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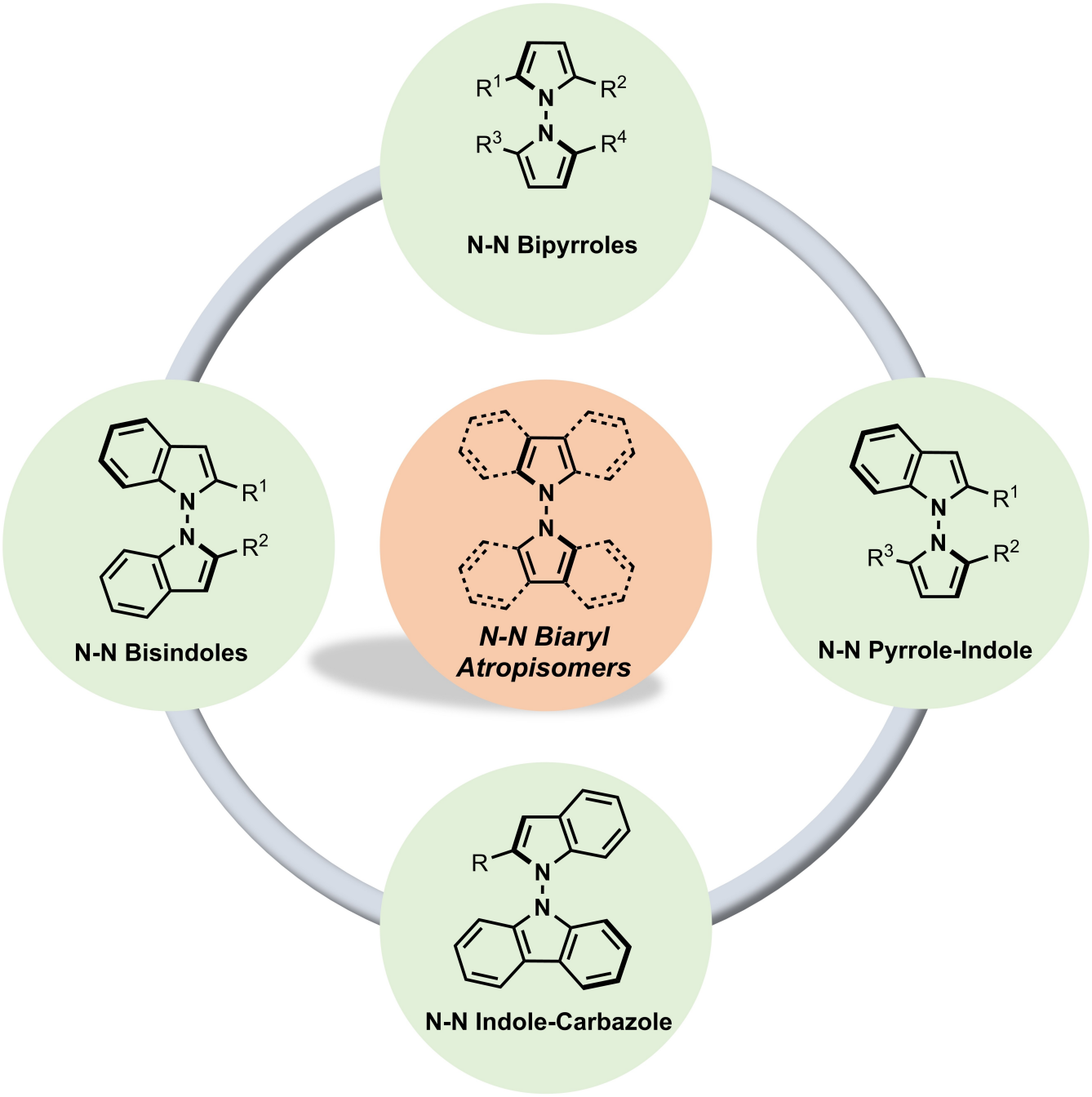
Catalytic Asymmetric Synthesis of N–N Biaryl Atropisomers

Jia Feng[a] and Ren-Rong Liu*[a]



