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Bifunctional Organocatalysts for the Enantioselective Synthesis of Axially Chiral Isoquinoline *N*-Oxides

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Supporting Information

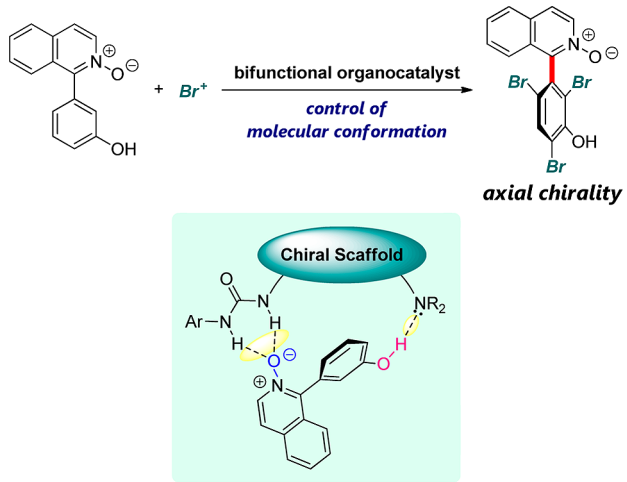
ABSTRACT: Bifunctional catalysts bearing amino and urea functional groups have been applied for a novel, highly enantioselective synthesis of axially chiral isoquinoline *N*-oxides, which are promising chiral ligands or organocatalysts in organic synthesis. This is the first example of highly enantioselective synthesis of axially chiral biaryls by bifunctional organocatalysts. Good-to-excellent enantioselectivities were obtained with a range of substrates.

Bifunctional organocatalysts have significantly contributed to the field of asymmetric synthesis.[1] In these catalysts, the (thio)urea and tertiary amino functional groups cooperatively realize the simultaneous activation of a nucleophile and an electrophile in a suitable spatial configuration. Previously, we have used these organocatalysts for several asymmetric cyclization reactions via intramolecular hetero-Michael addition,[2] in which multipoint recognition by the catalysts stabilizes the specific conformations of the substrates in the transition state before the construction of a chiral center. Inspired by the success of these results, we envisaged that the utility of this class of small-molecule catalysts could be expanded by translating the molecular torsion induced by bifunctional organocatalysts into axial chirality. Recently, although some organocatalysts have been reported to be useful for the enantioselective syntheses of axially chiral compounds,[3] thus far, methods employing this type of bifunctional organocatalysts have rarely been developed.[4] Here, we demonstrate the novel competence of bifunctional organocatalysts as an efficient avenue for the asymmetric construction of axially chiral compounds.

In this study, we report the highly enantioselective aromatic electrophilic bromination of 1-(3-hydroxyphenyl)isoquinoline 2-oxides (Scheme 1). The 1-(3-hydroxyphenyl)isoquinoline 2-oxide substrates have an isoquinoline *N*-oxide moiety, which can interact with a hydrogen-bond donor, and a phenol moiety, which can interact with a hydrogen-bond acceptor; such interactions are expected to twist the molecule in one direction. Meanwhile, the axially chiral *N*-oxides obtained are promising chiral ligands or organocatalysts in organic synthesis,[5] although thus far, their catalytic enantioselective synthesis has been underdeveloped, to the best of our knowledge.

Table 1 shows the optimization of reaction conditions. First, we investigated the reaction between 1-(3-hydroxyphenyl)-isoquinoline 2-oxide (**1a**) and *N*-bromoacetamide (NBA, **4a**) as the brominating reagent with 10 mol % of quinidine-derived

Scheme 1. Construction of Axially Chiral Structure by Using Bifunctional Organocatalysts



bifunctional catalyst **3a**[6] in CH_2Cl_2 at −40 °C. As expected, tribromide **2a** was obtained in good yield with moderate enantioselectivity (Table 1, entry 1). Second, the solvents were screened, and among those tested, THF was identified to be the most suitable solvent, demonstrating high enantioselectivity, albeit with an unsatisfactory product yield (Table 1, entry 5). Third, the effect of temperature on the reaction was studied: higher temperatures improved the product yield while maintaining excellent enantioselectivites (Table 1, entries 6 and 7); hence, we selected 0 °C as the reaction temperature for further investigations. Meanwhile, the effect of various brominating reagents besides NBA (DBH (**4b**), NBS (**4c**), and NBP (**4d**)) was also studied. Figure 1 shows their chemical structures. As can be seen, no significant effects were observed with respect to the yields and enantioselectivities (Table 1, entries 8−10). Next, the effect of different catalysts was also investigated; other cinchona-alkaloid-derived catalysts[6] also exhibited good stereoselectivities similar to that obtained with the use of **3a** (entry 6), and the use of **3c** and **3d** afforded the opposite enantiomer of the product with high enantioselectivities (Table 1, entries 11−13). Moreover, catalyst **3e**,[6] with a cyclohexanediamine framework, also afforded a quantitative product yield with a slightly lower enantioselectivity (Table 1, entry 14). On the other hand, catalyst **3f**,[6] which has a

