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N—N 单键阻转异构体的催化不对称合成

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摘要 N—N 单键广泛存在于天然产物和生物活性化合物中. 然而, 由于 N—N 轴不稳定的刻板印象, N—N 单键的阻转异构现象长期以来被忽视. 事实上, N—N 单键两端氮原子上的孤对之间存在排斥相互作用, 即电子能垒. 该电子能垒会导致 N—N 单键的旋转受阻, 从而产生稳定的 N—N 阻转异构体. 自 2021 年首次被报道以来, 催化不对称合成 N—N 阻转异构体迅速发展成为一个新兴领域. 这些反应包括不对称的 N—H 键功能化、不对称的去对称化和(杂)芳香烃环的阻转异构选择性从头构建. 综述了 N—N 单键阻转异构体催化不对称合成的最新进展.

关键词 N—N 单键; 阻转异构体; 催化不对称合成

Catalytic Asymmetric Synthesis of N—N Atropisomers

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Abstract The N—N bond is widely found in natural products and bioactive compounds. The atropisomerism of N—N bond, however, has been dismissed for a long time due to the stereotype that N—N axis is unstable. The electronic barrier stemming from the repulsive interaction between the lone pairs on the two nitrogen atoms leads to a rotationally hindered axis, resulting in stable N—N atropisomers. Since the first report in 2021, the catalytic asymmetric synthesis of N—N atropisomers has been developed rapidly into an emerging area. These reactions include asymmetric N—H bond functionalization, asymmetric desymmetrization and atroposelective *de novo* construction of (hetero-)aromatic rings. The N—N axially chiral compounds are valuable molecules, in terms of their potential application in chiral ligand/catalysts design and biological activity evaluation. Herein, the state-of-the-art catalytic asymmetric synthesis of N—N atropisomers is summarized.

Keywords N—N bond; atropisomer; catalytic asymmetric synthesis

1 Introduction

Atropisomerism represents among the fundamental chirality element in nature. As an unique subclass of conformers, atropisomers arise from the restricted rotation about a single bond (energy barrier >96.6 kJ•mol^{-1}).[1] The combination of prevalence in natural products, molecular devices, functional materials as well as bioactive molecules and applications in chiral ligands and catalysts have made atropisomerism extremely popular in the past two decades.[2] In this context, C—C atropisomers, including axially chiral biaryls, aryl alkenes, and aryl amides, are most common and have been extensively developed and applied (Figure 1, a).[3] Additionally, introducing a heteroatom (typically nitrogen, oxygen, sulfur and boron) into the axis leads to the C—X atropisomers that portray higher structural variability, which has been under active investigation in recent years (Figure 1, b).[4] The atropisomerism of N—N bond, however, eluded such serious attention for a long time (Figure 1, c). This anomaly might be attributed to the incorrect notion that N—N axis is unstable due to the deplanarization effect. Indeed, the electronic barrier stemming from the repulsive interaction between the lone pairs on the two nitrogen atoms can strongly favor the formation of such atropisomers.[5]

The first report of N—N atropisomerism can be traced back to 1931, wherein a diastereomeric salt of brucine was obtained in the crystallization of 2,2',5,5'-tetramethyl-1,1'-bipyrrole-3,3'-dicarboxylic acid.[6] However, the lack of investigation on this phenomenon has been going on for

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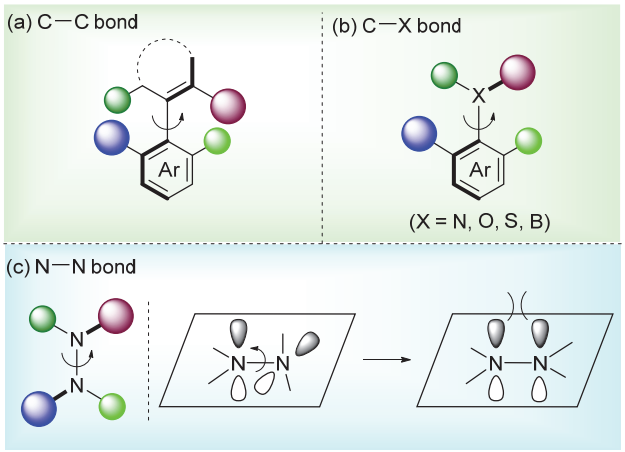
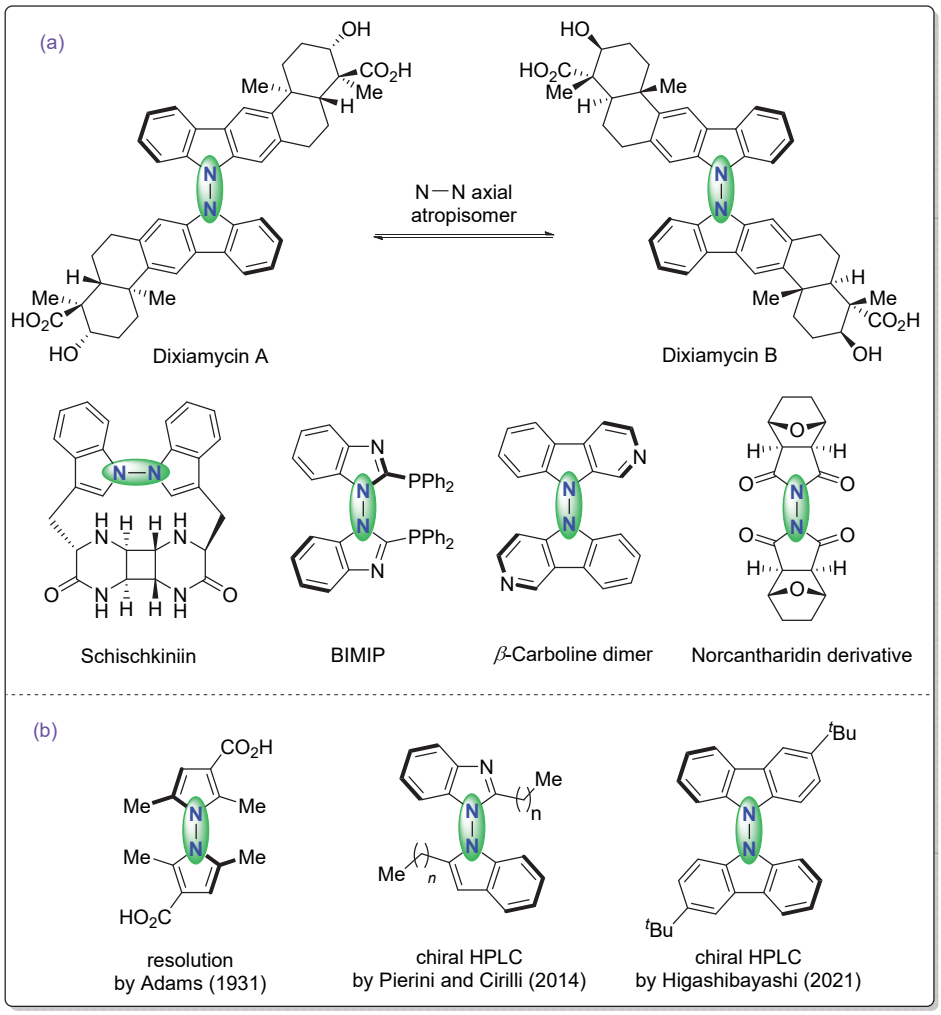