Atropisomers have emerged as important structural scaffolds in natural products, drug design, and asymmetric synthesis. Recently, N–N biaryl atropisomers have drawn increasing interest due to their unique structure and relatively stable axes. However, its asymmetric synthesis remains scarce compared to its well-developed C–C biaryl analogs. In this concept, we summarize the asymmetric synthesis of N–N biaryl atropisomers including N–N pyrrole–pyrrole, N–N pyrrole–indole, N–N indole–indole, and N–N indole–carbazole, during which a series synthetic strategies are highlighted. Also, a synthetic evolution is briefly reviewed and an outlook of N–N biaryl atropisomers synthesis is offered.

1. Introduction

The last decades have witnessed the boom of atropisomer synthesis due to its vital importance in natural products, the pharmaceutical industry, organic materials, and asymmetric synthesis.[1] Out of all types of atropisomers, C–C biaryl atropisomers[2] and C–N biaryl atropisomers[3] occupy the biggest part and have made considerable achievements in both asymmetric synthesis and application. Compared to the well-developed C–C atropisomers or C–N atropisomers, research on N–N atropisomers synthesis remains scarce (Scheme 1a). Biaryl atropisomers featuring an N–N axis are common structural units in natural products and bioactive molecules (Scheme 1b).[4] The asymmetric synthesis of N–N biaryl atropisomers is recognized as appealing, yet challenging, and has been overlooked for a long time until recently.[5]

The core concern of its asymmetric synthesis is the stability of the stereogenic N–N axis. The overlap between the ortho substituents of N–N biaryl atropisomers bearing a 5-membered ring is smaller than that bearing a 6-membered ring, which results in a relatively poor stability under similar conditions theoretically. In 1931, Adam achieved the resolution of 2,2′,5,5′-tetramethyl-1,1′-bipyrrole-3,3′-dicarboxylic acid successfully, which indicated that N–N bipyrroles atropisomers were conformationally stable to separate.[6] For a long time after that, the asymmetric synthesis of N–N biaryl atropisomers remains unexplored except for two examples of the resolution by chiral high-performance liquid chromatography (HPLC). In 2014, Pierini and Cirilli completed the resolution of N–N bibenzimidazoles via chiral HPLC.[7] Recently, Higashibayashi got the enantioenriched N–N biscarbazoles atropisomers by chiral HPLC assisted resolution and found that the obtained atropisomers didn't racemize until its degradation through control experiments.[8]

In 2021, Liu and Lu accomplished the asymmetric synthesis of N–N bipyrroles atropisomers through a desymmetrization process, which was ranked as the first catalytic asymmetric synthesis of N–N biaryl atropisomers.[9] After that, a series of synthetic strategies were developed to access N–N biaryl atropisomers. In this concept, we will focus on the asymmetric synthesis of the N–N biaryl atropisomers scaffolds including N–N bipyrroles atropisomers, N–N pyrrole–indole atropisomers, N–N bisindoles atropisomers, N–N indole–carbazole atropisomers. A conclusion and perspective on synthesis and application is given.

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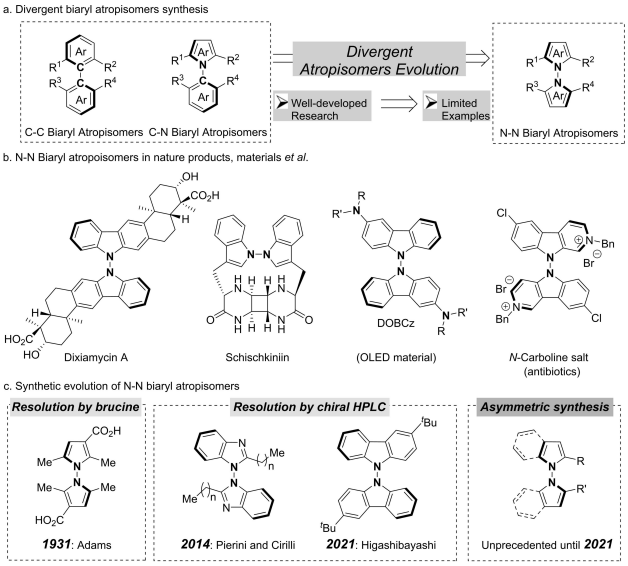
2. N–N Bipyrroles Atropisomers

