An Atropo-enantioselective Synthesis of Benzo-Linked Axially Chiral Indoles via Hydrogen-Bond Catalysis

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S Supporting Information



ABSTRACT: A variety of axially chiral biaryldiols were synthesized in good yields with excellent atropo-enantioselectivities through construction of axially chiral indoles catalyzed by asymmetric hydrogen-bond donors. In addition, the new axially chiral compounds were proved to be efficient and practical catalysts for asymmetric catalysis. The strategy not only provides a novel method to synthesize axially chiral compounds but also extends the scope of chiral catalysts.

ith the rapid development of chiral chemistry over the past decade, axially chiral compounds¹ have been extensively studied because of their widespread applications as bioactive molecules,² natural products,³ and chiral catalysts in asymmetric catalysis.⁴ However, most of the axially chiral compounds, especially commercially available catalysts, are synthesized by chiral resolution, an inefficient method with a yield of less than 50%.⁵ Some significant methods through asymmetric metal catalysis have been reported to realize the construction of axial chirality.^{3b,6} Compared with relatively mature metal catalysis, asymmetric organocatalysis is a rising star in the world of axial chirality,⁷ which includes phosphoric acid catalysis,⁸ bifunctional catalysis,⁹ amine catalysis, ammonium salt catalysis¹¹ and peptide catalysis.¹² Notably, to our knowledge, hydrogen-bond catalysis has never been reported for the direct construction of axial chirality.¹³

The synthesis and modifications of indole scaffolds have attracted much attention from organic chemists because of their enormous potential and widespread applications.¹⁴ Particularly, most of the research has been focused on the functionalization of indoles in the five-membered heterocyclic ring.¹⁵ In recent years, some effective strategies via organocatalysis have been demonstrated to achieve the enantioselective functionalization of indoles in the carbocyclic ring.¹⁶ However, all of these methods have constructed central

chirality of indoles in the carbocyclic ring. Consequently, the construction of axial chirality through functionalization of indoles in the carbocyclic ring is still an undiscovered area for synthetic chemists.

In 2018, our group successfully realized the asymmetric C-H functionalization of indoles in the carbocyclic ring via organocatalysis (Scheme 1a).^{16f} The groups of Tan^{8h} and Shi^{8d} reported effective strategies to construct axially chiral indoles through functionalization of indoles in the five-membered heterocyclic ring via phosphoric acid catalysis (Scheme 1b). On the basis of the previous works and our interest in asymmetric organocatalysis,¹⁷ we envisioned that the construction of axial chirality through functionalization of indoles in the carbocyclic ring might be achieved via hydrogen-bond catalysis (Scheme 1c).

The study was initiated by testing the model reaction of 5hydroxyindole (1a) and iminoquinone derivative 2a in the presence of hydrogen-bond donor I in CH_2Cl_2 (1 mL) at -20°C, and the expected axially chiral product 3a was successfully produced in moderate yield with an encouraging level of atropo-enantioselectivity (Table 1, entry 1). In this model

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Scheme 1. Construction of Axial Chirality through Functionalization of Indoles in the Carbocyclic Ring

a. Our previous work: the construction of central chirality through functionalization of indoles in the carbocyclic ring



b. Previous work: the construction of axial chirality through functionalization of indoles in the 5-membered heterocyclic ring



c. This work: the construction of axial chirality through functionalization of indoles in the carbocyclic ring



Table 1. Optimization of the Reaction Conditions⁴

HO N H 1a	+ CI	NTs Cl solvent	<u>⁄st (20 mol %)</u> ;, −20 °C, 12 h	
entry	catalyst	solvent	yield (%) ^b	ee (%) ^c
1	Ι	CH_2Cl_2	72	60
2	II	CH_2Cl_2	7	11
3	III	CH_2Cl_2	41	33
4	IV	CH_2Cl_2	90	93
5	V	CH_2Cl_2	58	-37
6	VI	CH_2Cl_2	trace	_
7	VII	CH_2Cl_2	trace	_
8	VIII	CH_2Cl_2	58	45
9	IX	CH_2Cl_2	NR	_
10	Х	CH_2Cl_2	91	-93
11	Х	DCE	>99	-93
12	Х	toluene	>99	-95
13	Х	THF	54	-7
14	Х	MeCN	trace	_
15	Х	EtOAc	78	-60
16 ^d	Х	toluene	>99	-97
17^e	Х	toluene	91	-94
$18^{d_{i}f}$	Х	toluene	>99	-97
19 ^{<i>d</i>,g}	Х	toluene	>99	-97