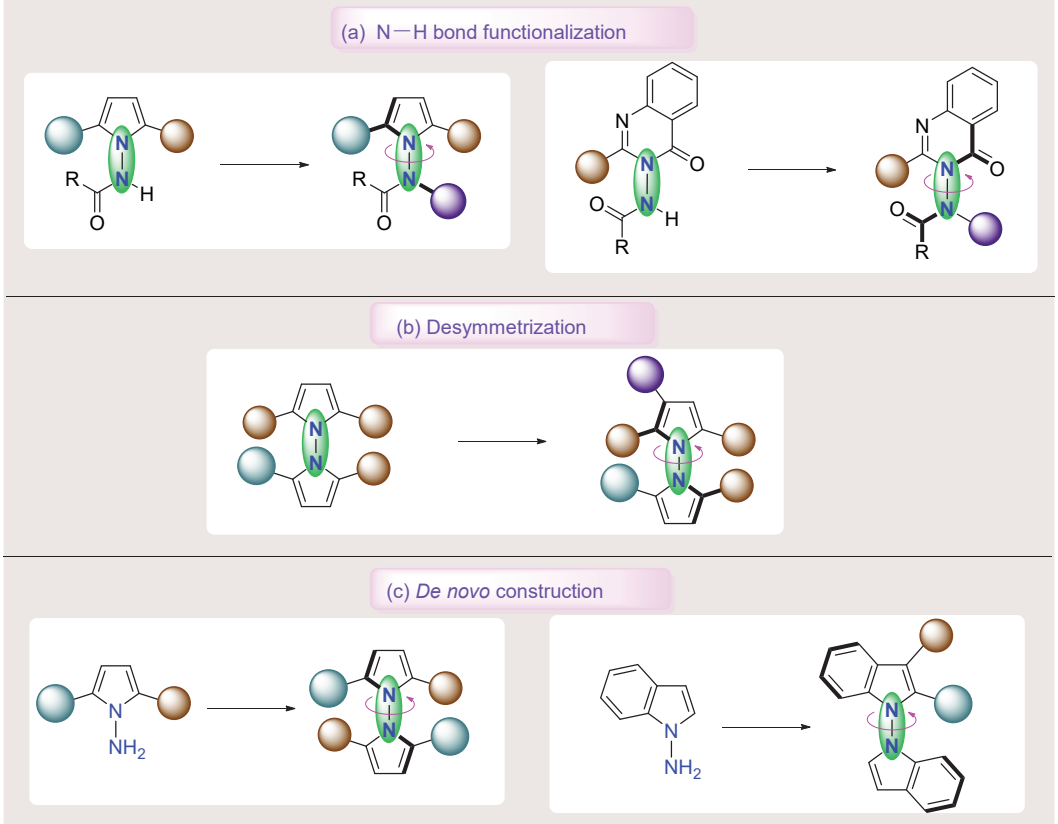
Figure 1 C—C, C—X and N—N atropisomers

many decades. Only in recent years, intriguing natural products, bioactive molecules, materials and ligands have been found to possess N—N axial chirality (Scheme 1, a).[7] For example, dixiamycin A and dixiamycin B are a pair of N—N atropisomers, and the former shows a higher activity against *Staph. aureus* and *B. thuringiensis* than the latter.[8] Furthermore, 2,2'-bis(diphenylphosphino)-1,10-bibenzimidazole (BIMIP) is known for an N—N atropisomeric phosphine ligand.[9] The traditional resolution methods by using chiral reagent or chiral column chromatography were the main way to obtain optically pure N—N atropisomers (Scheme 1, b).[6,10]

Direct catalytic asymmetric synthesis remained unexplored until 2021, when Lu/Houk[11] and Liu/Lu[12] independently reported their approaches to this issue. Since then, catalytic asymmetric preparation of N—N atropisomeric compounds has been developed rapidly into a booming field. Typically, there are three strategies for constructing various N—N axially chiral compounds (Scheme 2). Atroposelective N—H functionalization including *N*-allylic alkylation, *N*-acylation and *N*-alkylation represents among the effective means by modifying the central axis (Scheme 2, a). Catalytic asymmetric desymmetrization of prochiral substrates serves as an alternative to obtain excellent enantioselectivity (Scheme 2, b). In addition, the asymmetric assembly of N—N atropisomers can be achieved via *de novo* construction of pyrroles and indoles (Scheme 2, c). Despite these efforts, the stereotype that N—N atropisomers are unstable is still prevalent among chemists. Therefore, a timely review of this dynamic and fast-



Scheme 1 Representative molecules bearing an N—N axis and resolution strategy



Scheme 2 Catalytic asymmetric strategies for N—N atropisomers

developing research field appears to be of great significance to address this misconception. We hope to provide an overview of this emerging and exciting topic to our readers whose works are related to atropisomerism and beyond, facilitating their advances in asymmetric catalysis, natural product synthesis, and drug discovery.

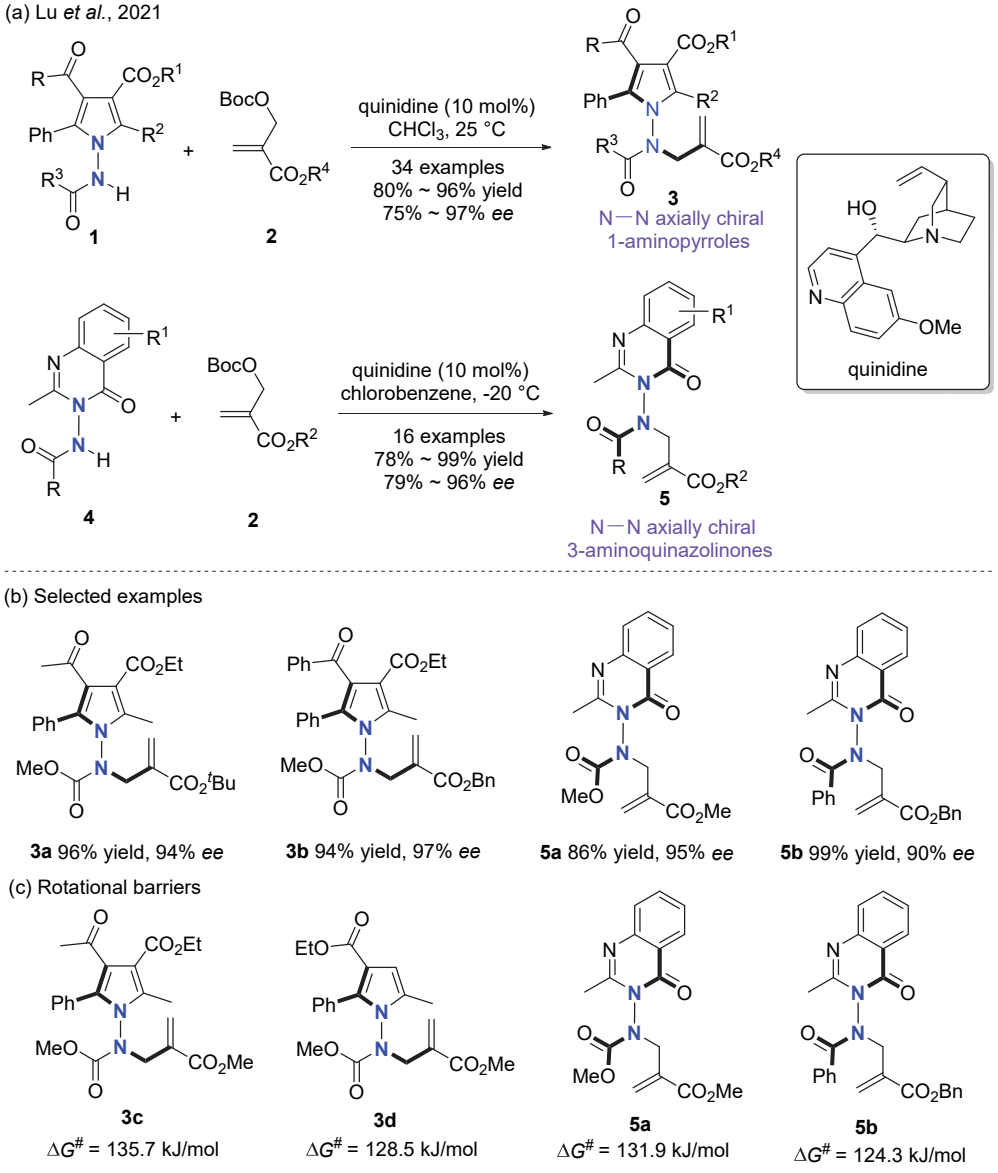
2 Asymmetric N—H bond functionalization

2.1 Asymmetric *N*-allylic alkylation

Asymmetric *N*-allylic alkylation is one of represents among the powerful reactions for N—H bond functionalization and is particularly benefit to the enantioselective preparation of C—X atropisomers.[13-14] In 2021, Lu/Houk and coworkers[11] creatively designed two classes of N—N axially chiral compounds and achieved their catalytic enantioselective synthesis via such an asymmetric *N*-allylic alkylation (Scheme 3). The chemical event involved a quinidine-catalyzed *N*-allylic alkylation reaction of 1-aminopyrroles **1** and 3-aminoquinazolinones **4** with Morita-Baylis-Hillman (MBH) carbonates **2**, providing a wide range of N—N axially chiral 1-aminopyrroles **3** and 3-aminoquinazolinones **5** in good yields and excellent enantioselectivities (Scheme 3, b). Density function theory (DFT) calculations had been carried out to elucidate the reaction mechanism of this quinidine-catalyzed *N*-allylic alkylation, and a remote enantio-control via hydrogen bonding interaction between the quinidine catalyst and the substrate was proved to be the key to success. The rotational barriers were also experimentally determined, demonstrating that these N—N axially chiral 1-aminopyrroles and 3-aminoquinazolinones were stable enough as common C—X atropisomers at ambient temperature (Scheme 3, c).