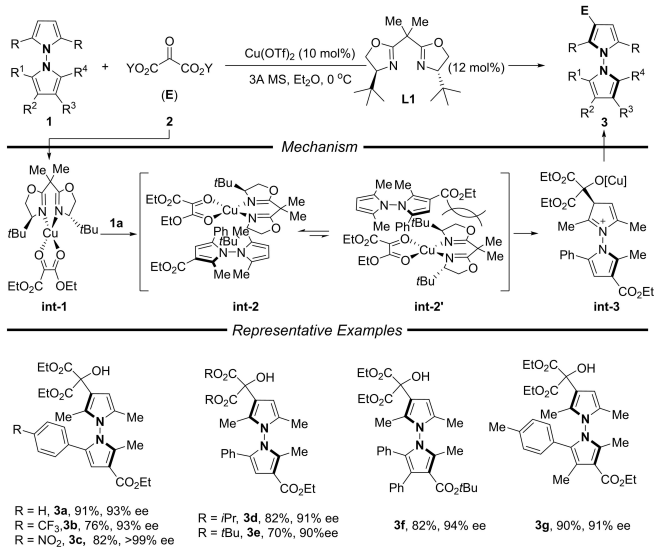
2.1. Desymmetrization Strategy

In recent years, desymmetrization of prochiral molecules has attracted considerable interests because of their synthetic utility in the preparation of atropisomers especially for C–C or C–N atropisomers.[10] When the simple substrates bipyrroles are used, the much more reactive sites on pyrroles offer access to achieve its asymmetric synthesis via desymmetrization. Some research base on nucleophilic addition, arylation, or alkylation has been conducted and furnished the enantioselective synthesis of N–N biaryl atropisomers efficiently.

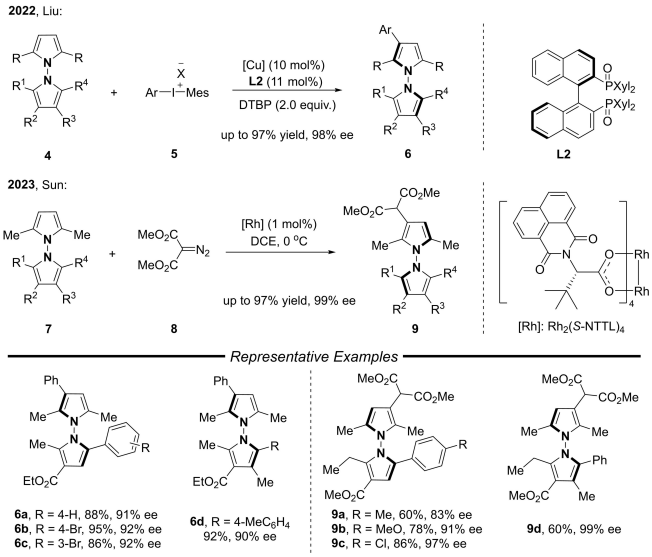
In 2021, Liu and the co-author achieved the first catalytic synthesis of N–N atropisomers through copper-catalyzed asymmetric Friedel-Crafts alkylation.[9] With Cu(II) and chiral oxazoline ligand as the catalyst, achiral bipyrroles went on the asymmetric nucleophilic addition smoothly to deliver axially chiral N–N biaryl atropisomers with excellent yield and enantioselectivity (Scheme 2). A plausible mechanism with a stereo-control process was proposed. Initiate coordination of ketomalonates **2** with copper and **L1** gave the **int-1**, which would be attacked by pyrroles in the further step. Due to the steric hindrance of **L1**, **int-2** is more favorable than **int-2′**. **Int-2** would conduct the



Scheme 1. N–N biaryl atropisomers scaffold and its asymmetric synthesis.



Scheme 2. Atropisomeric Friedel-Crafts alkylation for N–N biaryl atropisomers.



