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Copper-catalyzed atroposelective hydroarylation of 1-alkynylindoles

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Catalytic enantioselective hydroarylation of alkynes is a concise protocol towards axial, helical, and planar chirality. By using an enantioselective π-acid catalysis strategy, these enantioenriched hydroarylation products could be obtained in a green pathway; however, noble-metal catalysts are unavoidable. Here we report a copper-catalyzed intramolecular atroposelective hydroarylation of 1-alkynylindoles with (hetero)arenes, providing a modular platform for the construction of C—N axially chiral carbazolyl and phenanthryl indoles in excellent yields with good to excellent ee values. Moreover, the constructed C—N axially chiral indoles could be easily diversified to various functional group-containing chiral frameworks, and further applied as a chiral ligand in asymmetric catalysis. Importantly, this reaction represents a rare non-noble metal-catalyzed enantioselective hydroarylation of alkynes by π-acid catalysis.

Hydroarylation of alkynes with (hetero)arenes is a straightforward pathway for the construction of C–C bonds[1–4]. During the past years, the catalytic enantioselective hydroarylation of alkynes has been developed as an efficient protocol towards diverse chirality elements, such as axial, helical, and planar chirality[5–8]. Classified by reaction mechanism, the major strategies include enantioselective addition of arylmetallic intermediates onto alkynes and enantioselective addition of nucleophilic (hetero)arenes onto π-acid-activated alkynes. In the arylmetallic addition strategy, transition metal-catalyzed oxidative addition of aryl halides[9,10], transmetallation of aryl boronic acids[11], and directing group-oriented C–H activation[12–15] are responsible for the generation of arylmetallic intermediates. Alternatively, the π-acid catalysis[16–21] approach proceeds through a greener pathway, which does not require pre-functionalized aryl reagents, such as aryl halides, aryl boronic acids, and directing group-containing aryl compounds (Fig. 1a, path 1). In 2011, Tanaka and co-workers reported a palladium-catalyzed enantioselective hydroarylation of propiolamides for the synthesis of axially chiral 4-aryl 2-quinolinones, which represents a breakthrough in catalytic enantioselective intramolecular hydroarylation of alkynes[22]. The related gold-catalyzed hydroarylation of electron-deficient alkynones could also be applied to construct axial chirality[23]. In 2014, the Tanaka group further realized the enantioselective construction of S-shaped double azahelicenes through gold-catalyzed sequential intramolecular hydroarylation of diynes[24]. Alternatively, the Alcarazo group designed several α-cationic phosphonite chiral ancillary ligands to enable a series of gold-catalyzed intramolecular hydroarylation reactions of diynes[25–27] and diaryl alkynes[28–30], providing a convenient access towards various helically chiral skeletons. Moreover, the related gold- and platinum-catalyzed enantioselective hydroarylation was extended to the construction of planar chirality by Carreño[31], Shibata[32], Zhang[33], and others. Despite these impressive advances, noble-metal catalysts are required in the π-acid-catalyzed enantioselective hydroarylation of alkynes, and the construction of axial chirality is limited to electron-deficient alkynes (Fig. 1a, path 2). Therefore, the development of non-noble metal catalyzed enantioselective hydroarylation of alkynes with (hetero)arenes is imperative.

As a unique type of polarized alkynes, 1-alkynylindoles are useful synthetic intermediates in organic chemistry, and the related catalytic asymmetric transformations have been extensively explored in recent years. In 2021, Li and co-workers disclosed a rhodium-catalyzed asymmetric C–H activation/alkyne insertion cascade reaction of 1-alkynylindoles with arylnitrones for the formation of axially and centrally chiral indenes by directing group strategy[34], and this C–H activation methodology was then employed for the synthesis of other atropisomeric heterocycles and alkenes[35–39]. In addition to