2.2 Asymmetric *N*-acylation

The isothiourea-catalyzed enantioselective *N*-acylation reaction has been developed as a powerful tool in organic synthesis.[15] Mechanistically, the nucleophilic addition of chiral isothiourea catalyst to acyl reagent allows the formation of a reactive chiral intermediate, which subsequently transfers the acyl group to substrates via chiral recognition. Despite the great success has been made in the enantioselective acylation of central chiral alcohols and amines, the application of acyl transfer in atroposelective synthesis remains far less developed.[16] In 2022, by utilizing atroposelective *N*-acylation, the Li group[17] achieved the asymmetric synthesis of N—N axially chiral compounds (Scheme 4). The acylation of 3-aminoquinazolinones **4** with *in situ* generated chiral acylisothiouronium intermediates from cinnamic anhydrides **6** and isothiourea featured mild conditions and a broad substrate scope, and afforded N—N axially chiral quinazolinone derivatives **7** in high yields with good to excellent enantioselectivities (Scheme 4, b). It was worth noting that product **7** contains two rotatable N—CO axes in addition to the N—N axis, and

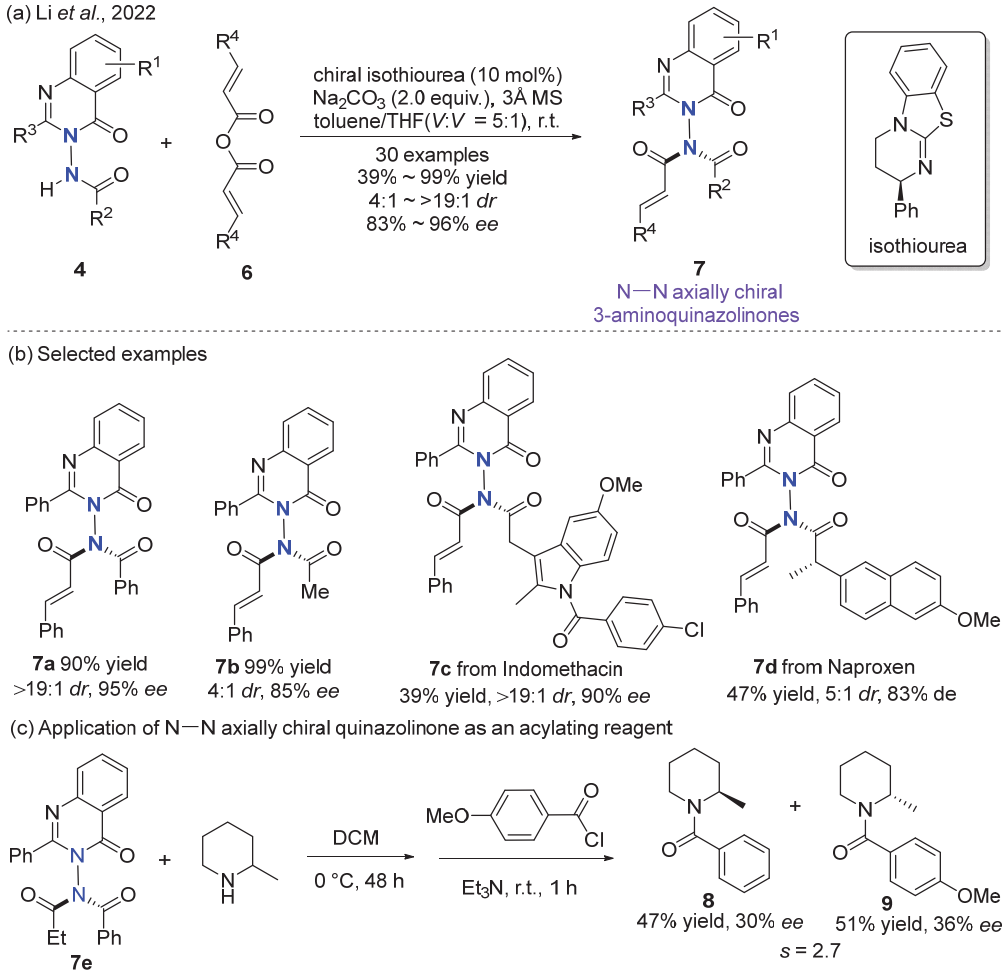


Scheme 3 Catalytic asymmetric *N*-allylic alkylation

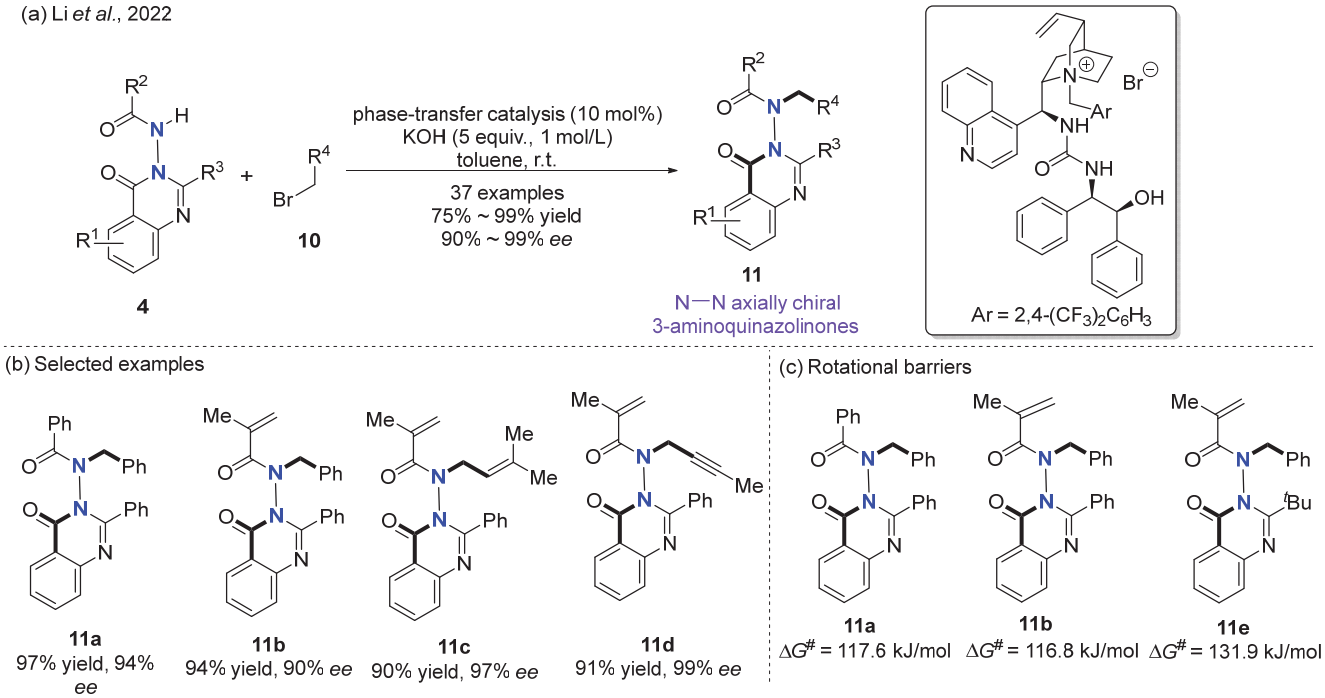
theoretically has eight isomers. DFT calculations suggested that the cooperation of multiple noncovalent interactions played a key role in the stereocontrol. Remarkably, the N—N axially chiral quinazolinone **7e** could be applied as a chiral acylation source in the kinetic resolution of racemic 2-methylpiperidine, albeit the selectivity factor was only 2.7 (Scheme 4, c).