Scheme 3. Desymmetrization of bipyrroles for N–N biaryl atropisomers synthesis.

asymmetric addition to give **int-3** bearing a stereogenic center, which affords axially chiral compound **3** by a central to axial chirality transfer process. Through the atropisomeric Friedel-Crafts alkylation, a series of N–N biaryl bipyrroles were achieved with more than 90% enantioselectivity.

Later, Liu completed the atropisomeric arylation of bipyrroles with diaryliodonium salt to give N–N biaryl atropisomers (Scheme 3).[11] With a bis(phosphine) dioxide ligand **L2**, the asymmetric copper-mediated arylation went on efficiently to yield N–N bipyrroles atropisomers with excellent enantioselectivity. Then, Sun achieved the synthesis of N–N bipyrroles atropisomers with similar substrates via a rhodium-catalyzed C–H bond insertion of carbene complex (Scheme 3).[12] Using Rh_2(*S*-NTTL)$_4$ as the catalyst, the atropisomeric C–H insertion went on successfully with up to 99% ee.

2.2. De Novo Construction of Pyrrole

De novo synthesis of pyrrole cycles with a chiral catalyst appeared to be an efficient approach to N–N biaryl atropisomers. Paal-Knorr reaction is recognized as a C–N coupling method featuring the condensation of ketone and amines, which has been applied in the construction of central[13] and C–N axial[14] chirality successfully. In 2022, Zhao and Yang accomplished the double Paal-Knorr reaction for the enantiodivergent synthesis of N–N bipyrroles via the pyrrole construction strategy (Scheme 4). Starting with the synthesis of N-amino pyrrole from diketone and hydrazine hydrate, the second pyrrole construction assisted with Lewis acid and chiral phosphoric acid (CPA) furnished the atropisomeric synthesis of N–N bipyrroles. With or without $Fe(OTf)_3$, both enantiomers of **14** could be achieved with excellent enantioselectivity. The methodology has a broad substrates scope and ortho aryl around N–N axis of **14** or ent-**14** could be substituted with different moieties.

3. N–N Pyrrole–Indole Atropisomers

3.1. De Novo Synthesis of Indole/pyrrole derivatives

With the N-amino indoles as starting materials, Shi and Zhang completed the N–N pyrrole–indole atropisomers synthesis via a CPA-catalyzed pyrrole ring formation in 2022 (Scheme 5).[15] The spiro skeleton phosphoric acid **C2** was approved to be optimal and a series of divergent substituted N–N atropisomers were

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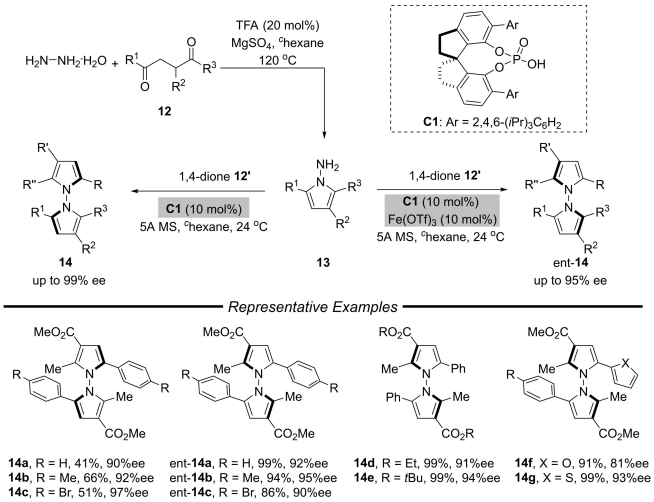
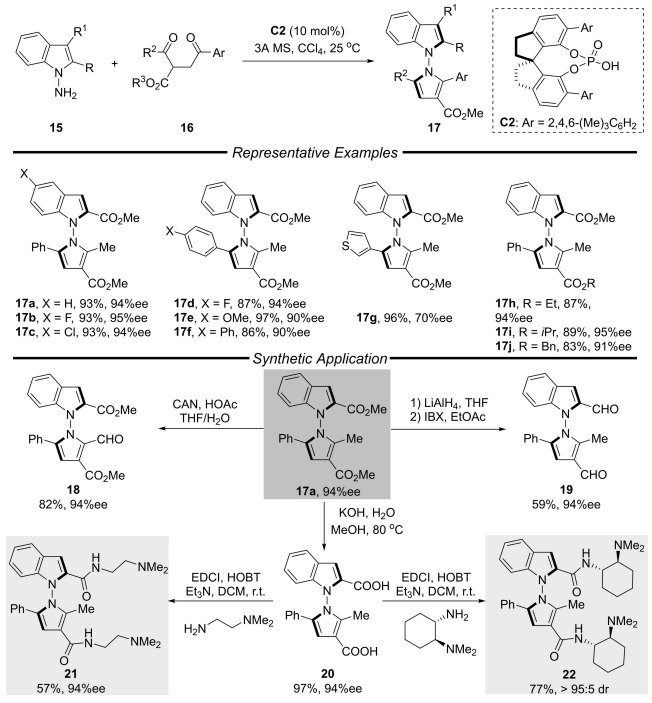