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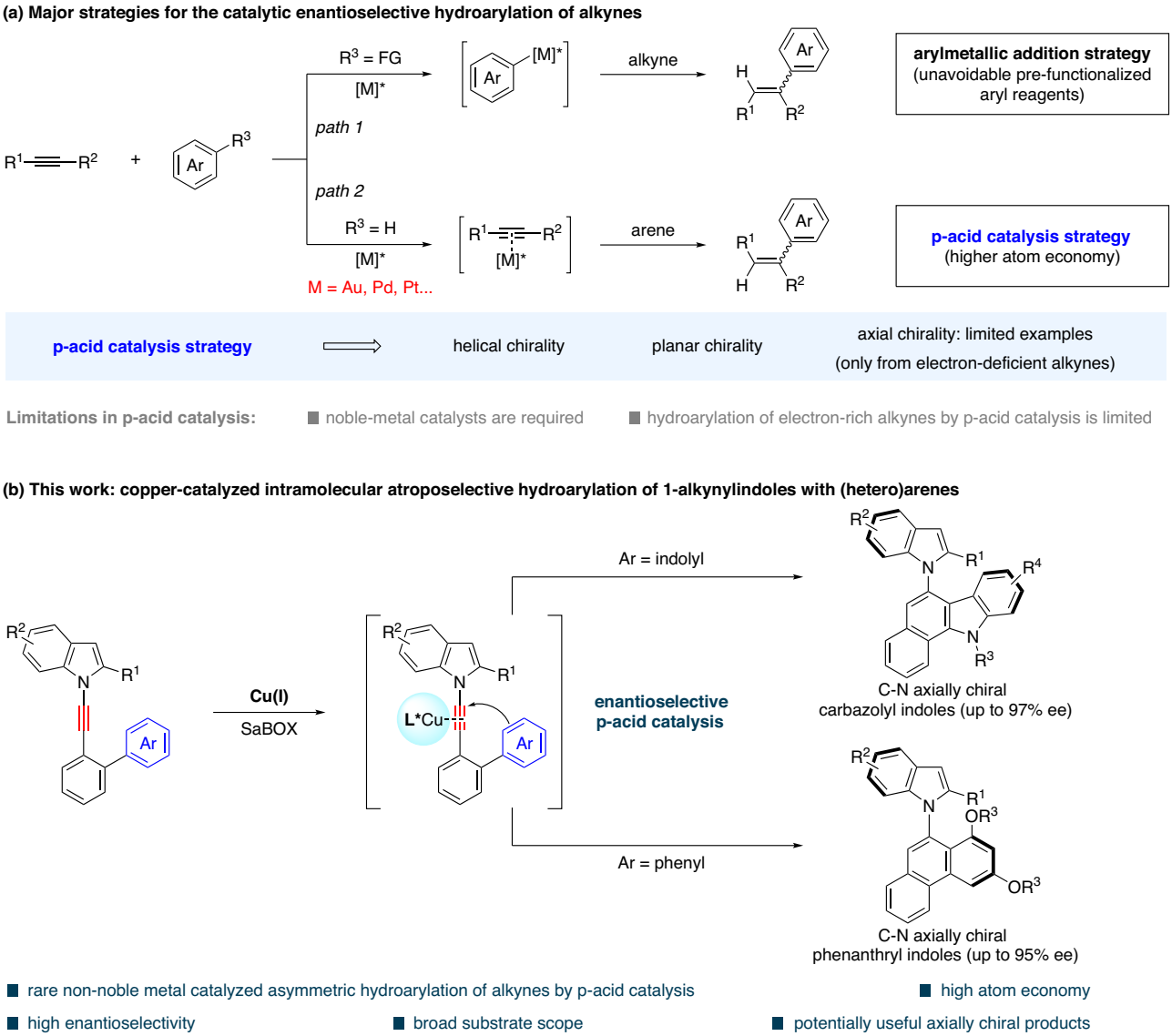

Fig. 1 | Catalytic enantioselective hydroarylation of alkynes. a Major strategies for the catalytic enantioselective hydroarylation of alkynes. **b** This work: copper-catalyzed intramolecular atroposelective hydroarylation of 1-alkynylindoles with (hetero)arenes.

C–H activation-initiated alkyne insertion, the enantioselective hydrophosphination[40], hydroamination[41], hydroarylation[11], click cycloaddition[42], and [2 + 2 + 2] cycloaddition[43,44] were successfully developed, delivering diverse C–N and N–N axially chiral frameworks efficiently. It should be pointed out that noble metal catalysts or directing groups are necessary in the enantioselective transformations of 1-alkynylindoles. To overcome these limitations and expand the repertoire of 1-alkynylindoles in asymmetric synthesis, it is highly desirable to develop a noble-metal-free catalytic system that operates by an atom-economical pathway.

During the past years, our group has been devoted to the catalytic atroposelective transformations of ynamides[45–52] for the construction of various axially chiral and planar-chiral skeletons[53–59]. In particular, a series of copper-catalyzed atroposelective diyne cyclization reactions could be realized by the remote control of enantioselectivity, such as oxidation and X–H insertion[54], formal C–C bond insertion into aldehydes[55], dehydro-Diels–Alder reaction[56], and C(sp^2)–H functionalization of arenes[57]. Among them, π-acid-catalyzed addition of ynamides was found to be the enantio-determining step for the reaction of sterically hindered diynes[54,55]. Therefore, we proposed to employ the efficient π-acid catalysis strategy for the enantioselective hydroarylation of alkynes. Herein, we describe the realization of such a copper-catalyzed intramolecular atroposelective hydroarylation of 1-alkynylindoles with (hetero)arenes, leading to the atom-economical synthesis of C–N axially chiral carbazolyl and phenanthryl indoles in excellent yields with good to excellent enantioselectivities (Fig. 1b)[60–63]. Further synthetic transformations led to the formation of an axially chiral phosphine, which is potentially useful in asymmetric catalysis. This reaction represents a rare non-noble metal-catalyzed enantioselective hydroarylation of alkynes by π-acid catalysis.

Results

To validate our hypothesis, indole-tethered 1-alkynylindole **1a** was chosen as the model substrate to evaluate this catalytic atroposelective hydroarylation, and the selected results are summarized in Table 1 (for more conditions, see Supplementary Table 1). At the outset, chiral bisphosphines **L1** ((*R*)-BINAP) and **L2** ((*R*)-SEGPHOS) were employed as ligands in the presence of $Cu(CH_3CN)_4PF_6$ (10 mol %) and DCE as solvent at 40 °C, affording C–N axially chiral carbazolyl indole **2a** in excellent yields with 8–12% ee (entries 1–2). To our delight, the replacement of chiral bisphosphine ligands with bisoxazoline (BOX) ligands **L3**–**L6** resulted in obviously improved enantioselectivities (entries