Given the operational simplicity, mild reaction conditions, and environmentally benign nature, the asymmetric phase-transfer catalytic reaction has been recognized as a practical protocol for stereoselective synthesis.[18] Moreover, the enantioselective synthesis of axially chiral compounds has also benefitted from the asymmetric phase-transfer catalysis.[19] In this context, the Li group[20] reported the asymmetric synthesis of N—N axially chiral compounds by phase-transfer-catalyzed *N*-alkylation (Scheme 5). Under the catalysis of chiral ammonium salt, the *N*-alkylation reaction between 3-aminoquinazolinones **4** and alkylation reagents **10** proceeded very well under mild conditions, affording a variety of N—N axially chiral quinazolinone derivatives **11** in very good yields with high enantioselectivities (Scheme 5, b). DFT calculations revealed that the catalyst recognized the steric difference between the *ortho* substituents on the N—N axis via bifurcated hydrogen bond along with the π-π interaction to obtain high enantioselectivity. The determined rotational barriers from racemization experiments indicated that these N—N axially chiral products had suitable stability (Scheme 5, c).

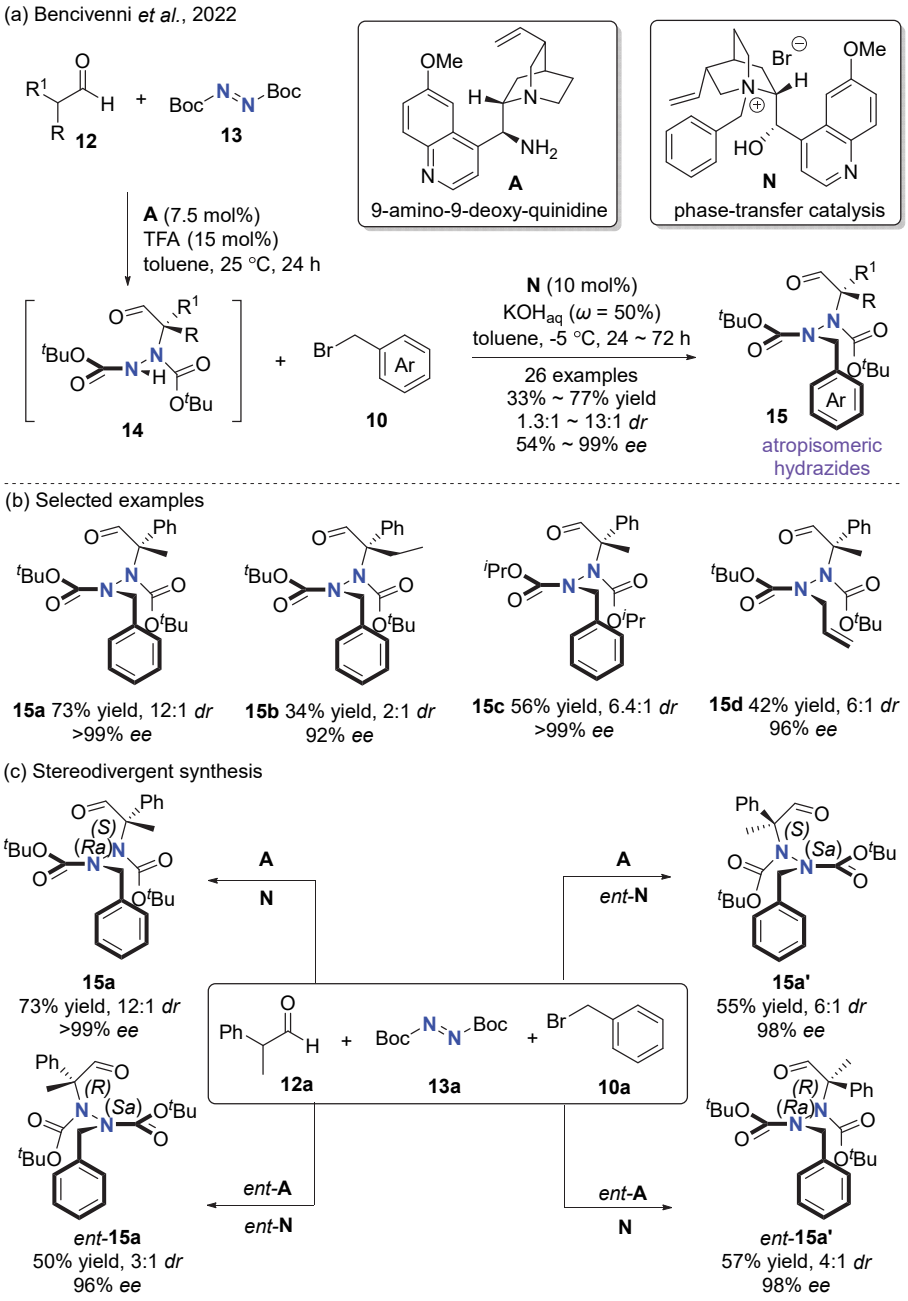
Very recently, the Bencivenni group[21] established a stereoselective synthesis of N—N atropisomeric hydrazides by a one-pot sequence protocol of enamine catalyzed *α*-amination of branched aldehydes and *N*-alkylation under phase-transfer catalysis (Scheme 6). Commercially available azodicarboxylate **13** was employed as precursors for the