Scheme 4. Double Paal-Knorr reaction for N–N bipyrrole atropisomers synthesis.



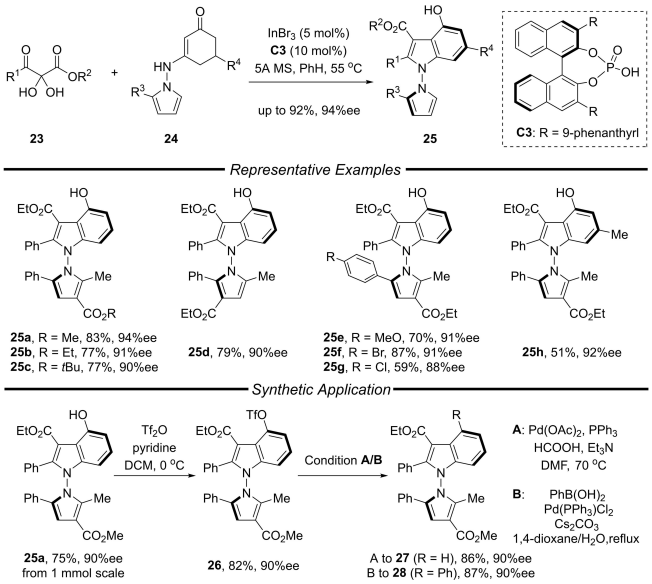
Scheme 5. De novo ring formation for N–N pyrrole–indole synthesis.

accessed with excellent yields and enantioselectivity. The obtained enantioenriched atropisomers was used as "platform molecules", which could be readily transformed into valuable molecules like chiral catalyst. With ceric ammonium nitrate (CAN) as the oxidant, the methyl group could be converted to aldehyde moiety smoothly (**17a** to **18**). After simple oxidation and reduction, the dialdehyde **19** could be obtained from **17a** without the erosion of enantioselectivity. Hydrolysis of diesters **17a** delivers **20**, which went on the amidation with acylic amines or chiral cyclic diamines to give **21** or **22**. The highly enantioenriched **21** or **22** could be used as a catalyst in (2 + 4) cyclization with moderate to excellent enantiocontrol.