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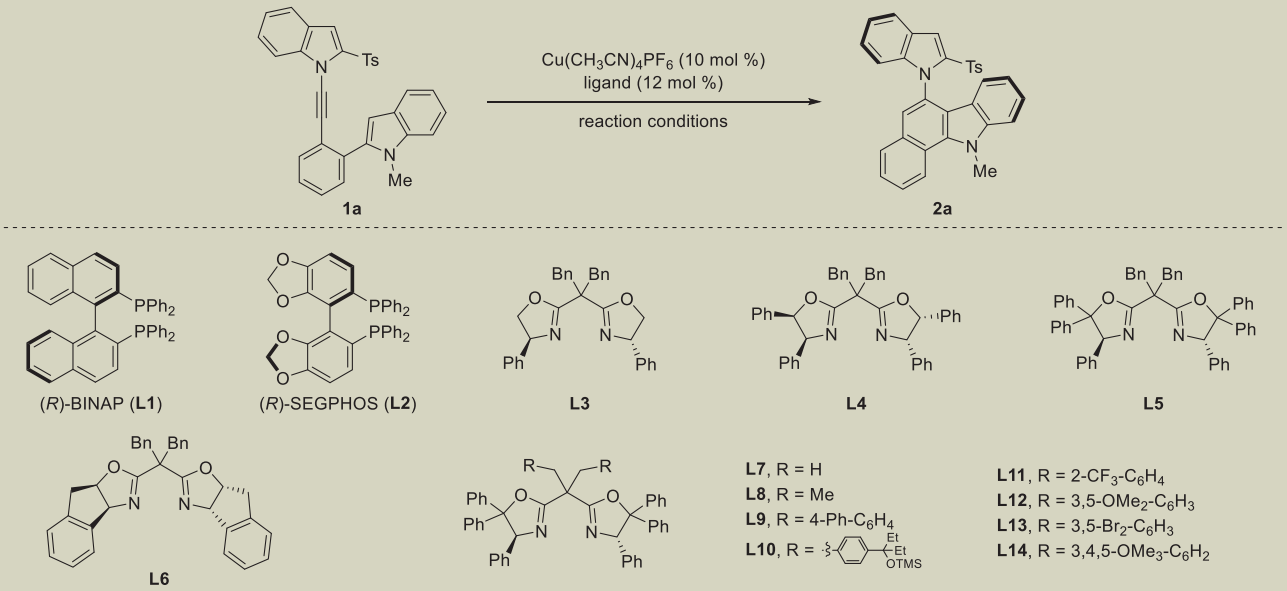
Table 1 | Optimization of reaction conditions for the atroposelective hydroarylation of 1-alkynylindole 1a



Entry	L	Reaction conditions	Yield (%)[a]	ee (%)[b]
1	**L1**	DCE, 40 °C, 5 min	96	8
2	**L2**	DCE, 40 °C, 5 min	97	12
3	**L3**	DCE, 40 °C, 35 min	97	43
4	**L4**	DCE, 40 °C, 5 min	98	42
5	**L5**	DCE, 40 °C, 5 min	97	44
6	**L6**	DCE, 40 °C, 20 min	95	43
7	**L7**	DCE, 40 °C, 5 min	96	5
8	**L8**	DCE, 40 °C, 15 min	97	26
9	**L9**	DCE, 40 °C, 10 min	98	30
10	**L10**	DCE, 40 °C, 5 min	97	35
11	**L11**	DCE, 40 °C, 5 min	97	19
12	**L12**	DCE, 40 °C, 5 min	96	23
13	**L13**	DCE, 40 °C, 5 min	97	60
14	**L14**	DCE, 40 °C, 5 min	98	90
15	**L14**	CH_2Cl_2, 40 °C, 5 min	97	66
16	**L14**	toluene, 40 °C, 5 min	98	79
17	**L14**	THF, 40 °C, 5 min	98	84
18	**L14**	DCE, 10 °C, 2 h	99	93
19	**L14**	**DCE, −10 °C, 21 h**	**98**	**96**
20[c]	**L14**	DCE, −10 °C, 22 h	98	94

Reaction conditions: **1a** (0.05 mmol), $Cu(CH_3CN)_4PF_6$ (0.005 mmol), **L** (0.006 mmol), solvent (2 mL), −10–40 °C, 5 min–21 h, in vials; [a]Measured by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard; [b]Determined by HPLC analysis; [c]With $Cu(CH_3CN)_4PF_6$ (0.0025 mmol) and **L14** (0.003 mmol).

3–6), and **L5**, containing 4,5,5-triphenyl-4,5-dihydrooxazole moiety, produced **2a** in 97% yield with 44% ee (entry 5). Motivated by these results, Tang's sidearm-modified bisoxazoline (SaBOX) ligands[64] were next explored based on the optimized oxazoline framework. The screening of different SaBOX ligands **L7**–**L14** indicated that the sidearm with a 3,4,5-trimethoxyphenyl group (**L14**) can further improve the enantioselectivity (entries 7–14), and the expected product **2a** was generated in 98% yield with 90% ee (entry 14). However, the screening of other solvents, including CH_2Cl_2, toluene, and THF, failed to improve the enantiocontrol (entries 15–17). Gratifyingly, an obvious temperature influence was observed, and the carbazolyl indole **2a** could be synthesized in 98% yield with 96% ee by lowering the reaction temperature to −10 °C (entries 18 and 19). A slightly lower ee was observed after decreasing the catalyst loading to 5 mol % (entry 20).