Scheme 4 Catalytic asymmetric *N*-acylation



Scheme 5 Catalytic asymmetric *N*-alkylation



Scheme 6 Sequential catalysis protocol of *α*-amination and *N*-alkylation

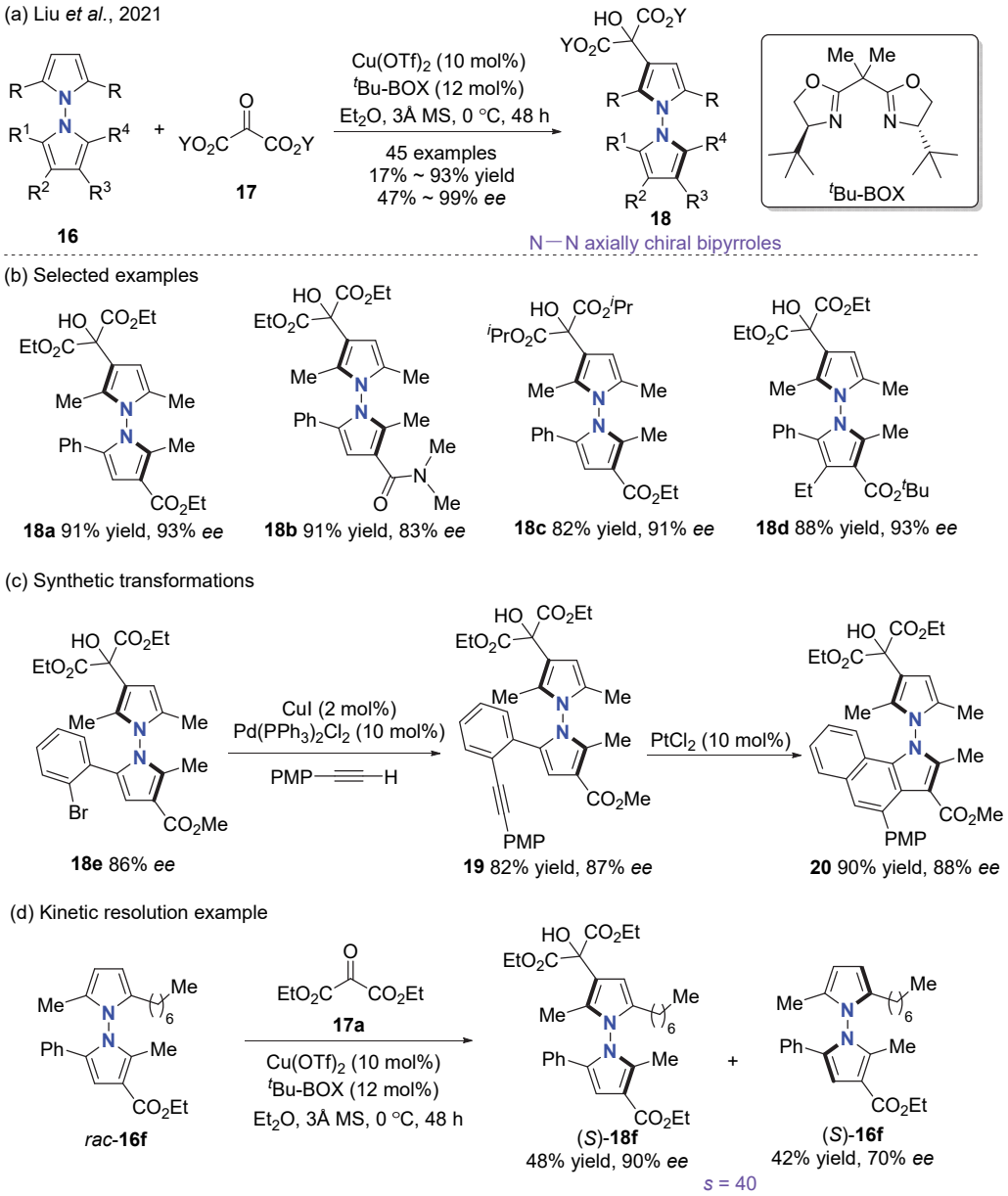
N—N single bond. The steric hindrance around the axis was increased sequentially in two distinct catalytic steps to produce rotationally stable chiral tetrasubstituted hydrazides **15**. Firstly, the 9-*epi*-9-amino-9-deoxy-quinidine (**A**) catalyzed nucleophilic addition reaction of azodicarboxylate **13** to aldehydes **12** gave highly enantioenriched trisubstituted hydrazides. The following phase-transfer catalytic *N*-alkylation of the second nitrogen atom ensured the formation of N—N rotationally hindered hydrazides **15** in a diastereoselective manner (Scheme 6, a). Notably, this multicomponent one-pot sequence could be applied to the stereodivergent synthesis of all four isomers in terms of the two distinct elements of central chirality and N—N axial chirality (Scheme 6, c). The author assumed that the favorable interaction between the ammonium cation of phase-transfer catalyst and the anion precursor of stereogenic N—N axis could be responsible for the stereocontrol.

3 Desymmetrization of prochiral N—N bipyrroles

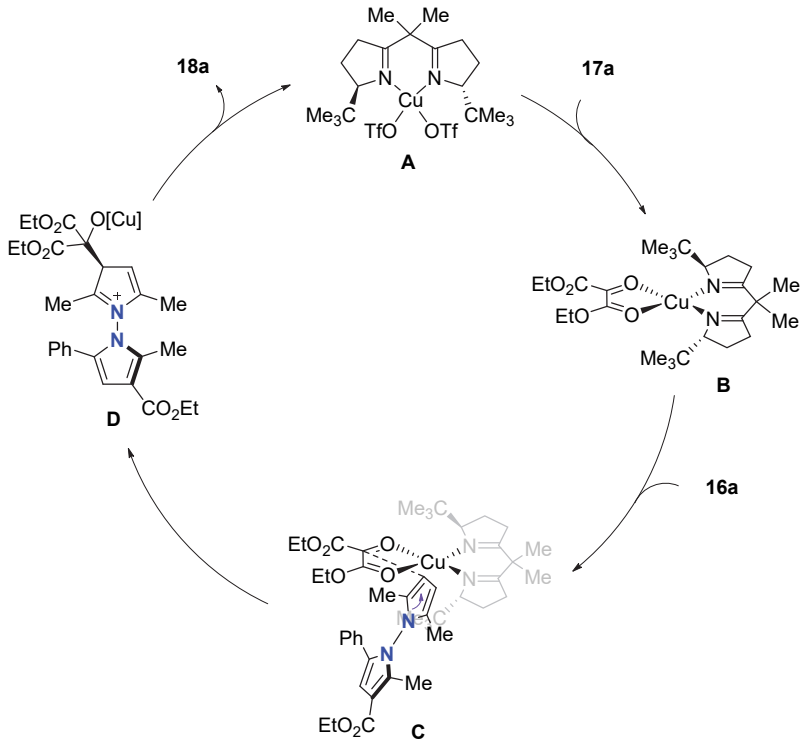
Desymmetrization has emerged as a powerful tool for the rapid construction of enantiomerically enriched molecules, especially those bearing challenging stereogenic axes.[22] In this context, Tan and co-workers[23] pioneered the atroposelective desymmetrization of prochiral pyrroles bearing a C—N axis via chiral phosphoric acid (CPA)-catalyzed Friedel-Crafts reaction. In 2021, Liu/Lu and co-workers[11]

successfully extended such desymmetrization strategy to the enantioselective synthesis of N—N bipyrroles (Scheme 7). Under the catalysis of Cu-bisoxazoline-complex, the Friedel-Crafts alkylation reaction of prochiral bipyrroles **16** with ketomalonates **17** took place in a high enantioselective manner and showcased good functional group compatibility (Scheme 7, b). Large-scale synthesis and derivatization of the N—N axially chiral bipyrroles **18** demonstrated the reliability and synthetic utility of this methodology (Scheme 7, c). Moreover, when racemic bipyrroles were employed, catalytic kinetic resolution occurred, affording the Friedel-Crafts products in excellent *ee* values but with low conversion even at the enhanced temperature (Scheme 7, d). To account for the observed stereochemical outcome, a plausible catalytic cycle was suggested (Scheme 8). The formation of a squareplanar Cu(II) complex **B** was crucial, wherein the nature of the C_2-symmetric BOX ligand formed a chiral pocket for chiral induction (**C** to **D**).

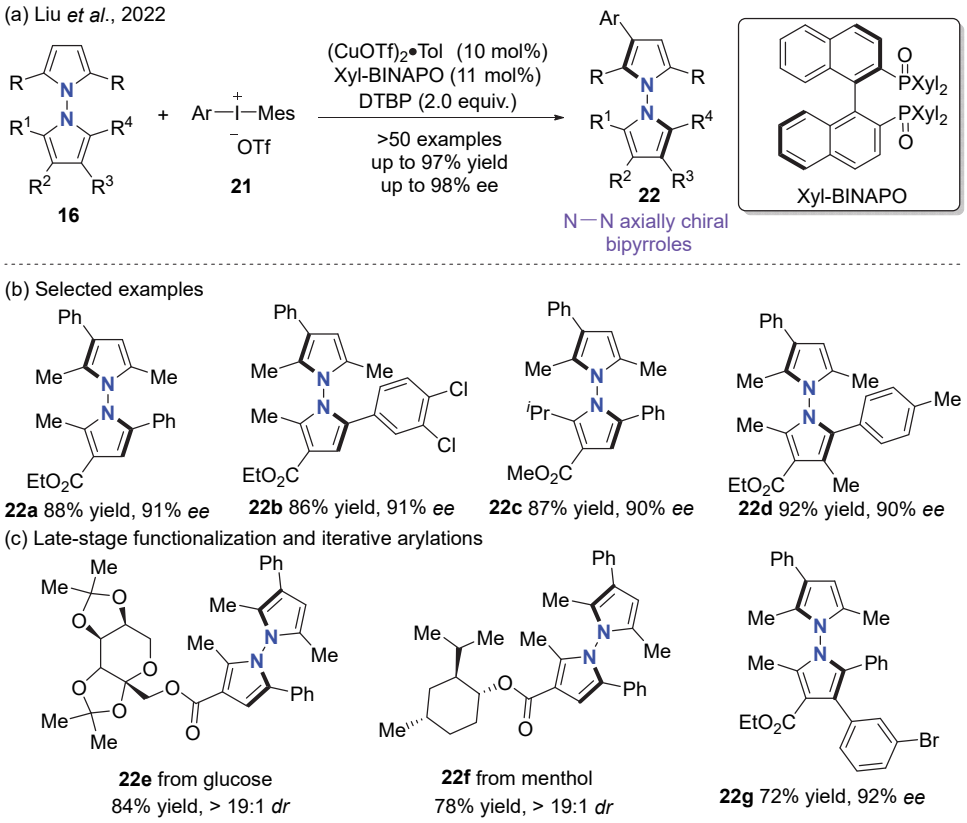
Cu-catalyzed electrophilic C—H arylation with diaryliodonium salts has been one of the most useful arylation strategies for C—C bond formations and synthesis of complex compounds.[24] However, the catalytic asymmetric version remains challenging and very few examples had been reported which all were established to construct central chirality.[25] Building on their previous work, Liu/Lu and co-workers[26] reported the copper(I) catalyzed desymmetric C—H arylation of prochiral bipyrroles **16** with diaryliodonium salts **21** (Scheme 9). The approach featured mild condition, broad substrate scope, good yield and excellent enantioselectivity (Scheme 9, b). Moreover, late-stage functionalization of natural products and iterative arylations have been demonstrated to afford valuable optically active polyaryl bipyrrole compounds (Scheme 9, c).



