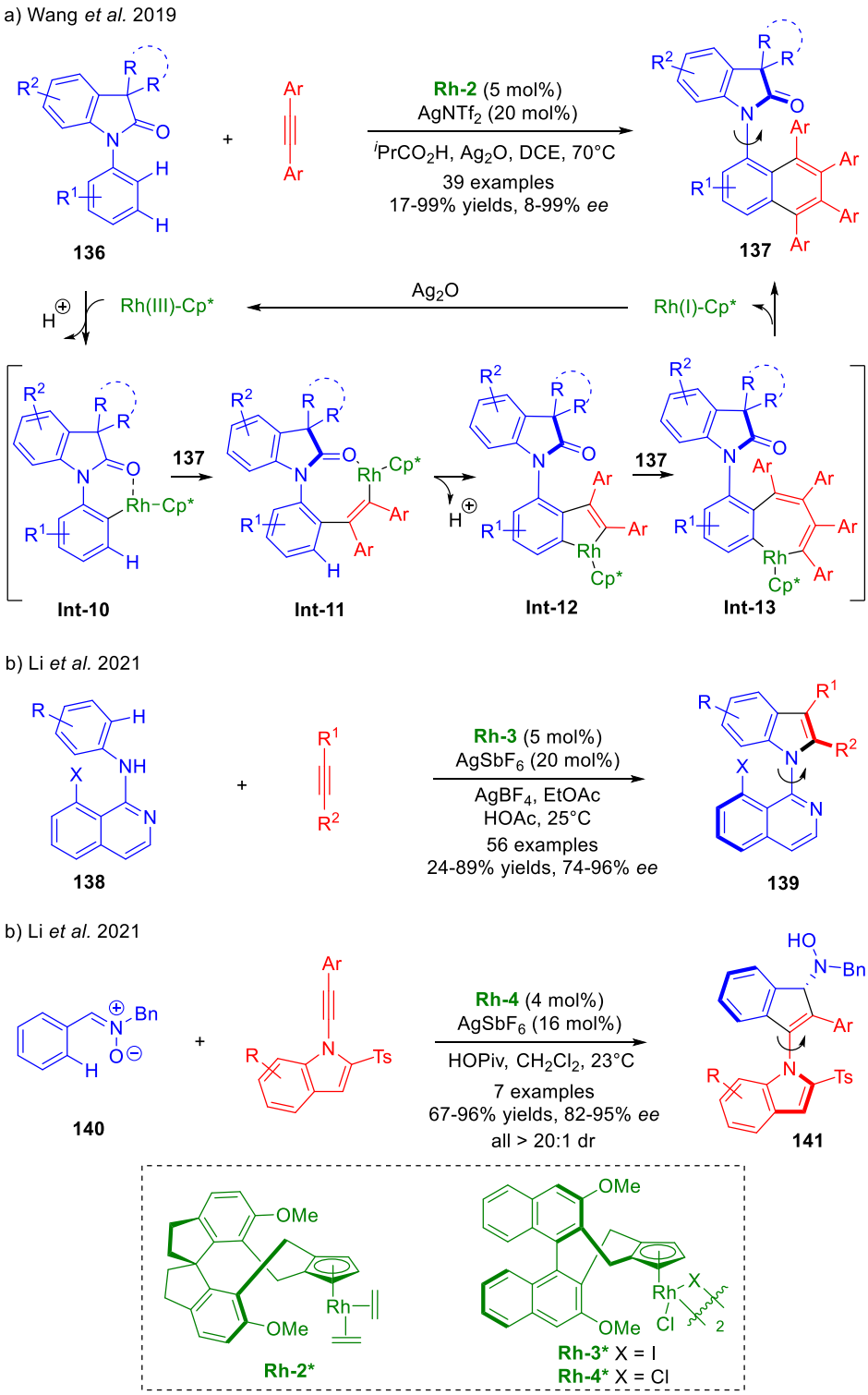
Scheme 20. Catalytic atroposelective electrophilic halogenation.