After establishing the optimal reaction conditions (Table 1, entry 19), the substrate scope of this copper-catalyzed atroposelective hydroarylation was then evaluated in Fig. 2 (for more details, see Supplementary Fig. 1). Indole-tethered 1-alkynylindoles **1** equipped with different sulfonyl groups on the 2-position of indole ring, including Ts, SO_2Ph, $SO_2(4\text{-F-}C_6H_4)$, and $SO_2(4\text{-Cl-}C_6H_4)$, could undergo the enantioselective transformation smoothly to forge C—N axially chiral carbazolyl indoles **2a**–**2d** in 98–99% yields with 95–96% ee. The switch of sulfonyl group to CO_2Ph and $P(O)Ph_2$ delivered **2e** and **2f** in excellent yields with 91–97% ee, which could be easily diversified or transformed into chiral ligand. The introduction of

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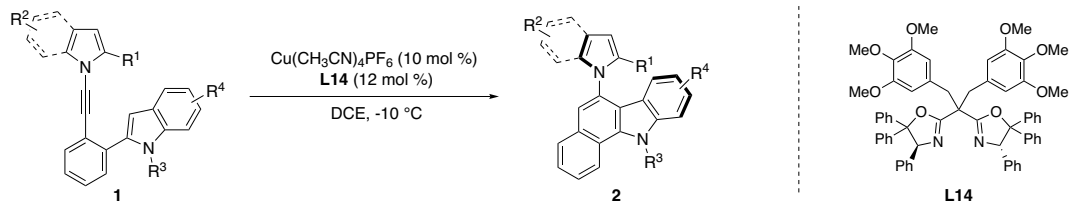

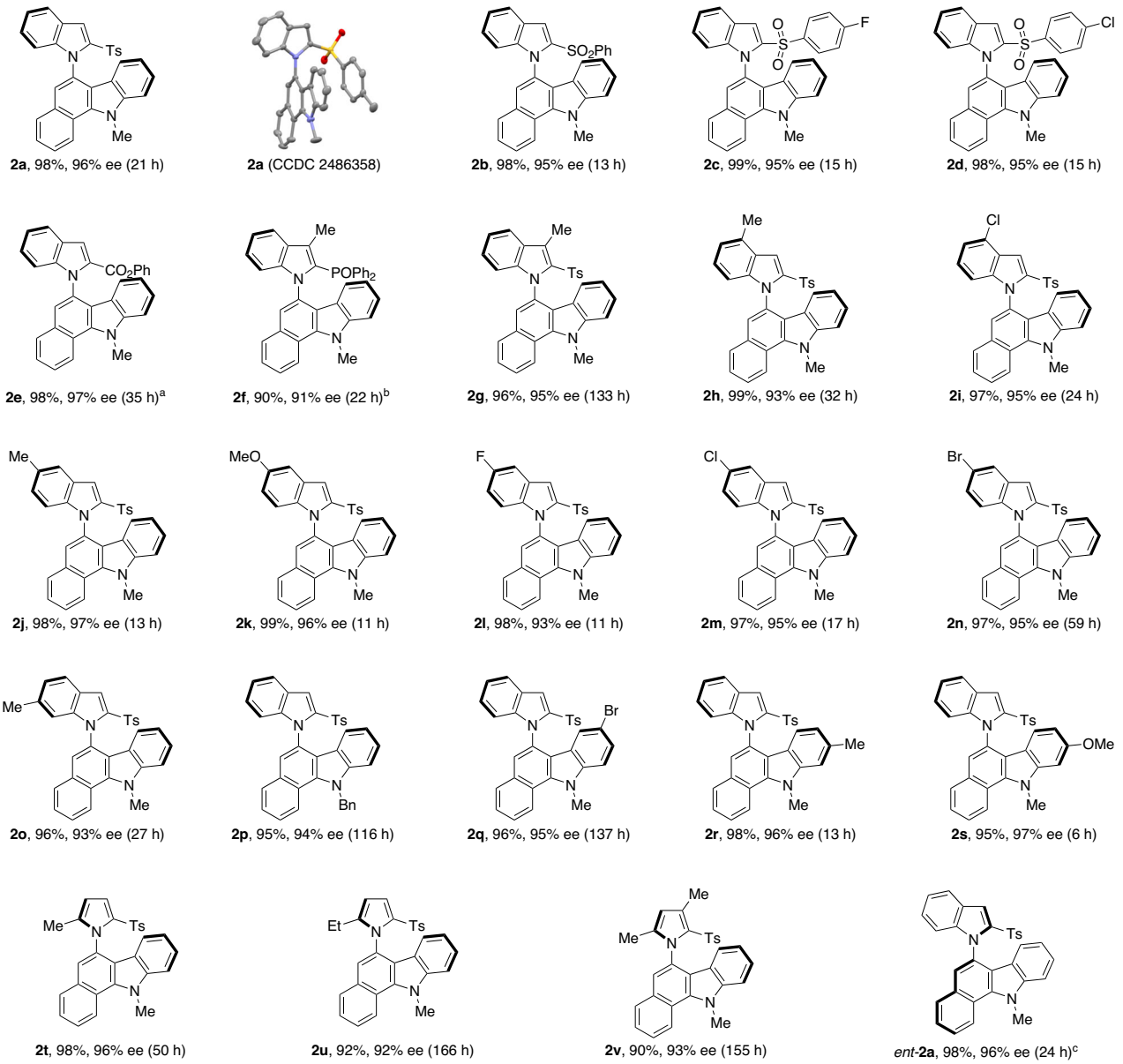

Fig. 2 | Substrate scope for the synthesis of C–N axially chiral carbazolyl indoles 2. Reaction conditions: **1** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (0.01 mmol), **L14** (0.012 mmol), DCE (4 mL), −10 °C, in vials; yields are those for the isolated products; ee values are determined by HPLC analysis. [a]**L10** (0.012 mmol). [b]**L8** (0.012 mmol), 15 °C. [c]*ent*-**L14** (0.012 mmol).