Scheme 7 Desymmetrization via enantioselective Friedel-Crafts alkylation



Scheme 8 Plausible catalytic cycle



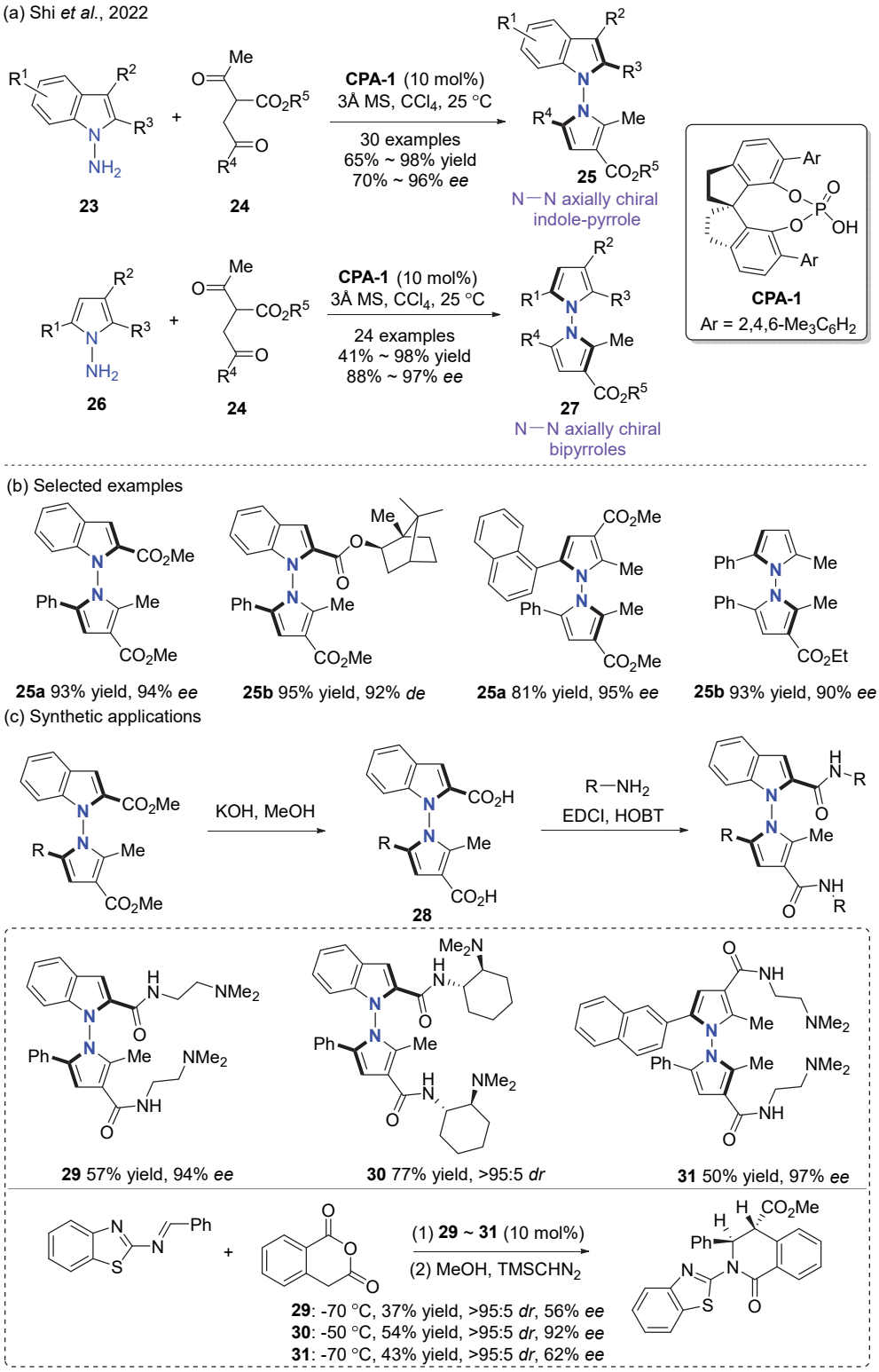
Scheme 9 Desymmetrization via enantioselective C–H arylation

4 *De novo* construction of aromatic rings

4.1 *De novo* construction of pyrroles

The atroposelective *de novo* construction of the (hetero-)aromatic ring provides an alternative strategy for the assembly of structurally diverse C—C and C—N atropisomers. In 2017, the Tan group[27] achieved the first catalytic asymmetric Paal-Knorr reaction, which enabled the

facile atroposelective synthesis of C—N axially chiral *N*-arylpyrroles via *de novo* construction of the pyrrole ring. In recent years, many groups have constructed a range of axially chiral indole-based scaffolds,[4e] including *N*-arylindoles,[28] C(3)-arylindoles,[29] C(2)-arylindoles,[30] bisindoles[31] and other axially chiral indoles.[32] However, the synthesis of N—N axially chiral indole is rarely reported and is more challenging. In 2022, by using this elegant strategy of *de novo* pyrrole formation, Shi/Zhang and coworkers[33] established a highly atroposelective synthesis of N—N axially chiral indole-pyrrole **25** and bispyrrole **27** scaffolds (Scheme 10). This CPA-catalyzed asymmetric



Scheme 10 Atroposelective *de novo* construction of the pyrrole ring by Shi/Zhang and coworkers

Paal-Knorr reaction of *N*-aminoindoles **23** or *N*-aminopyrroles **26** with 1,4-diketones **24** was conducted smoothly at ambient temperature. It was reported that some of the prepared N—N axially chiral molecules displayed potent anticancer activities (Scheme 10, b). Additionally, further transformations of the products could lead to some new organocatalysts **29**～**31**, exhibiting promising applications for asymmetric catalysis (Scheme 10, c). A plausible reaction pathway involving a dual-hydrogen-bonding transition state was suggested (Scheme 11). The **CPA-1** catalyst played an important role in this process by facilitating the condensation of the *N*-aminoindole with the 1,4-diketone, the cyclization of enamine **B**, as well as the dehydration of intermediate **C**. It is worth noting that these N—N axially chiral heterocycles show preliminary cytotoxicities against QGP-1 cancer cells and reveal the underlying application for the drug discovery.