C2-Functionalizations of pyrrole and indole derivatives are among the most straightforward approaches to axially chiral frameworks.[5] In this context, Meggers *et al.* accomplished a highly atroposelective electrophilic aromatic substitution of *N*-arylpyrroles by employing their developed chiral-at-rhodium catalyst, which strongly discriminates between configurationally labile substrates **131** (Scheme 21a).[81] The presented reaction served as a highly feasible approach to alkylated *N*-arylpyrrole products **133** with C–N axial chirality. Follow-up transformations readily afforded structurally diverse *N*-arylpyrroles. The origins of the stereoselectivity was investigated via DFT calculations. Besides, Kown *et al.* reported an unprecedented atroposelective Pictet–Spengler reaction of *N*-arylindoles in 2021 (Scheme 21b).[82] It was reported that the dual hydrogen-bonding interaction between CPA and substrates **134** was essential to achieve high enantioselectivity. Highly enantioenriched *N*-aryl-tetrahydro-*β*-carbolines **135** with C–N axial chirality were obtained with a wide substrate scope. Moreover, this enantioselective Pictet–Spengler cyclization was applicable to electron-withdrawing group-substituted benzaldehydes, enabling the simultaneous control of both axial and central stereogenicity. The promising antiproliferative activity of **135** further demonstrated the importance of the presented atroposelective process.



Scheme 21. Catalytic atroposelective C2-functionalization of *N*-arylpyrroles and *N*-arylindoles.

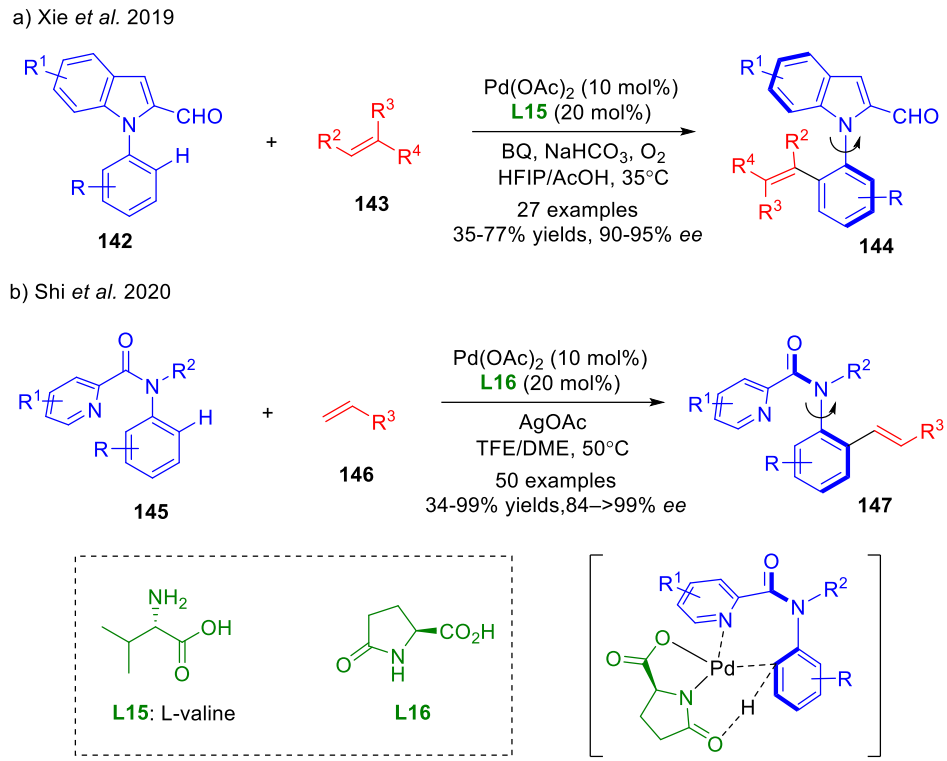
Recently, transition-metal-catalyzed enantioselective C–H functionalization of arenes has become a powerful and efficient strategy towards atropisomers.[4] For instance, the first example of the asymmetric synthesis of C–N axially chiral compounds had been established by Wang *et al.* via such C–H activation strategy (Scheme 22a).[83] In the proposed mechanism, the reaction went through an enantioselective Satoh–Miura-type process involving dual C–H activation. The first C–H bond cleavage led to a six-membered rhodacyclic intermediate (**Int-10**). The following alkyne insertion gave C–N axially chiral **Int-11**. The second round of C–H activation, alkyne insertion as well as the final reductive elimination built up the naphthalene ring. A broad range of C–N axially chiral *N*-aryloxindoles **137** were provided with high yields and enantioselectivities. Preliminary mechanistic studies indicated that the C–H activation step was not the turnover-determining step. In 2021, Li *et al.* reported an elegant enantioselective oxidative [3 + 2] annulation of anilines with alkynes via rhodium(III)-catalyzed C–H activation for atroposelective construction of indoles with C–N axial chirality (Scheme 22b).[84] Preliminary mechanistic studies were conducted via DFT calculations, implying the final C–N reductive elimination constituted the stereo-determining step. The reaction featured a broad substrate scope, mild conditions, and high enantioselectivity. In addition, they achieved an asymmetric [3 + 2] annulation of arylnitrone **140** with sterically hindered alkynes using a similar C–H activation (Scheme 22c) in the same year,.[85] In this chemical event, nitrone acted as an electrophilic directing group. Two chiral elements, C–N axial and C-central chirality, were well compatible in the corresponding products **141**. Excellent enantio- and diastereo-selectivities were obtained under mild reaction conditions. Notably, the employment of different classes of alkynes could effectively result in the other two classes of chiral indenes/indenones bearing C-central or C–C axial chirality.