various electron-donating (Me, and OMe) and -electron-withdrawing (F, Cl, and Br) groups onto the different positions of the indole ring for 1-alkynylindoles **1g**–**1o** led to the formation of desired atropisomeric indoles **2g**–**2o** in 96–99% yields with 93–97% ee. Then, we turned to explore the generality of the nucleophilic indole moiety. The protecting group of the indole moiety could be changed to an easily removable benzyl group, delivering **2p** in excellent yield and atroposelectivity. Substrates containing electron-donating (Me, and OMe) and -electron-withdrawing (Br) substituents on the 5- and 6-positions of nucleophilic indole were all compatible, affording the corresponding **2q**–**2s** in 95–98% yields with 95–97% ee. Interestingly, the strategy could be extended to the enantioselective hydroarylation of 1-alkynylpyrroles, and the expected C–N axially chiral carbazolyl pyrroles **2t**–**2v** were generated in 90–98% yields with 92–96% ee. In addition, the enantiomer of **2a** could be easily obtained by using *ent*-**L14** as a ligand. The absolute configuration of product **2a** was unambiguously determined by single-crystal X-ray crystallographic analysis (for more details, see Supplementary Fig. 6).

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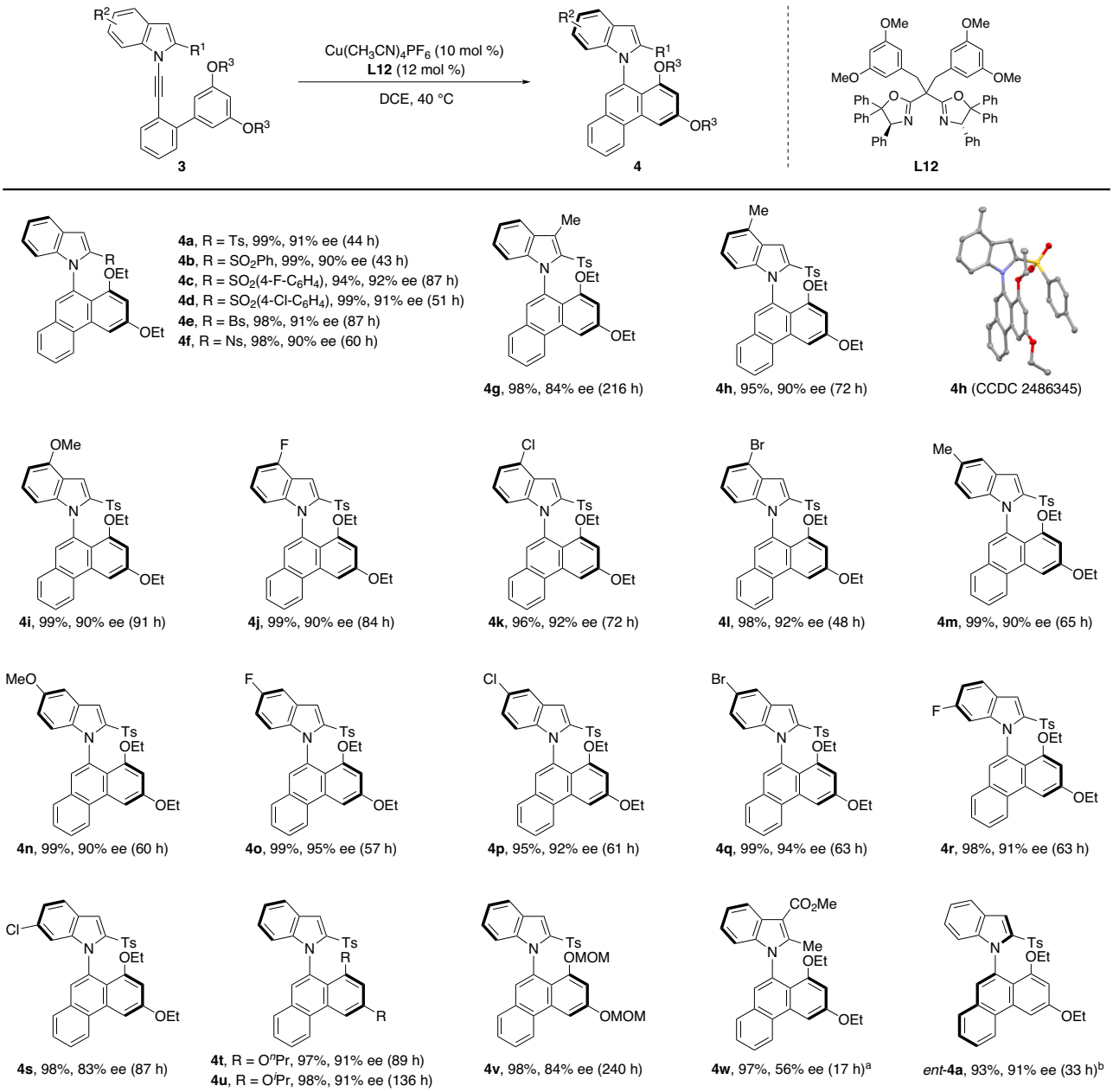

Fig. 3 | Substrate scope for the synthesis of C–N axially chiral phenanthryl indoles 4. Reaction conditions: **3** (0.1 mmol), $Cu(CH_3CN)_4PF_6$ (0.01 mmol), **L12** (0.012 mmol), DCE (4 mL), 40 °C, in vials; yields are those for the isolated products; ee values are determined by HPLC analysis. [a]**L10** (0.012 mmol). [b]*ent*-**L12** (0.012 mmol). Bs = 4-bromobenzenesulfonyl, Ns = 4-nitrobenzenesulfonyl.