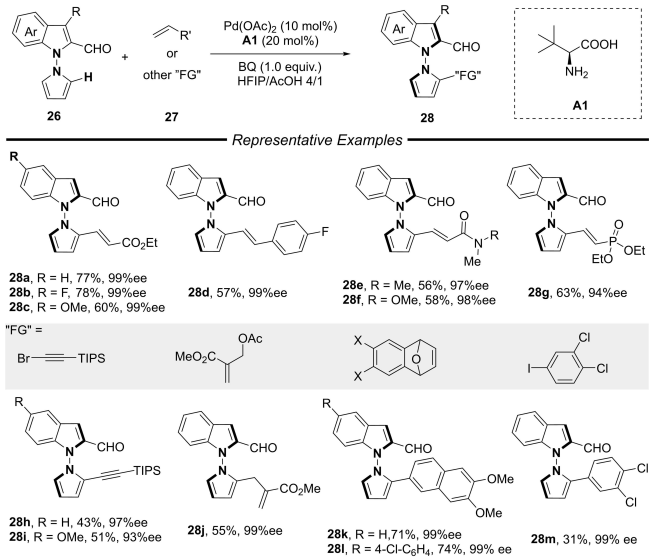
Doyle indolization is an efficient tool to construct indole cycles, which has been applied to asymmetric synthesis.[16] Inspired by the Doyle's pioneer work,[17] Lin accomplished the C–N atropisomers synthesis via a CPA-mediated three-component cascade reaction.[18] Recently, Yang and Zhao reported a CPA-catalyzed indolization of 2,3-diketoesters and N–pyrrole/indole enamines to offer N–N pyrrole–indole atropisomers (Scheme 6).[19] Through the protocol, divergent substituted N–N pyrrole–indole atropisomers were obtained with excellent enantioselectivity. Also, N–N indole–indole atropisomers could be accessed with an average of 81 % ee, which was lower than that of N–N pyrrole–indole atropisomers. The hydroxyl group on **25a** could be converted into triflate, which could conduct palladium-mediated hydrogenation or Suzuki–Miyaura coupling to give **27** or **28** respectively.

3.2. Asymmetric C–H Functionalization

Asymmetric C–H functionalization has been used as a highly efficient and economical method to construct chirality during the last decades, which includes center chirality, axial chirality, and planar chirality et al. Recently, C–H activation especially directing C–H activation has been applied to N–N atropisomers synthesis along with C–C atropisomers and C–N atropisomers successfully. Transient directing group (TDG) mediated C–H activation was first reported by Yu,[20] and further developed for atropisomers synthesis by Shi and others later.[21] Inspired by these achievements, Liu achieved a TDG-directed atropisomeric C–H activation for N–N pyrrole–indole atropisomer synthesis (Scheme 7).[22] With the assistance of $Pd(OAc)_2$ and chiral amino acid **A1**, achiral substrates **26** undergo the asymmetric C–H activation and coupling with functional reagents like alkenes, alkynyl bromides, acrylates, or other arylated reagents smoothly to afford N–N pyrrole–indole atropisomers with excellent



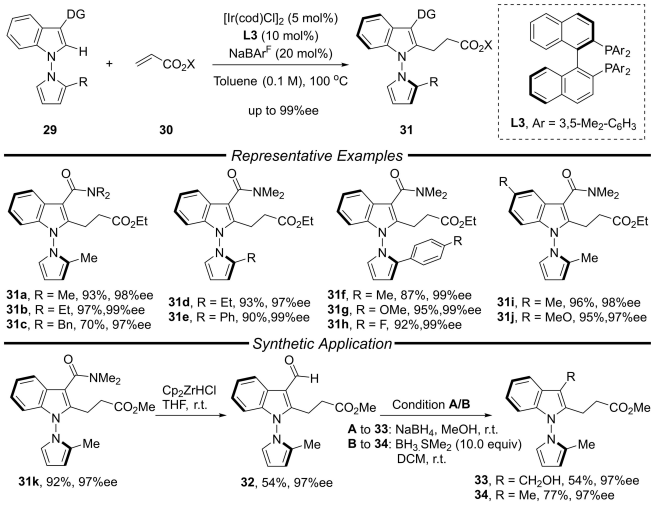
Scheme 6. Asymmetric indolization for N–N pyrrole–indole synthesis.



Scheme 7. Transient directing group mediated asymmetric synthesis.

enantioselectivity. The methodology offers an excellent approach to the divergent N–N atropisomers.

Iridium-catalyzed asymmetric C–H alkylation has a broad application in asymmetric synthesis, ranking as an efficient way to construct chirality.[23] Very recently, You developed an elegant iridium-catalyzed asymmetric C–H alkylation reaction to deliver a series of N–N pyrrole–indole atropisomer scaffolds (Scheme 8).[24] Under iridium-catalysis derived from $[Ir(COD)Cl]_2$ and chiral ligand **L3**, achiral substrates **29** went on the asymmetric C–H alkylation smoothly to afford N–N atropisomers with excellent yield and enantioselectivity. Also, N–N bipyrroles atropisomers could be achieved through the protocol. The obtained enantioenriched product **31k** could be transformed to aldehydes **32**, of which the aldehyde group could be converted to alcohol or methyl group under different reductive conditions.