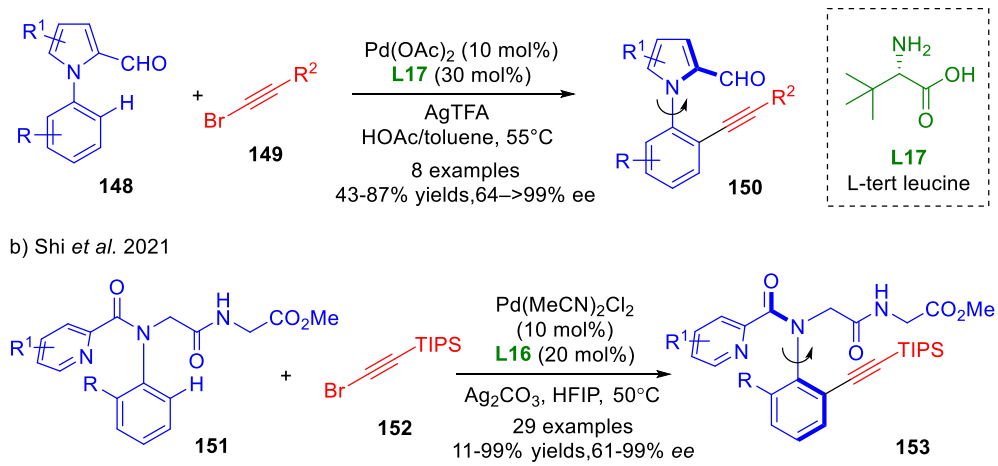
Scheme 22. Rh-catalyzed atroposelective C–H functionalization.

In 2019, Pd-catalyzed atroposelective C–H olefination of *N*-aryl heterocycles had been disclosed by Xie *et al.*, representing the first synthesis of N–C axially chiral arylindoles via C–H activation (Scheme 23a).[86] The assistance of chiral amino acid as a cocatalyst was crucial in the regio- and stereo-control. The reaction featured a good tolerance of various indole derivatives and functional alkenes, including bulky internal and trisubstituted alkenes. Then, in 2020, a straightforward approach to atropisomeric anilides, one of the most challenging

types of axially chiral compounds, had been accomplished by Shi *et al.* via Pd(II)-catalyzed asymmetric C–H olefination (Scheme 23b).[87] Experimental studies and DFT calculations were conducted to elucidate the reaction mechanism, which revealed that the amino acid ligand distortion accounted for the enantio-control in the C–H bond activation step. Using readily available L-pyroglutamic acid **L16** as an inexpensive chiral ligand, a wide range of chiral anilides **147** were prepared in high yields and excellent enantioselectivities under mild conditions. In addition, racemization experiments were carried out to study the atropostability of **147**, indicating that both steric and electronic effects were essential.



