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Remote Copper-Catalyzed Atroposelective Synthesis of N–N Axially Chiral Compounds Bearing Minimally Different Alkyl Groups

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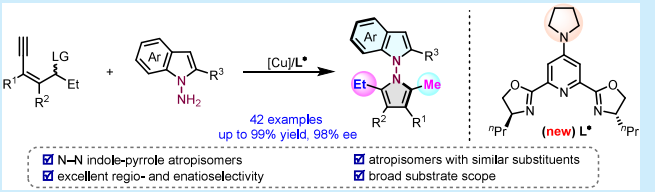
ABSTRACT: Herein, we report a copper-catalyzed remote asymmetric [4+1] annulation/aromatization between yne-allylic esters and *N*-aminoindoles, providing axially chiral *N*,*N*′-indolepyrroles that contain sterically comparable *ortho* substituents, such as methyl and ethyl. This reaction proceeds smoothly under mild conditions, affording products with excellent regio- and enantioselectivities while demonstrating broad functional group compatibility. The synthetic utility of this approach is further showcased through the late-stage modification of biologically relevant scaffolds. Additionally, preliminary mechanistic investigations indicate that remote nucleophilic substitution is the enantio-determining step.



Atropisomers, particularly those with biaryl frameworks, are ubiquitous structural motifs found in a wide range of natural products, pharmaceuticals, chiral catalysts, and ligands.[1] Due to their significance, the catalytic asymmetric synthesis of biaryl atropisomers has been intensively investigated, leading to remarkable progress over the past several decades.[2] However, a survey of the literature reveals that most synthesized biaryl atropisomers are limited to structures in which the two substituents exhibit a large steric difference. The catalytic asymmetric construction of atropisomers with substituents of similar steric bulk remains largely unexplored and presents a considerable challenge in chiral induction.[3] Among these, atropisomers bearing N–N axial chirality have garnered significant attention due to their great potential in drug discovery, catalyst and ligand design, as well as functional material development.[4] However, to the best of our knowledge, no catalytic enantioselective approach has been reported for the synthesis of axially chiral compounds bearing these minimally different alkyl groups such as methyl and ethyl (Figure 1a). Therefore, developing a robust catalytic strategy to address this challenge is highly desirable.

On the other hand, compared with the well-developed C–C and C–N atropisomers,[2] the asymmetric synthesis of N–N atropisomers remained relatively underdeveloped.[5] In 2021, Lu's group has pioneered the first asymmetric construction of N–N atropisomers via quinidine-catalyzed *N*-allylic alkylation reaction.[6a] After that, the catalytic enantioselective construction of N–N axially chiral scaffolds has attracted considerable attention, and various elegant protocols have been established by Liu, Shi, Zhao, Bencivenni, You, Li, and other groups.[6−15] Moreover, the catalytic asymmetric construction of axially chiral indole-based scaffolds has become an emerging focus of research, and many excellent research works have been reported.[2f,16] To achieve the divergent synthesis of N–N

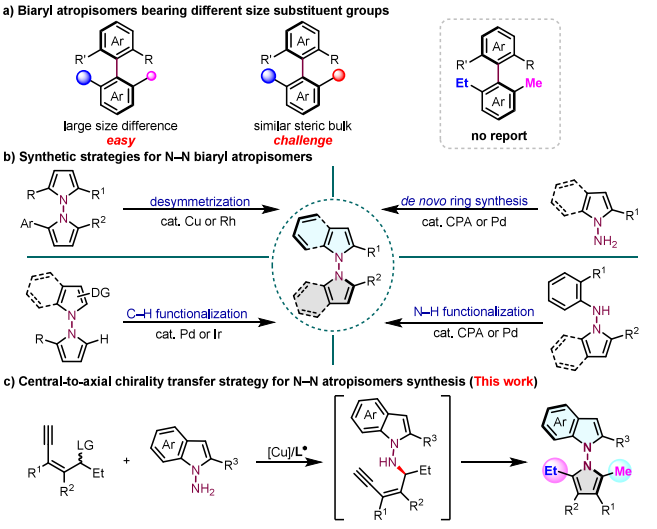


Figure 1. Challenges and atroposelective syntheses of N–N biaryl atropisomers.

biaryl atropisomers, a series of synthetic strategies have been developed, including desymmetrization,[12] atroposelective *de novo* ring formation,[13] enantioselective C–H functionalization,[14] and asymmetric N–H functionalization[15] (Figure 1b). Despite these advancements, expanding substrate generality

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and product diversity is highly desirable for enriching the synthetic toolbox for N−N biaryl atropisomers.