Based on the efficient reaction of indole-type nucleophiles, we proposed to extend this transformation to the enantioselective hydroarylation of more challenging benzene-type nucleophiles, which could realize the construction of C–N axially chiral phenanthryl indoles. Therefore, 3,5-diethoxy benzene-tethered 1-alkynylindole **3a** was employed as a model substrate to conduct the condition optimization, and the desired product **4a** was obtained in almost qualitative yield with 91% ee by using $Cu(CH_3CN)_4PF_6$ as a catalyst and **L12** as a ligand in DCE at 40 °C (for more conditions, see Supplementary Table 2). As demonstrated in Fig. 3 (for more details, see Supplementary Fig. 2), 1-alkynylindoles **3** bearing different sulfonyl substituents were evaluated, such as SO_2Ph, $SO_2(4\text{-F-}C_6H_4)$, $SO_2(4\text{-Cl-}C_6H_4)$, Bs, and Ns, and the desired axially chiral phenanthryl indoles **4b**–**4f** could be synthesized in 94–99% yields with 90–92% ee. A range of electron-donating (Me, and OMe) and -withdrawing (F, Cl, and Br) functional groups on the 3-, 4-, 5- and 6-positions of the indole moiety were tolerated well in this reaction, forging the anticipated products **4g**–**4s** in 95–99% yields with 83–95% ee. In addition to 3,5-diethoxy benzene, 3,5-dipropoxy, 3,5-diisopropoxy, and 3,5-dimethoxymethoxy benzene-type nucleophiles could participate in the enantioselective hydroarylation, providing atropisomeric phenanthryl indoles **4t**–**4v** in excellent yields with 84–91% ee. Interestingly, 2-methyl 1-alkynylindole **3w** bearing an ester group at the 3-position of indole gave **4w** in 97% yield with 56% ee. The absolute configuration of **4h** was confirmed by X-ray diffraction (for more details, see Supplementary Fig. 7).

To further demonstrate the synthetic potential of this atroposelective hydroarylation, the scale-up reactions of indole-tethered 1-alkynylindoles **1e** and **1f** were first carried out, resulting in C–N axially chiral carbazolyl indole **2e** in 95% yield with 96% ee and **2f** in 92% yield with 90% ee (Fig. 4a). The treatment of **2e** with KOH produced an

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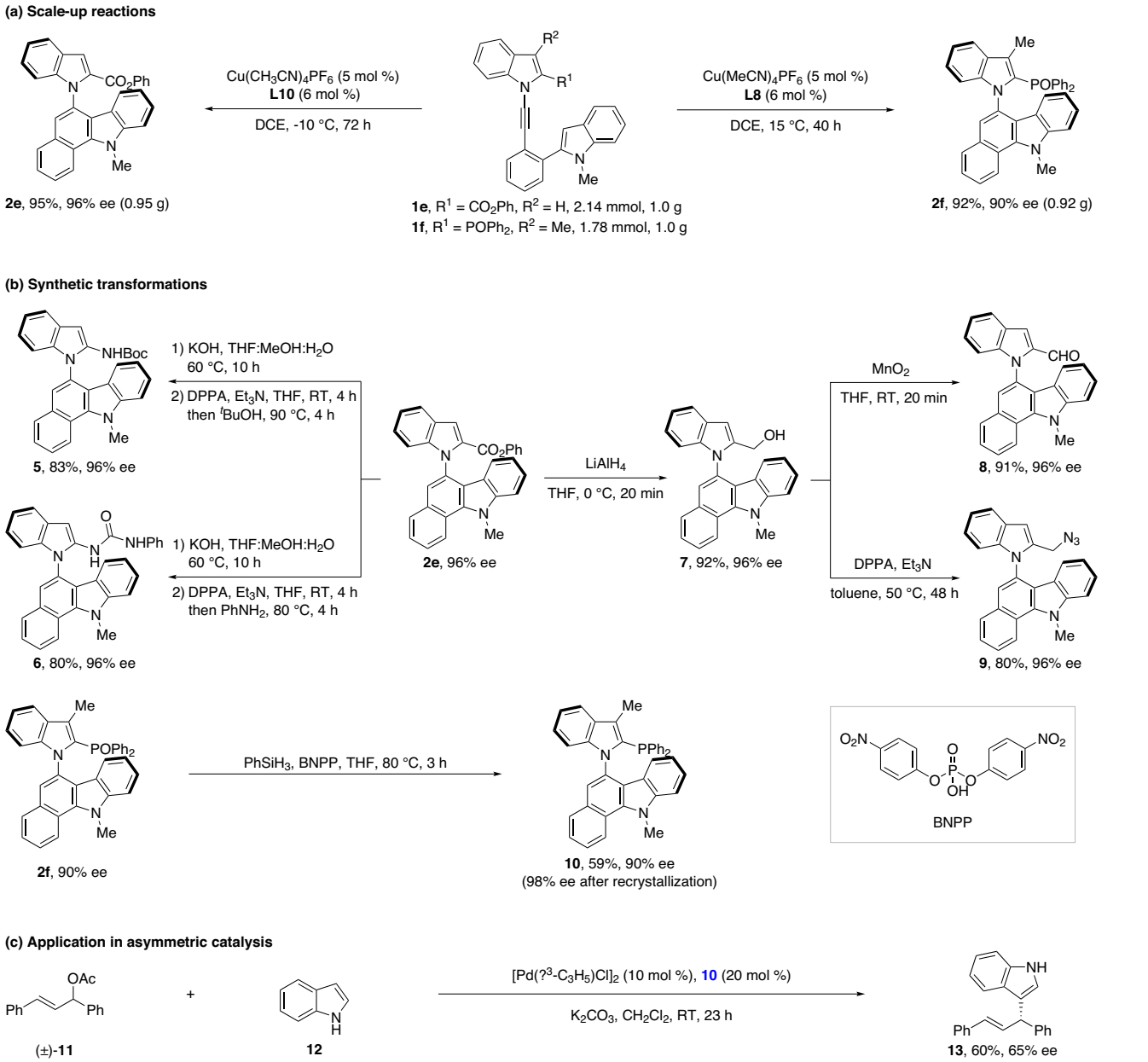