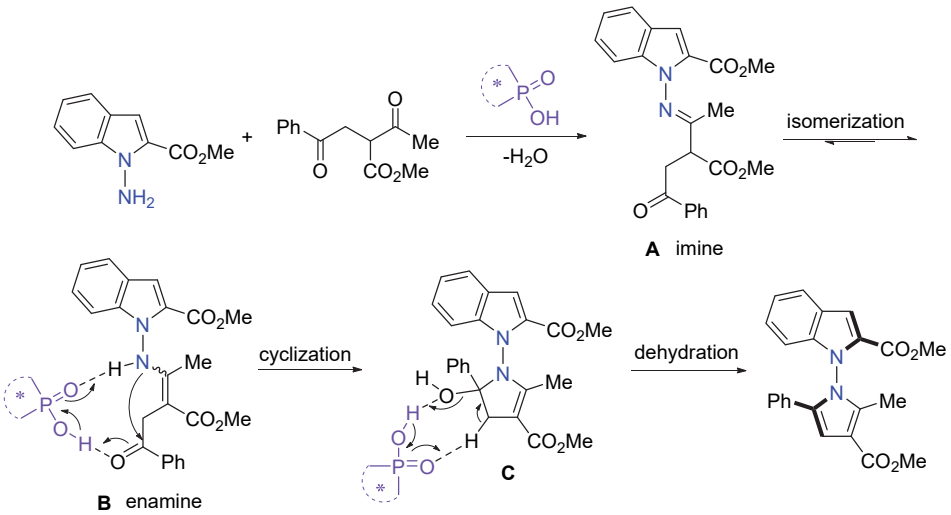
Independently, Zhao/Yang and coworkers[34] presented a similar asymmetric Paal-Knorr pyrrole formation for the highly efficient atroposelective synthesis of axially chiral 1,1'-bipyrroles bearing an N—N linkage from simple hydrazine and 1,4-diones (Scheme 12). Interestingly, with or without a Fe-co-catalyst, this CPA-catalyzed transformation proceeded in an intriguing enantiodivergent manner. Namely, **CPA-2** catalyst led to (*R*)-bipyrroles, while the combination of **CPA-2** catalyst and $Fe(OTf)_3$ resulted in (*S*)-products. Both catalytic systems allowed the synthesis of N—N axially chiral bipyrroles **32** in good yields with excellent enantioselectivities (Scheme 12, b). To demonstrate the utility, the derivatizations of the readily constructed N—N axially chiral compounds were implemented (Scheme 12, c). Among them, the diacid derivative **36** bearing the axially chiral N—N bipyrrole framework showed a preliminary potential as a chiral catalyst in an enantioselective allylation of aldehydes with allyl-Bpin.

4.2 *De novo* construction of indoles

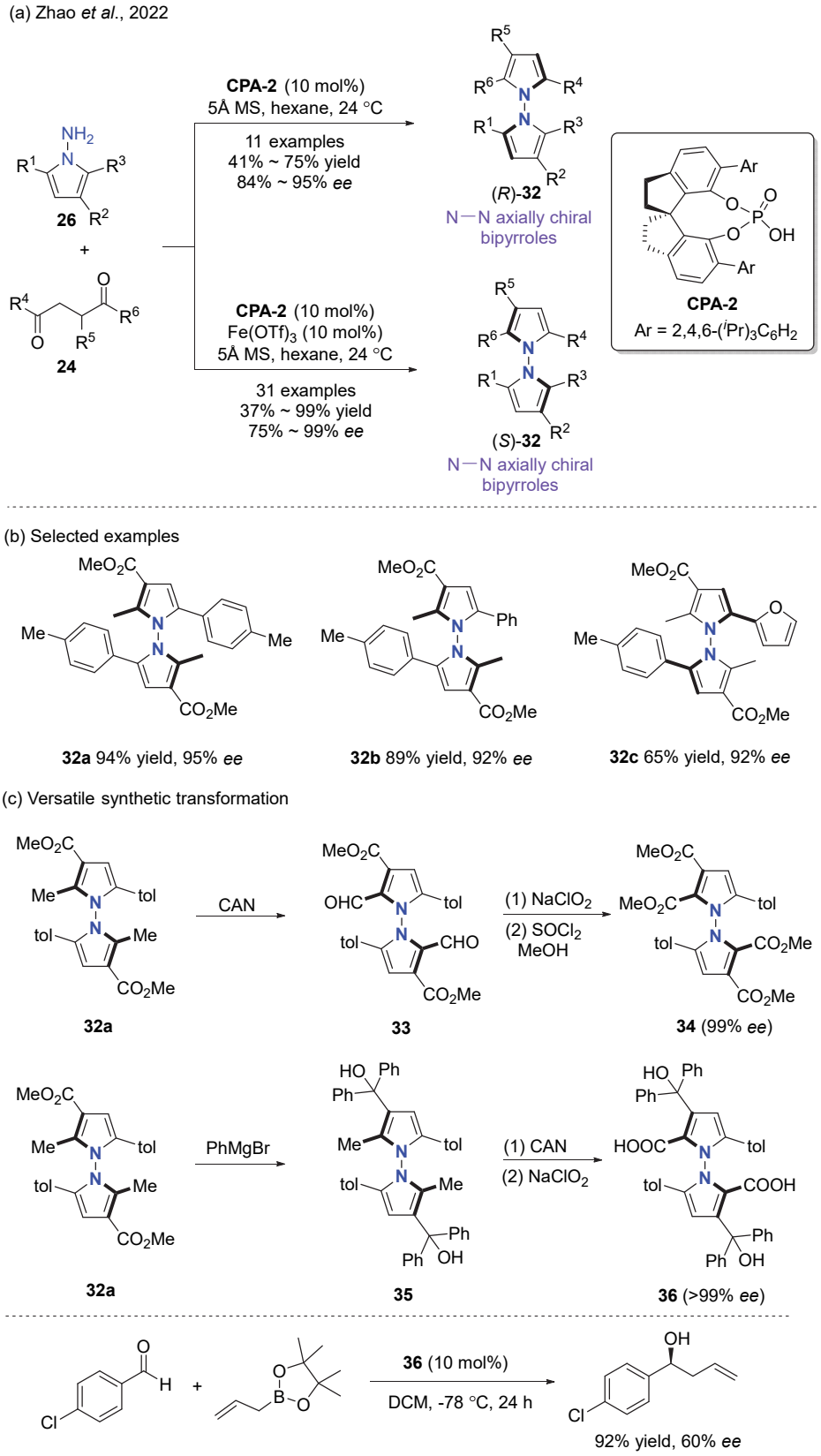
N—N bisindole atropisomers are a common motif in natural products (Scheme 1), which are of great importance for exploration in modern pharmaceuticals and organic chemistry. In this context, Liu/Li and coworkers[35] documented an elegant enantioselective synthesis of N—N bisindole atropisomers via the palladium-catalyzed *de novo* construction of one indole ring (Scheme 13). The chemical event involved a two-step enamine formation/asymmetric *N*-arylation process. Under the catalysis of TsOH, *α*-arylketoesters **37** were condensed with 1-amine indoles **23** to yield (*Z*)-specific enamine isomers **38**. The subsequent intramolecular cyclization was enabled by a chiral Pd-complex catalyzed Buchwald-Hartwig amination. By using this cascade protocol, structurally diverse N—N axially chiral bisindole **39**, indole-pyrrole, indolecarbazole, and non-biaryl-indole atropisomers were obtained in good yields with excellent enantioselectivities (Scheme 13, b). The experimental determination and theory calculation indicated that those synthesized N—N bisindoles processed high rotational barriers and were configurationally stable at a higher temperature (Scheme 13, c). Furthermore, through density functional theory (DFT) calculations, mechanistic investigations concluded that the reaction proceeded with aryl bromide oxidative addition, N—H deprotonation, intramolecular rearrangement to form a six-membered palladacycle, and reductive elimination. While the deprotonation was the rate-limiting step, the rearrangement process was the origin of enantioselectivity.