Scheme 23. Pd-catalyzed atroposelective C–H olefination.



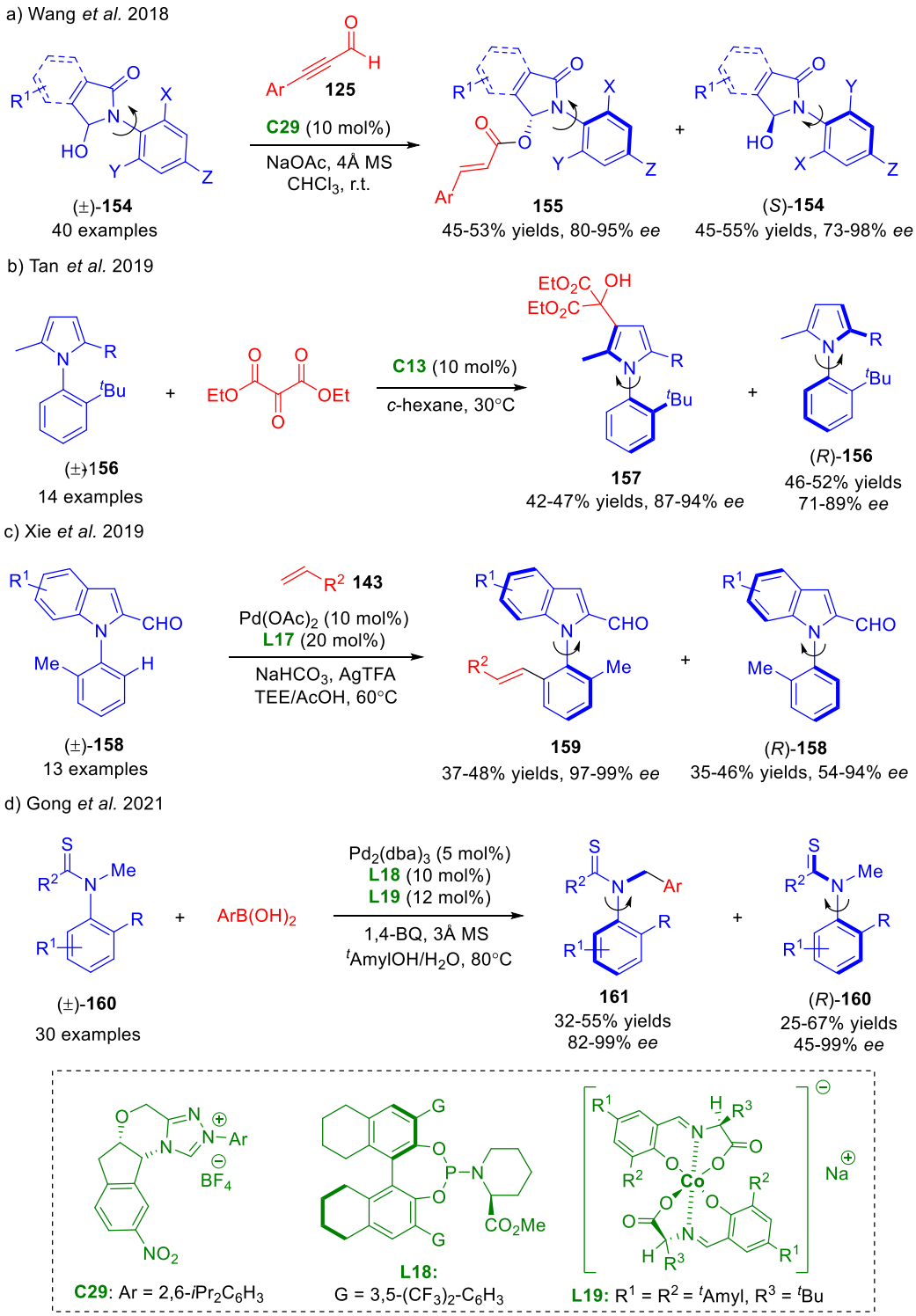
Scheme 24. Pd-catalyzed atroposelective C–H alkynylation.