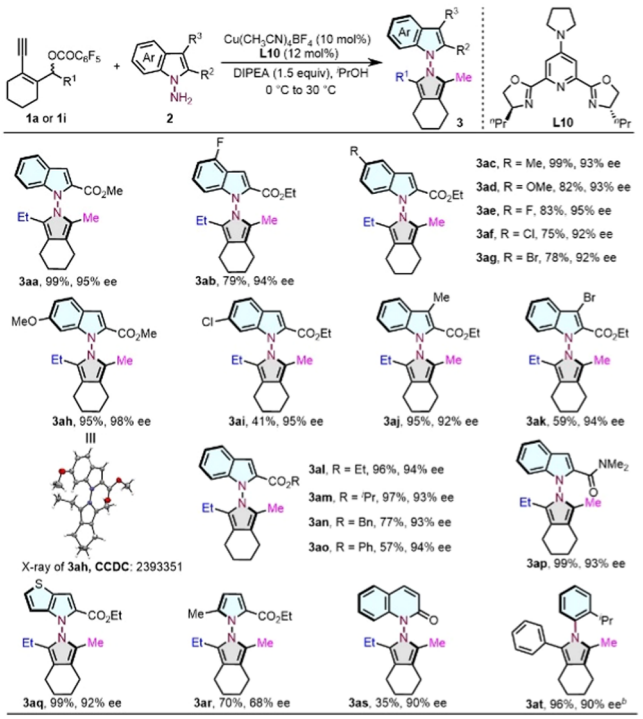
In recent years, copper-catalyzed asymmetric remote substitution or annulation of yne-allylic and yne-thiophene esters has proven to be highly valuable for constructing various stereocenters.[17−21] Notably, the generated copper-vinylallenylidene, which bears two reactive sites, serves as a versatile platform for synthesizing various chiral spirocycles and axially chiral arylpyrroles.[18,21] As part of our continuous interest in copper-catalyzed remote functionalization, we envisioned a novel method for synthesizing N−N biaryl atropisomers with sterically similar substituents, such as methyl and ethyl, via a central-to-axial chirality transfer strategy (Figure 1c).

We began our investigation using yne-allylic ester **1a** and *N*-aminoindole **2a** as model substrates, with DIPEA as the base and $Cu(CH_3CN)_4BF_4$ as the catalyst (see Table S1). Initially, the use of BINAP **L1** afforded only trace amounts of **3aa**, with a 15% ee (entry 1). We then switched to tridentate PyBox ligands and discovered that the reaction with **L2** delivered **3aa** in 43% yield with 58% ee (entry 2). Considering that electronic properties at the C4 position could influence the chiral environment of the ligands and thus impact enantiodifferentiation, we further investigated the electronic properties of substituents on PyBox. Notably, the ee of **3aa** was significantly enhanced with C4-NMe_2-substituted PyBox **L6** (entries 3−6). On this basis, we explored PyBox with various side chain groups (entries 7−9). Fortunately, the reaction with **L7** afforded **3aa** with higher enantioselectivity than **L6**. In addition, we have designed a set of new ligands **L10**−**L12**, incorporating electron-donating groups at the C4 position of ^{n}Pr-PyBox. To our delight, the enantioselectivity of **3aa** improved to 89% ee when using **L10** (entries 10−12). After further optimizing the reaction parameters, including the ratio of the substrates, solvents, and temperature, **3aa** can be obtained in 99% yield and 95% ee (entries 13−16).

After establishing the optimal reaction conditions, we next investigated the substrate generality of the reaction. A wide range of *N*-aminoindoles with functional groups, such as Me, OMe, F, Cl, and Br at the different (C3−C6) positions of the indole ring, afforded products **3ab**−**3ak** in 41−99% yields with 92−98% ee (Scheme 1). Meanwhile, the absolute configuration of product **3ah** was unambiguously confirmed by X-ray crystallographic analysis. Importantly, *N*-aminoindoles bearing different ester and amide groups were also viable substrates, achieving comparable efficiency and enantioselectivity in the reactions (**3al**−**3ap**). Furthermore, thiophene-fused and pyrrole-derived substrates were well tolerated, providing the desired products **3aq** and **3ar,** respectively, in good to excellent yields and enantioselectivities. Interestingly, this strategy is not limited to biaryl atropisomers. *N*-aminoquinolinone could also serve as a bis-nucleophile, affording N−N axially chiral pyrrolylquinolinone **3as** in good enantioselectivity. On this basis, we further investigated whether this protocol could also be extended to the synthesis of C−N atropisomers. Fortunately, the desired C−N atropisomer **3at** was obtained in 96% yield with 90% ee.