4.3 *De novo* construction of bis-quinazolinones

Despite the achievements in enantioselective synthesis of N—N axially chiral pyrroles and indoles via a mono ring formation strategy, constructing the N—N atropisomers by dual ring formation remains challenging and elusive. Meanwhile, the N—N axially chiralquinazolinone is a privileged skeleton, which is widely found in natural products and biologically active compounds.[7a] In 2017, the Tan group[36] developed a general and efficient one-pot approach to access enantiomerically pure *N*-arylquinazo-

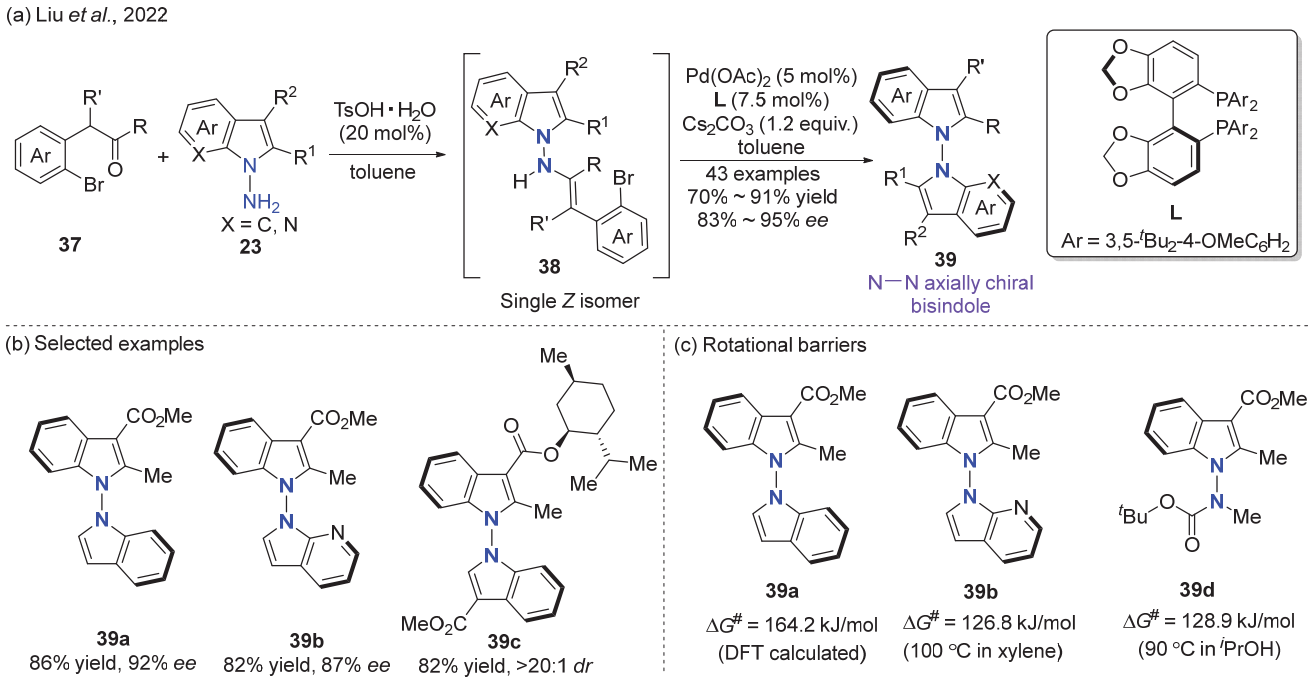


Scheme 11 Plausible mechanism

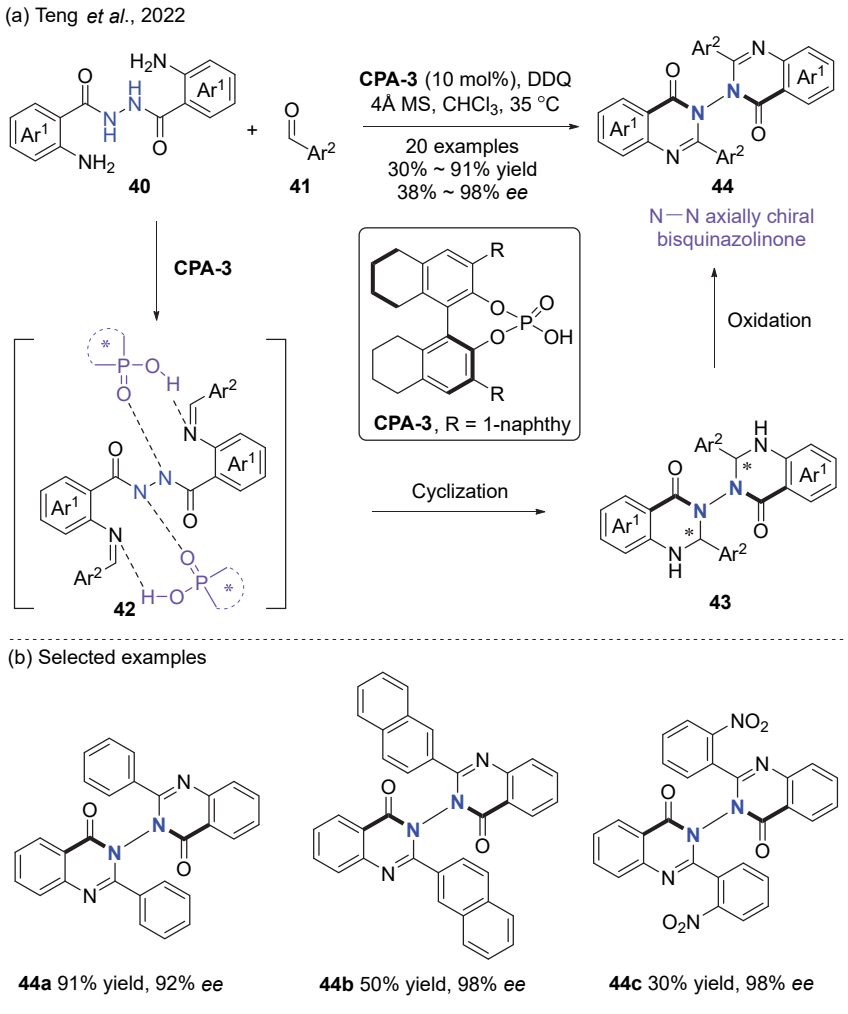


Scheme 12 Atroposelective *de novo* construction of the pyrrole ring by Zhao/Yang and coworkers

linones via CPA-catalyzed atroposelective *de novo* construction of mono-quinazolinone ring. Inspired by Tan's work, Liu/Teng and coworkers[37] very recently reported their CPA-catalyzed *de novo* dual ring formation strategy for the enantioselective synthesis of N—N bis-quinazolinone atropisomers (Scheme 14). The reaction was initiated



Scheme 13 Atroposelective *de novo* construction of the indole ring



Scheme 14 Atroposelective *de novo* construction of the dual quinazolinone rings

by the condensation of 2-amino-*N*′-(2-aminobenzoyl)benzohydrazides **40** with benzaldehydes **41**. The resulting imine intermediate **42** underwent two enantioselective intramolecular cyclization processes via CPA-catalysis, leading to the centrally chiral intermediate **43**. Finally, oxidation-enabled central-to-axial chirality transfer yielded the desired N—N axially chiral 3,3'-bisquinazolinones **44** in good yields with good enantioselectivities (Scheme 14, b).

5 Summary and outlook

The N—N bond is widely found in natural products and bioactive compounds. The atropisomerism of N—N bond, however, had been dismissed for a long time. Since the first report in 2021, catalytic asymmetric synthesis of N—N atropisomers has attracted considerable research efforts and has been developed rapidly into an emerging area. In this timely review, we critically illustrate these recent achievements according to the reaction types, which mainly include the asymmetric N—H bond functionalization, the asymmetric desymmetrization, and the atroposelective *de novo* construction of (hetero-)aromatic rings. Despite these impressive advances, this field is still in its infancy and far less developed compared to the well-established C—C and C—N atropisomers. In addition to further developing the abovementioned methods, new catalytic asymmetric strategies for N—N atropisomers are highly desired. For instance, (dynamic) kinetic resolution of molecules with pre-existing stable stereogenic axes is a traditional protocol to obtain C—C atropisomers, but has not been successfully applied to N—N atropisomers. While challenging, atroposelective construction of a N—N bond is the most direct approach and worth more efforts. Furthermore, the scope of N—N atropisomers is mainly limited to cyclic compounds linked by a N—N bond, such as bispyrroles and bisindoles. Therefore, we expect more well-designed N—N atropisomeric molecules to emerge. The last but not the least, it is highly desirable to exploit the practical values of these prepared N—N axially chiral frameworks, *i.e*., applications in asymmetric catalysis, pharmaceutical industry, or materials science. This review aims to provide a timely overview of this exciting and emerging research area, with a view to attracting more attention from both industry and academia, and pushing this promising research field to a greater height.

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