^{*a*}Conditions: the reactions were performed with 1a (0.15 mmol), 2a (0.1 mmol), and the catalyst (20 mol %) in CH_2Cl_2 (1 mL) at -20 °C for 12 h. For detailed experimental procedures, see the Supporting Information. ^{*b*}Isolated yields. ^{*c*}Determined by chiral-phase HPLC analysis. ^{*d*}At -40 °C. ^{*c*}At -78 °C. ^{*f*}50 mg of 4 Å MS was added. ^{*g*}0.1 mmol of 1a was used.

reaction, 5-hydroxyindole was used as the substrate instead of 4-hydroxyindole, which was used in our previous work to achieve the asymmetric C–H functionalization of indole in the carbocyclic ring, because of the higher rotation barrier. Various hydrogen-bond donors (Figure 1) were then examined, and



Figure 1. Catalysts investigated in the reaction.

chiral cyclohexanediamine-derived thiourea IV turned out to be the optimal catalyst (Table 1, entries 1-7). Notably, the bifunctional catalyst successfully produced the product, albeit with modest enantioselectivity (Table 1, entry 8). However, the chiral phosphoric acid, which has been commonly used to construct axial chirality, could not promote the reaction (Table 1, entry 9). Adjusting the configuration of catalyst IV afforded the product with opposite configuration (Table 1, entry 10). Next, various solvents were screened, and toluene was found to be optimal (Table 1, entries 11–15). THF and MeCN, which are hydrogen-bond acceptors, inhibited the reaction (Table 1, entries 13 and 14). Further study of the reaction temperature indicated that low temperature could improve the enantioselectivity (Table 1, entry 16), but a much lower temperature was not better for the reaction because of reduced solubility of the catalyst (Table 1, entry 17). Finally, the addition of 4 Å molecular sieves did not affect the reaction (Table 1, entry 18), and 1 equiv of substrate 1a was enough (Table 1, entry 19).

With the optimal reaction conditions established, various hydroxyindoles 1 and iminoquinone derivatives 2 with different electronic and steric properties were investigated for the reaction (Table 2). All of the reactions proceeded smoothly to afford the axially chiral products when substituted 5-hydroxyindoles were used as substrates (Table 2, 3a-e), and 2-methyl-5-hydroxyindole gave the best enantioselectivity (Table 2, 3c).¹⁸ When the *p*-toluenesulfonyl substituent of substrate 2 was changed to a methylsulfonyl group, the reaction could also produce the product but with a relatively low yield and enantioselectivity (Table 2, 3f vs 3a), probably because of the weaker interaction between substrate 2 and the catalyst. In addition, the electronic properties of substrates 2 had pronounced effects on the stereoselectivity and yield. In general, substrates 2 with electron-donating substituents (Table 2, 3g and 3h) or electron-rich aromatic rings (Table 2, 3i–1) exhibited higher reactivities compared with those with electron-withdrawing substituents, which needed a higher reaction temperature (Table 2, 3m). More electron-withdrawing substituents (Br or NO₂) inhibited the reaction. Furthermore, halogen-monosubstituted quinone derivatives were well-tolerated (Table 2, 3n and 3o), and substrates 2

Table 2. Scope of the Asymmetric Synthesis of Axially Chiral Biaryldiols^a



^{*a*}Conditions: the reactions were performed with 1 (0.1 mmol), 2 (0.1 mmol), and catalyst X (20 mol %) in toluene (1 mL) at -40 °C for 12 h. For detailed experimental procedures, see the Supporting Information.

with relatively low reactivities showed more satisfactory results when 2-methyl-5-hydroxyindole was used as the substrate (Table 2, 3p-s). Unfortunately, naphthoquinone derivatives could not produce the desired products, and the materials were completely recycled.