Introduction of a bulky protected alkynyl group to replace the smaller C–H via C–H activation, could render C–N axial chirality. In the enantioselective synthesis of atropisomers featuring pentatomic heteroaromatics, Shi *et al.* showcased that *N*-arylpyrroles displaying a stereogenic C–N axis could be readily created by Pd-catalyzed atroposelective C–H

alkynylation (Scheme 24a).[88] Good to excellent enantioselectivities were obtained in the presence of *tert*-leucine **L17** as an efficient, catalytic, and transient chiral auxiliary. Later, the same group employed this Pd-catalyzed asymmetric C–H alkynylation strategy into the atroposelective synthesis of *N*-aryl peptoid atropisomers (Scheme 24b),[89] The introduction of chirality into peptoids are important to identify a discrete and robust secondary structure and this reaction served as a streamlined method for peptoid modifications in a highly efficient, practical, atom-economical and isolable manner.

Kinetic resolution

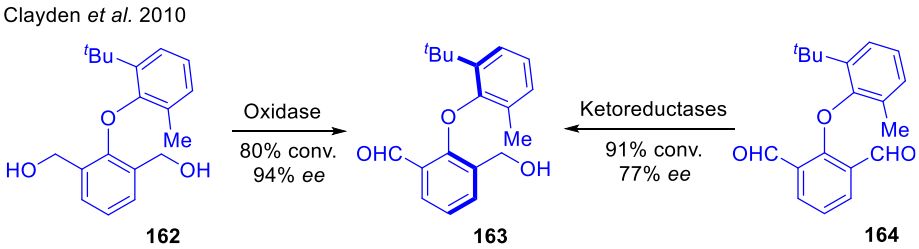
Kinetic resolution has proven to be a robust tool in asymmetric catalysis, owing to its reliable ability to deliver enantiomerically pure products from racemic materials.[3, 90] In this regard, catalytic asymmetric synthesis of C–N atropisomers could be contributed by kinetic resolution strategy. In 2018, Wang *et al.* developed a NHC-catalyzed enantioselective kinetic resolution of anilides (Scheme 25a).[91] The two enantiomers of racemic hemiaminals **154** were well separated via NHC-catalyzed acylation. The corresponding products with both C–N axial and C-central chirality were yielded with a broad substrate scope in excellent enantioselectivities. In 2019, Tan *et al.* achieved the kinetic resolution of *N*-arylpyrroles by using CPA catalysis (Scheme 25b).[51] The enantio-event featured a remote control. Various C–N axially chiral *N*-arylpyrroles were prepared with good to high selectivity factors. In the same year, the Xie group found that kinetic resolution of *N*-arylindoles with C–N axis could be enabled by atroposelective C–H olefination (Scheme 25c).[86] This palladium/amino acid cooperative catalysis afforded excellent selectivity factors. The divers and easily accessible transformations of the olefination products demonstrated the practicality and synthetic value of this protocol. Very recently, Ackermann *et al.* reported a similar kinetic resolution process via an unprecedented atroposelective palladaelectro-catalyzed C–H activation.[92] In addition, Gong *et al.* found the synergistic action of anionic chiral Co-complex and phosphoramidite ligand actually served as a general platform to address stereoselectivity issues in their previous asymmetric thioamide-directed C–H functionalization. Very recently, the same group elegantly extended this steric and rigid chiral system to Pd-catalyzed kinetic resolution of atropisomeric thioanilides **160** via asymmetric C(sp3)–H functionalization (Scheme 25d).[93] A wide range of C–N atropisomeric arylation thioanilides **161** were created in excellent enantioselectivities. Notably, the enantiomer with the opposite configuration could be synthesized via arylation of the remaining enantioenriched substrate (*R*)-**160** with an achiral anionic ligand.