Fig. 4 | Scale-up reactions and synthetic applications. a Scale-up reactions. **b** Synthetic transformations. **c** Application in asymmetric catalysis.

axially chiral carboxylic acid intermediate, which could be transformed into Boc-protected amine **5** and urea derivative **6** through one-pot azidation/Curtius rearrangement/nucleophilic addition. The $LiAlH_4$ reduction of the ester moiety on **2e** produced atropisomeric alcohol **7** in 92% yield, which could undergo oxidation with MnO_2 and azidation with diphenylphosphoryl azide (DPPA) to give aldehyde **8** and azide **9** efficiently. To illustrate the potential utility of constructed chiral skeleton in asymmetric catalysis, the phosphine oxide moiety of product **2f** was easily reduced to give phosphine **10** (Fig. 4b). Notably, axially chiral phosphine **10** could be employed as a chiral ligand in palladium-catalyzed enantioselective allylic arylation of *rac*-1,3-diphenylallyl acetate **11** with indole **12**, leading to the arylated product **13** in 60% yield with 65% ee (Fig. 4c). The enantiopurities of all compounds were well retained in these transformations.

Furthermore, the photophysical and chiroptical properties of selected C—N axially chiral indoles **2** and **4** were explored (Fig. 5, for more details, see Supplementary Figs. 3-5). The UV/Vis absorption spectra indicated that a panel of carbazolyl indoles (**2a**, **2j**, **2k**, **2l**, **2n**, **2p**, and **2u**) displayed the maximum absorption peaks around 285 nm, and the maximum absorption peaks of phenanthryl indoles (**4a**, **4h**, **4i**, **4l**, **4n**, **4o**, and **4r**) ranged from 236 nm to 246 nm (Fig. 5a). Subsequently, the fluorescent properties of these atropisomeric indoles were investigated. Carbazolyl indoles (**2a**, **2j**, **2k**, **2l**, **2n**, and **2p**) demonstrated maximum fluorescence emission peaks ranged from 455 nm to 474 nm, and the maximum emission peak of carbazolyl pyrrole **2u** was at 365 nm. However, phenanthryl indoles **4** showed maximum emission peak around 370 nm (Fig. 5b). Moreover, the circular dichroism (CD) spectra of the two enantiomers of **2a** and **4a** exhibited a clear mirror-image relationship (Fig. 5c). The substituent-dependent photophysical and chiroptical properties of C—N axially chiral indoles might be beneficial for material science.

Guided by the above experimental results and our previous studies on copper-catalyzed enantioselective reaction of ynamides, a possible reaction mechanism of this copper-catalyzed atroposelective hydroarylation is postulated (Fig. 6). Initially, 1-alkynylindole **1a** coordinates with **L14**-ligated chiral copper complex to generate

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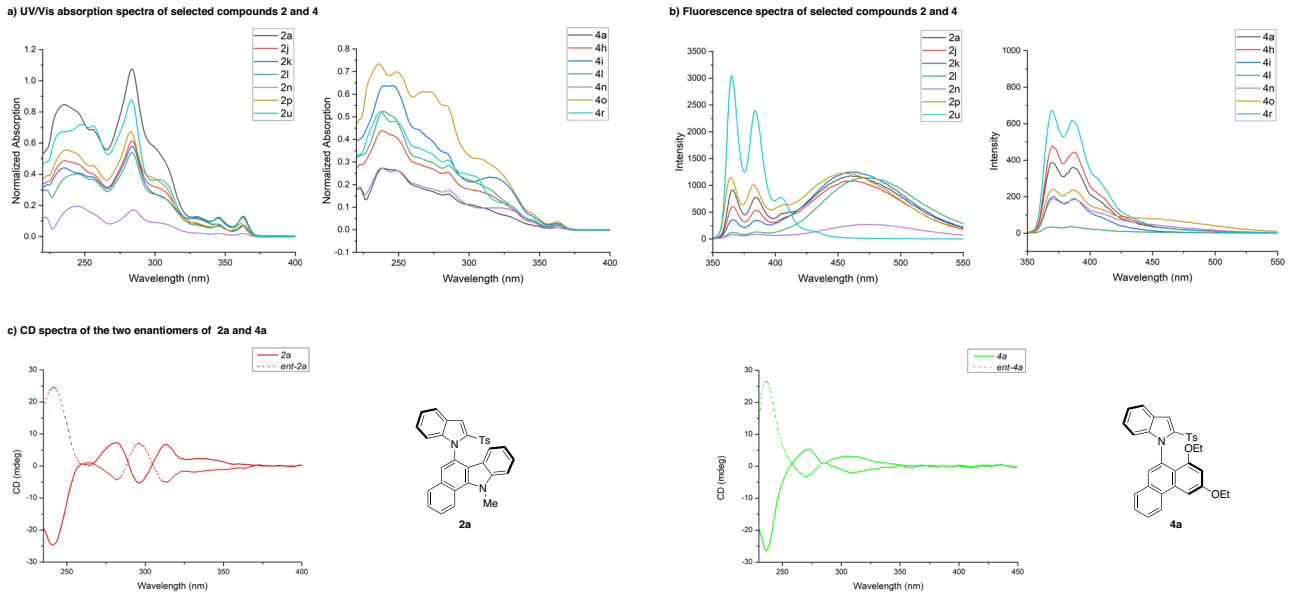