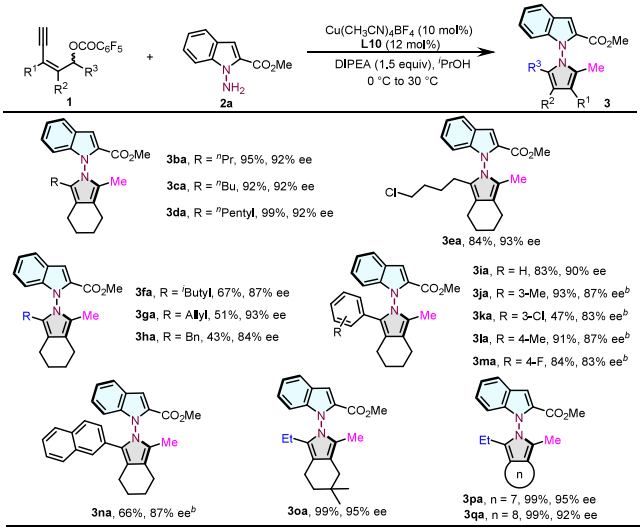
Subsequently, we evaluated the scope of yne-allylic esters **1** (Scheme 2). A panel of aliphatic-, allyl-, and benzyl-substituted yne-allylic esters all worked smoothly, delivering products **3ba**−**3ha** in 43−99% yields with 84−93% ee. Additionally, various aryl-substituted electron-donating and withdrawing groups, as well as bicyclic naphthalene rings, were well tolerated, providing products **3ia**−**3na** in moderate to high

Scheme 1. Scope of *N*-Aminoheterocycles[a]



[a]Unless otherwise noted, all reactions were carried out under the standard conditions. [b]Reacted at −5 °C for 12 h.

Scheme 2. Scope of Yne-Allylic Esters[a]



[a]Unless otherwise noted, all reactions were carried out under the standard conditions. [b]Reacted at −10 °C for 24 h and then at 30 °C for an additional 12 h.

yields with good enantioselectivities. Meanwhile, dimethyl-substituted six-, seven-, and eight-membered rings were also suitable reaction partners, giving products **3oa**−**3qa**, with overall good yields and excellent enantioselectivities.

To further evaluate the scalability and practicality of this protocol, several structurally complex *N*-aminoindoles derived from drugs and natural products were subjected to the transformation (Scheme 3a). Gratifyingly, varieties of N−N axially chiral products **3au**−**3az**, bearing biologically relevant

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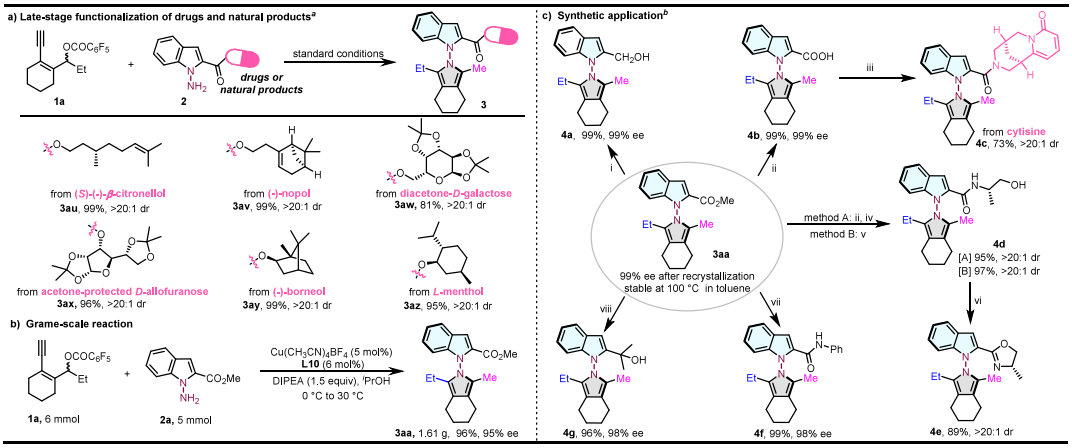
Scheme 3. Synthetic Potentials