To demonstrate the application of axially chiral biaryldiols as asymmetric catalysts, an enantioselective allylboration of a ketone catalyzed by the axially chiral product **3c** was carried out. The experimental results revealed that this new type of axially chiral biaryldiol had more efficient catalytic activity and stereocontrol ability than traditional binaphthols report previously¹⁹ (Scheme 2). Notably, when the chiral biphenol, which has a wider bite angle than BINOLs, was used as the catalyst, the reaction could provide only the racemic products. This result indicated that the Ts group and indole may play important roles in the process.

To further explore the practicability of the axially chiral product, a large-scale asymmetric synthesis of **3c** was

Scheme 2. Application of Axially Chiral Biaryldiol 3c



performed, and the hydrogen-bond catalyst was recycled (Table 3). Fortunately, the reaction proceeded smoothly to





entry	no. of recovery cycles	yield of catalyst (%)	yield of 3c (%)	ee (%)
1	0	_	90	>99
2	1	99	89	>99
3	2	99	89	>99
4	3	98	89	>99
5	4	98	88	>99
6	5	98	88	>99

afford the axially chiral product with excellent results, and the catalyst remained active even after five recycles (Table 3, entry 6).

NMR experiments on mixtures of substrates and catalysts were conducted to explore the reaction mechanism (Figure 2). The ¹H NMR spectrum of the mixture revealed that the catalyst interacted with quinone derivative 2a via hydrogen bonding to generate a new activated complex. With the stepwise addition of the catalyst, the ¹H NMR spectrum of the mixture showed that the signal of substrate 2a gradually weakened and the signal of the new activated complex was



Figure 2. Continuous NMR experiments.

enhanced gradually (Figure 2). Additionally, when 0.5 equiv of the catalyst was used (Figure 2), completely transformed **2a** (the signal of substrate **2a** disappeared completely) demonstrated a 1:2 binding interaction between the catalyst and **2a**. The hydroxyl group of substrate **1a** was proved to have weak interaction with the catalyst on the basis of the obvious changes of the chemical shifts between the mixture and pure 5hydroxyindole (Figure 3), and the Lewis basic property of the



Figure 3. Exploration of the reaction mechanism.

sulfur atom was thought to play a role in the reaction. Further experiment showed that 5-methoxyindole could not produce the product because of the lack of the interaction between a hydroxyl group and the catalyst (Scheme 3a).

Scheme 3. Control Experiments



On the basis of our experimental results and previous reports, a plausible reaction mechanism is proposed (Figure 4).



Figure 4. Proposed mechanism.

First, enantioselective conjugate addition of 5-hydroxyindole to the iminoquinone catalyzed by hydrogen-bond donor **X** proceeds to form the intermediate. Next, aromatization with central-to-axial chirality conversion affords the axially chiral biaryldiol. It is noticeable that another cascade pathway involving sequential aminal formation/[3,3]-rearrangement/ aromatization could be ruled out because the corresponding product at C6 of the indole and the O-addition product of imine were not observed (the materials were completely recycled) when 4-fluoro-5-hydroxyindole was used as the substrste (Scheme 3b).^{8c}

In summary, we have developed a practical and efficient approach for constructing axial chirality through functionalization of indoles in the carbocyclic ring catalyzed by hydrogenbond donors, and a series of axially chiral biaryldiols with asymmetric catalysis potential were obtained in moderate to high yields with good atropo-enantioselectivities. Notably, the axially chiral product showed more efficient catalytic activity and stereocontrol ability than traditional binaphthols, complementing and extending the scope of chiral catalysts. Furthermore, mechanistic studies provided new insights into the construction of axially chiral indoles via hydrogen-bond catalysis. Further studies of applications of these compounds as ligands and catalysts for asymmetric catalysis are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01828.

Experimental details, characterization data, and HPLC data for all compound derivatives (PDF)

Accession Codes

CCDC 1898795 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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