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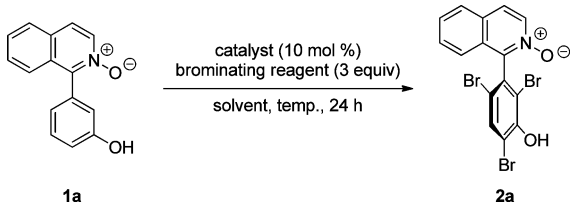
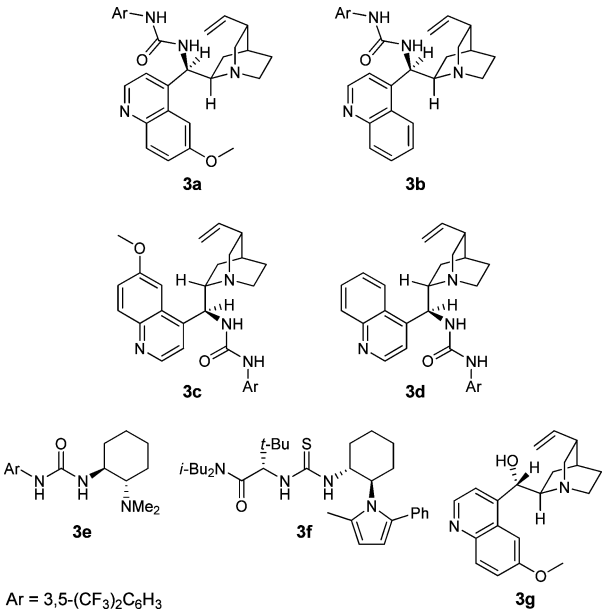
Table 1. Optimization of Conditions[a]



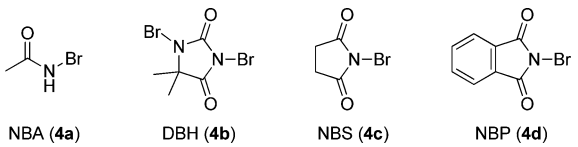
1a 2a

entry	catalyst	brominating reagent	solvent	temp. (°C)	yield (%)[b]	ee (%)
1	**3a**	NBA (**4a**)	CH_2Cl_2	−40	95	54
2	**3a**	NBA (**4a**)	toluene	−40	7	74
3	**3a**	NBA (**4a**)	EtOAc	−40	50	93
4	**3a**	NBA (**4a**)	Et_2O	−40	<5	–
5	**3a**	NBA (**4a**)	THF	−40	32	99
6[c]	**3a**	NBA (**4a**)	THF	0	99	99
7[d]	**3a**	NBA (**4a**)	THF	25	99	97
8[c,e]	**3a**	DBH (**4b**)	THF	0	99	98
9[c]	**3a**	NBS (**4c**)	THF	0	99	98
10[c]	**3a**	NBP (**4d**)	THF	0	99	98
11[c]	**3b**	NBA (**4a**)	THF	0	99	98
12[c]	**3c**	NBA (**4a**)	THF	0	85	−96
13[c]	**3d**	NBA (**4a**)	THF	0	84	−94
14[c]	**3e**	NBA (**4a**)	THF	0	99	−91
15[c]	**3f**	NBA (**4a**)	THF	0	46	1
16[c]	**3g**	NBA (**4a**)	THF	0	91	−42

[a]Reactions were run using **1a** (0.1 mmol), the brominating reagent (0.3 mmol), and the catalyst (0.01 mmol) in the solvent (10 mL). [b]Isolated yields. [c]Reactions were run for 6 h. [d]Reaction was run for 5 h. [e]1.5 equiv of **4b** was used for the reaction.