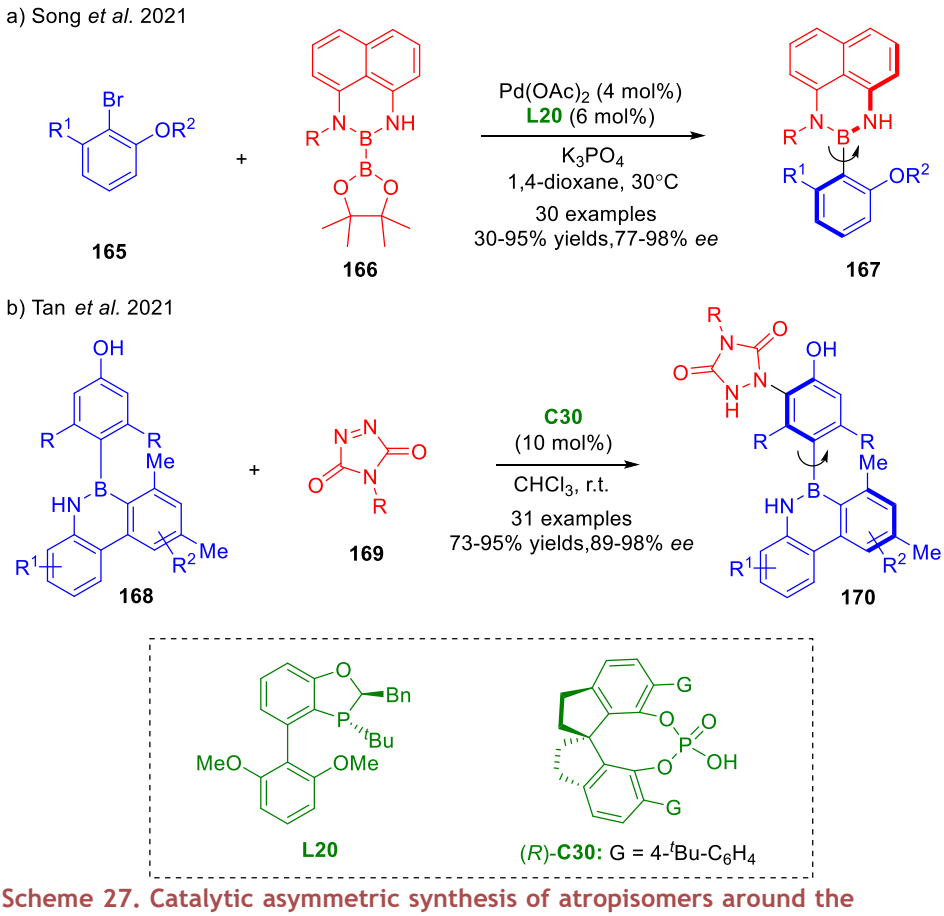
Scheme 25. Atroposelective kinetic resolution.

ATROPISOMERS AROUND OTHER BOND

In spite of the great achievements of atropisomers around C–N axis in catalytic asymmetric synthesis, atropisomerism arising from restricted rotation around other bonds, such as C–O, C–S, C–B, and N–N bond, is largely overlooked. Indeed, there was a decade of silence since the pioneering study on biocatalytic desymmetrization of an atropisomer with the C–O axis by Clayden *et al.* (Scheme 26).[94] Two complementary biocatalytic approaches to the enantioselective synthesis of atropisomeric diaryl ethers **163**, a structural unit of vancomycin, by desymmetrization of appropriate prochiral substrates had been established. While oxidase catalyzed the atroposelective oxidation of diol **162** in an excellent enantioselective manner, ketoreductases enabled the atroposelective reduction of dialdehyde **164**. Importantly, kinetic resolution of **163** via overoxidation was observed during the oxidation process, which contributed to the excellent *ee* value.



Scheme 26. Catalytic asymmetric synthesis of atropisomer around the C–O bond.