Scheme 8. Iridium mediated asymmetric C–H activation.

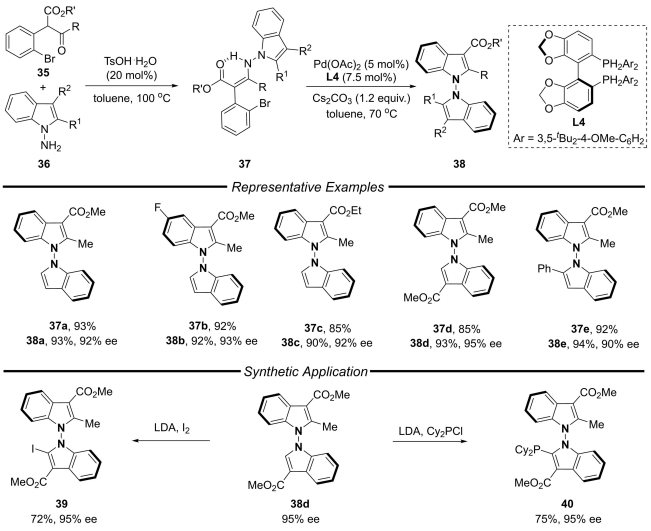
4. N–N Indole–Indole Atropisomers

Due to its high efficiency and selectivity, the Buchwald-Hartwig reaction has emerged as a highly efficient method for asymmetric synthesis.[25] In 2021, Liu disclosed an asymmetric Buchwald-Hartwig amination of amidine to construct C–N benzimidazole atropisomers.[26] Subsequently, the same group completed a two-step cascade reaction to afford N–N indole–indole atropisomer, which was demonstrated by an intramolecular Buchwald-Hartwig reaction (Scheme 9).[27] Using palladium and chiral ligand **L4** as catalyst, the cyclization proceeded smoothly to deliver N–N atropisomer with excellent enantioselectivity. Treating N–N bisindoles **38d** with lithium diisopropylamide (LDA) and iodine, iodide **39** was readily obtained without erosion of the enantioselectivity. Furthermore, dicyclohexyl phosphate group could be installed into **38d** to afford **40**, which could be used as an N–N atropisomeric scaffold ligand.

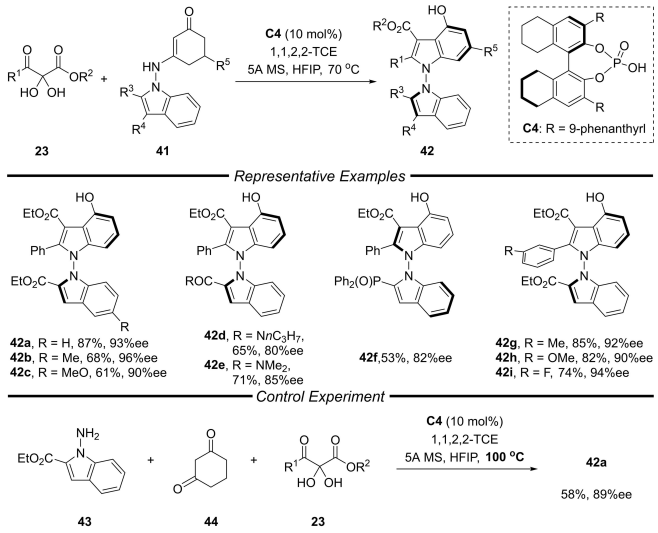
In 2023, Shi reported the CPA-catalyzed N–N indole–indole atropisomers synthesis via a de novo indole formation strategy (Scheme 10).[28] With BINOL-scaffold **C4** as a catalyst, the asymmetric indolation went on smoothly to give atropisomers **42** with excellent enantioselectivity. The methodology featured a broad substrate scope and the obtained N–N indole–indole atropisomers showcase some degree of biological activity towards cancer cells. Also, a series of N–N pyrrole–indole atropisomers could be obtained with up to 98% ee. To extend the potential application, a three-components experiment using N-amino indole, diketone, and 2,3-diketoester was conducted, affording 58% yield with 89% enantioselectivity.