Fig. 5 | Photophysical and chiroptical properties of selected C–N axially chiral indoles 2 and 4. a UV/Vis absorption spectra of selected compounds **2** and **4**. **b** Fluorescence spectra of selected compounds **2** and **4**. **c** CD spectra of the two enantiomers of **2a** and **4a**.

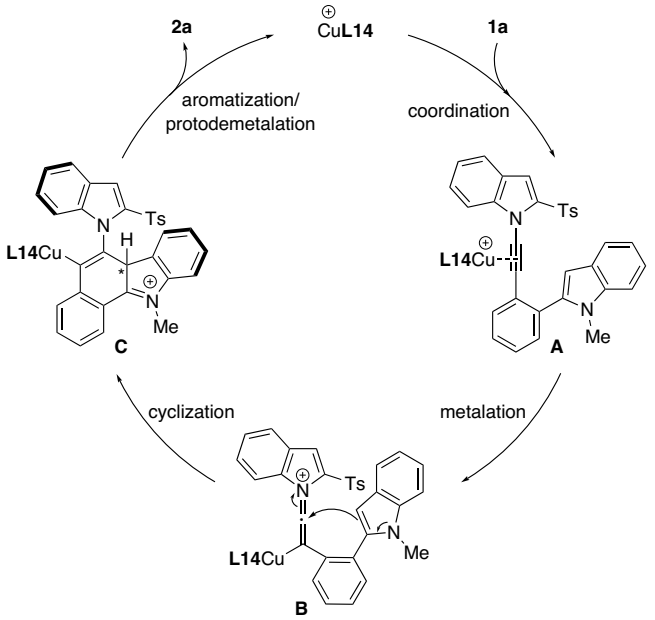

Fig. 6 | Plausible reaction mechanism. Mechanism for the copper-catalyzed atroposelective hydroarylation of 1-alkynylindole **1a**.

intermediate **A**. Then, the coordinated-alkyne moiety undergoes metalation to produce copper-tethered keteniminium intermediate **B**, which triggers a regioselective cyclization to afford atropisomeric iminium ion intermediate **C**. Finally, aromatization and protodemetalation take place to deliver the desired C–N axially chiral carbazolyl indole **2a**, and regenerate the copper catalyst.

Discussion

In summary, we have established a copper-catalyzed intramolecular atroposelective hydroarylation of 1-alkynylindoles with (hetero)arenes via a π-acid catalysis pathway, leading to the practical and atom-economical assembly of C–N axially chiral carbazolyl and phenanthryl indoles. Notably, this methodology continues a rare non-noble metal catalyzed enantioselective hydroarylation of alkynes by π-acid catalysis, as well as an important advancement in the construction of axial chirality by π-acid-catalyzed asymmetric reaction of electron-rich alkynes. The utility of this reaction has been demonstrated by scale-up reactions, synthetic transformations, chiral ligand synthesis, application in asymmetric catalysis, and investigation into photophysical and chiroptical properties. The effective enantiocontrol uncovered in this study could have broad implications for the further development of enantioselective π-acid catalysis.

Methods

General

For ^{1}H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectra of compounds in this manuscript and details of the synthetic procedures as well as more reaction condition screening, see Supplementary Information.

General procedure for the synthesis of C–N axially chiral carbazolyl indoles 2

To an oven-dried vial charged with a stir bar were added $Cu(MeCN)_4PF_6$ (3.7 mg, 0.01 mmol), **L14** (11.7 mg, 0.012 mmol), and anhydrous DCE (4 mL) sequentially. The mixture was stirred at room temperature for 2 h. After cooling to −10 °C, the 1-alkynylindole **1** (0.1 mmol) was introduced into the reaction, and the resulting mixture was stirred at −10 °C for 6–166 h, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: PE/CH_2Cl_2) to give the desired C–N axially chiral carbazolyl indole **2**.

General procedure for the synthesis of C–N axially chiral phenanthryl indoles 4

To an oven-dried vial charged with a stir bar were added $Cu(MeCN)_4PF_6$ (3.7 mg, 0.01 mmol), **L12** (11.0 mg, 0.012 mmol), and anhydrous DCE (4 mL) sequentially. The mixture was stirred at room temperature for 2 h. After warming to 40 °C, the 1-alkynylindole **3** (0.1 mmol) was introduced into the reaction. The resulting mixture was stirred at 40 °C for 43–240 h, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was concentrated

under reduced pressure and purified by column chromatography on silica gel (eluent: PE/EA) to give the desired C—N axially chiral phenanthryl indole **4**.

Data availability

Data for the crystal structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the deposition numbers CCDC 2486358 (**2a**) and 2486345 (**4h**). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this study, including experimental procedures and compound characterization, are available within the paper and its Supplementary Information files or from the corresponding authors on request.

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H.-J.X., C.-M.C., and Z.Z. performed experiments. L.-W.Y. and B.Z. revised the paper. B.Z. conceived and directed the project and wrote the paper. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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