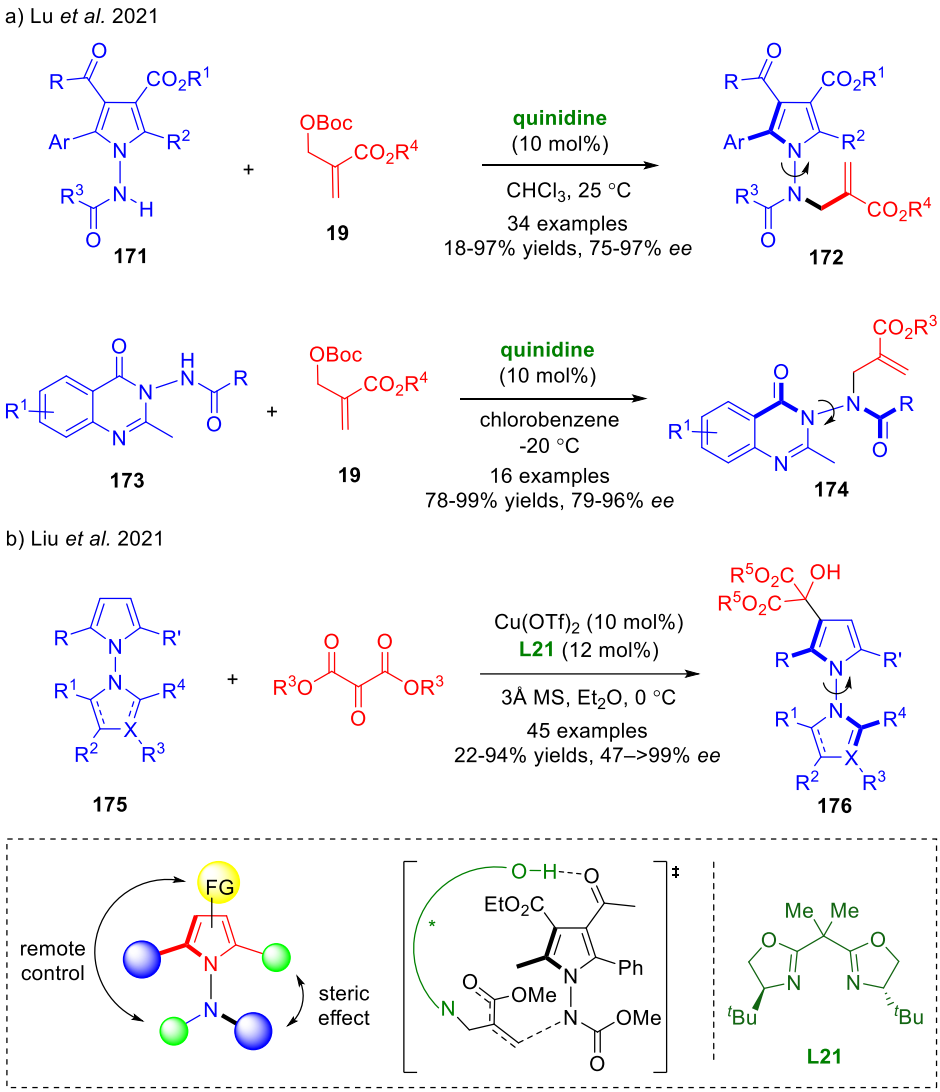


Scheme 27. Catalytic asymmetric synthesis of atropisomers around the C–B bond.

Chiral organoboron compounds are important synthetic intermediates. However, in contrast to the well-developed centrally chiral organoboron, C–B axially chiral chemistry remains

challenging, stemming from the longer C–B bond which lowers the rotational barrier. To address this issue, Song *et al.* established the first catalytic asymmetric synthesis of optically active atropisomeric arylborons **167** via Miyaura borylation of bromoarenes **165** with unsymmetrical diboron reagents **166** (Scheme 27a).[95] The development of a suitable unsymmetrical diboron reagent was the key to the success of this direct atroposelective C–B bond formation. Axially chiral organoborons were created in a broad substrate scope with high yields and enantioselectivities. Elaboration and racemization experiments were performed to examine their preliminary applications and stereochemical stability. Around the same time, the Tan group reported a chiral phosphoric acid-catalyzed desymmetrization strategy to construct the C–B stereogenic axis (Scheme 27b).[96] A class of axially chiral 4-azaborine-phenol compounds **170** containing a stereogenic B–C bond were well prepared with outstanding efficiency under mild conditions. Multiple well-defined H-bonding interactions of chiral phosphoric acid with both substrates were proposed to account for the setting of the stereogenic B–C axis in a remote control manner. The synthetic utility of this protocol was demonstrated by scale-up synthesis and representative downstream transformations.