5. N–N Indole–Carbazole Atropisomers

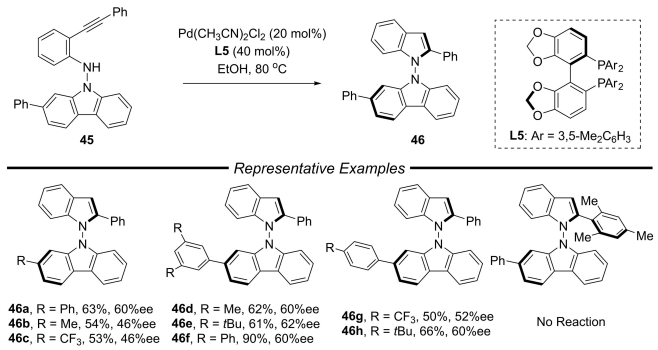
Asymmetric hydroamination was regarded as a challenging task, which was utilized for the C–N atropisomers synthesis by



Scheme 9. Asymmetric Buchwald-Hartwig amination for N–N indole–indole atropisomers synthesis.



Scheme 10. CPA catalyzed asymmetric indolization.



Scheme 11. Asymmetric hydroamination for N–N indole–carbazole atropisomers.

Kitagawa in 2010.[29] In the very recent, Sparr accomplished the asymmetric hydroaminocyclizations for N–N indole–carbazole atropisomers synthesis via palladium catalysis (Scheme 11).[30] With the assistance of palladium and **L5**, the cyclization process starting from the alkyne **45** went on smoothly to afford N–N atropisomers with moderate to good yields and enantioselectivity. A variety of N–carbazole anilines was applied to the protocol that provides N–N indole–carbazole atropisomers with up to 60% ee. However, there was no reaction with ortho steric hindrance on the phenyl group.

6. Conclusion and Perspective

Given its importance in natural products, drug design, and asymmetric synthesis, the asymmetric synthesis of N–N biaryl atropisomers scaffolds has drawn considerable attention and has achieved tremendous development in the last decade. A series of structure-divergent atropisomers including N–N bipyrroles atropisomers, N–N pyrrole–indole atropisomers, N–N bisindoles atropisomers, and N–N indole–carbazole atropisomers have been obtained through catalytic asymmetric synthesis. Also, N–N biaryl atropisomers scaffolds-based ligands were simply applied to the asymmetric synthesis, and its biological activity was explored.

However, the N–N biaryl atropisomers synthesis is still in its infancy, numerous efforts should be made to address the great challenges in synthesis and application. For example, the asymmetric synthesis of other scaffolds like N–N bicarbazoles or N–N bibenzimidazoles going to be exploited. The potential application of ligands derived from the N–N biaryl atropisomers scaffold needs to be explored.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: atropisomers · asymmetric synthesis · enantioselectivity · indoles · palladium

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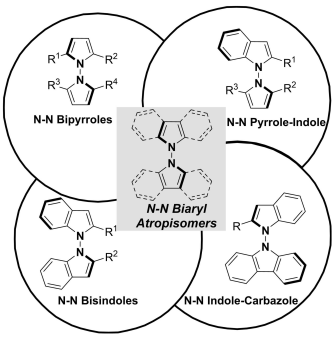
CONCEPT

Although N–N Biaryl atropisomers has emerged into valuable scaffolds in natural products, drug design and asymmetric synthesis, its asymmetric synthesis is scare until recently. This concept will focus on the asymmetric synthesis of the divergent N–N biaryl atropisomers scaffolds including N–N bipyrroles atropisomers, N–N pyrrole–indole atropisomers, N–N bisindoles atropisomers, N–N indole–carbazole atropisomers.



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Catalytic Asymmetric Synthesis of N–N Biaryl Atropisomers