[a]Unless otherwise noted, all reactions were carried out under the standard conditions; the dr value was determined by crude ^{1}H NMR. [b](i) $LiAlH_4$, THF, 0 °C to rt; (ii) KOH, 3:1 MeOH/H_2O, 70 °C; (iii) HATU, Et_3N, DCM, rt; (iv) *L*-alaninol, TBTU, Et_3N, THF, rt; (v) *L*-alanino, LiHMDS, toluene, rt; (vi) *p*-TsCl, DMAP, Et_3N, DCM, 70 °C; (vii) aniline, LiHMDS, toluene, rt; (viii) MeLi, THF, −20 °C to rt.

skeletons, were obtained with high enantiopurity. All of these results indicated that this robust approach offers new opportunities for the direct late-stage functionalization of natural products, potentially aiding in new drug discovery. Furthermore, a gram-scale reaction also proved to be efficient without loss of yield or enantioselectivity, even when the catalyst loading was halved (Scheme 3b). Moreover, racemization experiments were performed to evaluate the conformational stability of the N−N atropisomers. When **3aa** was heated in toluene at 100 °C for 24 h, no erosion of enantiopurity was observed (Scheme 3c), confirming the configurational stability of these compounds. Notably, the ester group of **3aa** serves as a versatile handle for the conversion into various functional groups (Scheme 3c). After recrystallization, product **3aa** with 99% ee could be readily reduced to alcohol **4a** in almost quantitative yield using $LiAlH_4$. Subsequently, hydrolysis of **3aa** yielded carboxyl acid **4b**, which was then amidated with cytisine to produce **4c** in high yield. Moreover, newly obtained chiral amino alcohol moiety **4d** was further successfully transformed into novel oxazoline ligand **4e**. Nucleophilic addition of methyl lithium to the ester group proceeded smoothly, giving tertiary alcohol **4g** in 96% yield. Importantly, the enantiomeric purity of all of the derivatives obtained from **3aa** remained well-preserved throughout these transformations.

To gain further insight into the reaction pathway, a series of control experiments were conducted (see Figure S4). First, when phenyl-substituted **1a′** was used in place of terminal yne-allylic ester **1a**, no corresponding product **7** was obtained under the standard conditions. This highlights the critical role of the terminal alkyne in initiating the reaction (Figure S4a). Moreover, when the reaction temperature was decreased to −10 °C, remote asymmetric substitution intermediate **9** was obtained in 95% yield with 98% ee. Subsequently, treatment of **9** with **L10** under the standard conditions afforded **3aa** in 89% yield with 93% ee, suggesting that the reaction likely proceeds through a tandem sequence involving remote substitution, cyclization, and aromatization. In addition, when an achiral ligand **L15** was employed, chiral intermediate **9** could still be successfully converted into **3aa** in 15% yield with 93% ee, while unreacted intermediate **9** was recovered in 78% yield without a loss of enantioselectivity (Figure S4b). These observations suggested that the enantioselective control occurs during the initial nucleophilic substitution step, followed by central-to-axial chirality transfer to afford axially chiral *N,N′*-indolepyrroles.

In conclusion, we have developed a general and efficient method for synthesizing axially chiral *N,N′*-indolepyrroles bearing two sterically similar *ortho* substituents through a central-to-axial chirality transfer strategy. The reaction proceeds smoothly under mild conditions with excellent functional group tolerance, enabling access to a variety of N−N atropisomers in high yields with excellent enantioselectivities. Furthermore, the scalability of the reaction and its broad synthetic versatility further underscore the practicality of this method. Preliminary mechanistic studies suggest that the reaction likely follows a tandem sequence of remote asymmetric substitution, cyclization, and aromatization. This work not only extends the scope of the atroposelective synthesis of *N,N′*-indolepyrroles but also holds broader implications for future studies in asymmetric synthesis.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c01316.

Experimental procedures, complete characterization data, and copies of NMR and HPLC spectra (PDF)

Accession Codes

Deposition Number 2393351 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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