The N–N bond containing motifs are widely present in natural products, pharmaceutical agents, and organic materials. Although various methods have been developed for these structural units, the N–N atropisomerism phenomenon is largely overlooked. The access to N–N axial chirality is highly challenging because deplanarization of the two N-containing planes upon rotation leads to a low rotational barrier. The formation of such non-carbon containing axis could be favored by shorter N–N bond length and a more crowded axis 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 remains elusive prior to Lu's work in 2021 (Scheme 28a).[97] They accomplished the first catalytic asymmetric synthesis of N–N axially chiral compounds via quinidine catalyzed N-allylic alkylation reaction. The mild conditions allowed facile access to a variety of N–N axially chiral 1-aminopyrroles **172** and 3-aminoquinazolinones **174** in high yields and excellent enantioselectivities. These N–N axially chiral frameworks are new addition to the families of axially chiral molecules. Notably, the authors found an interesting remote enantiomeric control phenomenon, where the functional groups at C_3- or C_4-position of pyrrole ring, far away from the axis can significantly affect the *ee* value. DFT calculations revealed that the origins of enantioselectivity stemmed from hydrogen bonding interactions between the quinidine catalyst and the substrate. Independently, Liu *et al.* documented a Cu-bisoxazoline-catalyzed Friedel–Crafts alkylation reaction for the enantioselective synthesis of N–N biaryl atropisomers **176** (Scheme 28b).[98] The reaction could be enabled by both desymmetrization and kinetic resolution strategies, affording a wide range of N–N axially chiral bisazaheterocycle compounds in excellent efficiency.



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

CONCLUSION AND OUTLOOK

In summary, atropisomers bearing X–Y axis serve as an important addition to the repertoire of axially chiral compounds, and have received increasing attentions from various disciplines of chemical science. 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 challenging due to the relatively lower rotational barriers. However, the intrinsic shorter bond length and electron-repelling effect lead to a congested hetero X–Y axis, which result in stable and novel axially chiral frameworks. Recent years have witnessed rapid progresses in this emerging domain. A number of catalytic atroposelective approaches have been established for accessing these synthetically challenging skeletons, including N–H functionalization, desymmetrization, C–X bond formation, Ar *de novo* construction and functionalization, as well as kinetic resolution. The practicability of these strategy is highlighted by the ease of these X–Y axially chiral compounds to be converted into new ligands or catalysts, which could in turn contribute to the discovery of new types of atropisomers.

Even though C–N bonds dominate the significant breakthroughs made so far, the catalytic atroposelective synthesis of other X–Y optically active atropisomers is still very much in its infancy. For instance, C–O axial chirality, displayed by highly substituted biaryl ethers, is an

important structural element, but it is not common. Although the first report can be traced back to 1958, research in axial chiral diaryl ethers around a C–O bond remains challenging and elusive. In this context, Clayden *et al*. documented a biocatalytic desymmetrization approach, representing the only example of catalytic enantioselective synthesis of C–O axially chiral compounds. Similarly, highly substituted sulfides, sulfoxides, and sulfones exhibit C–S atropisomerism, despite the longer C–S bond length which caused slightly lower axial stability. However, up to now, the asymmetric synthesis of C–S axially chiral diaryl sulfones could only be established by resolution. When it comes to C–B axially chiral chemistry, the catalytic enantioselective approach remains unknown before the two very recent independent works from the Song and the Tan group. Additionally, non-carbon containing X–Y (X, Y ≠ C) axes (as exampled by N–N bond) which are prevalent in natural products and pharmaceuticals, are often neglected in terms of atropisomerism. Encouragingly, this situation has been changed by the two original and creative works from the Lu group and the Liu group. Along with advances in this field, the development of more efficient catalytic atroposelective methodologies and synthetic applications for these novel axially chiral frameworks are highly desirable. Besides, atropisomers around other bonds, such as C–P, C–Si, N–P, N–O, N–B, O–B bond *etc.*, and their catalytic atroposelective synthesis are highly desired. We hope this timely review would provide an overview to chemists currently in or outside the field, and facilitate their findings in axial chirality, asymmetric catalysis, natural product synthesis, and drug discovery.

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AUTHOR CONTRIBUTIONSL

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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