3a **3b** **3c** **3d** **3e** **3f** **3g**



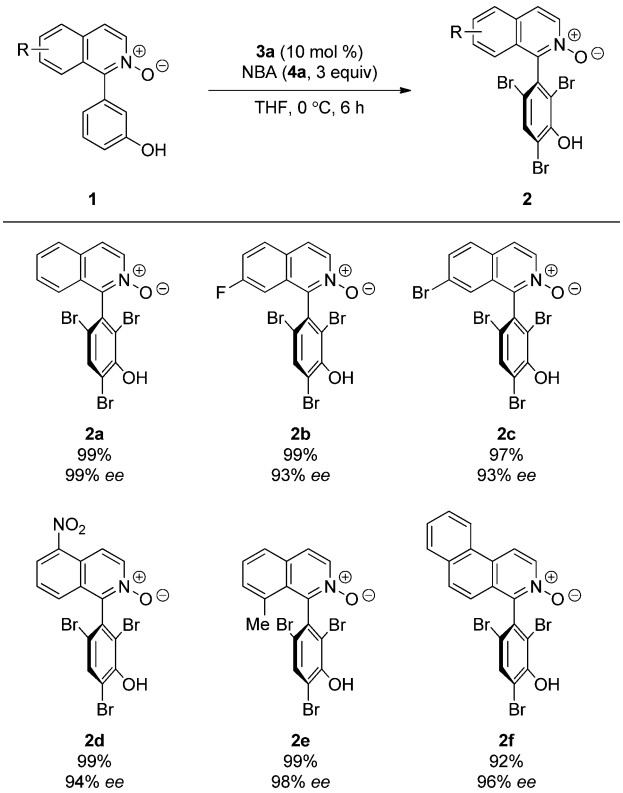
NBA (**4a**) DBH (**4b**) NBS (**4c**) NBP (**4d**)

Figure 1. Brominating reagents.

significantly less basic nitrogen atom, failed to attain enantioselectivity (Table 1, entry 15). Moreover, quinidine (**3g**) also demonstrated enantioselectivity significantly lesser than those exhibited by catalysts **3a**−**3e** (Table 1, entry 16). These results demonstrate the significance of the bifunctionality of the catalyst containing amino and urea functional groups toward enantioselectivity.

Next, the substrate scope was investigated, and the robustness of this synthetic method was confirmed. Table 2 shows the

Table 2. Substrate Scope[a]



1 2

[a]Reactions were run using **1** (0.1 mmol), **4a** (0.3 mmol), and **3a** (0.01 mmol) in THF (10 mL). Yields represent material isolated after silica gel column chromatography.

results. For substrates bearing fluoro and bromo functional groups on the isoquinoline ring, the desired products **2b** and **2c** were obtained with high enantioselectivities. Moreover, a nitro group was also tolerated, affording the corresponding product **2d** in high enantioselectivity. Furthermore, a substrate with a methyl group near the biaryl axis yielded the brominated product **2e** in excellent yield and enantioselectivity. In addition, a derivative bearing an expanded π-conjugate plane afforded the brominated product **2f** in good yield and stereoselectivity. Moreover, as shown in Scheme 2, substrates bearing substituted phenols were also investigated. A meta substituent on the phenol ring did not affect the reaction, affording **2g** in excellent yield and enantioselectivity. Moreover, when the reaction was carried out using **1h**, which has a substituent ortho to the hydroxy group, dibromination proceeded with quantitative yield with excellent enantioselectivity. Meanwhile, the absolute configuration of **2a** was determined by X-ray analysis (see the Supporting Information for details), and the configurations of all other examples were assigned analogously.

To gain insight into the reaction mechanism, the reactions were performed using substrates previously monobrominated at the ortho positions of the biaryl axis, and almost racemic products were obtained in both reactions (Scheme 3). These

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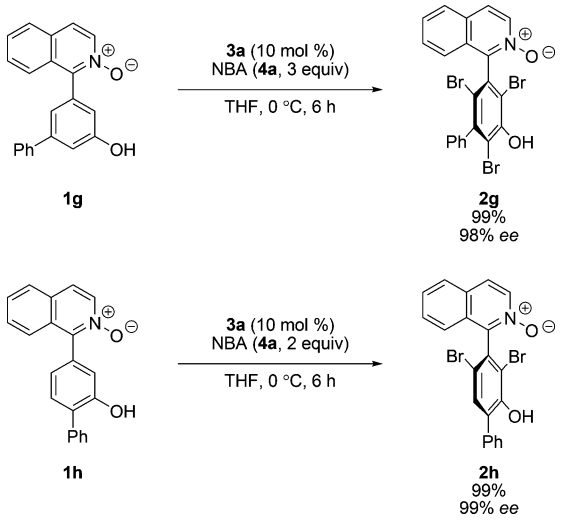
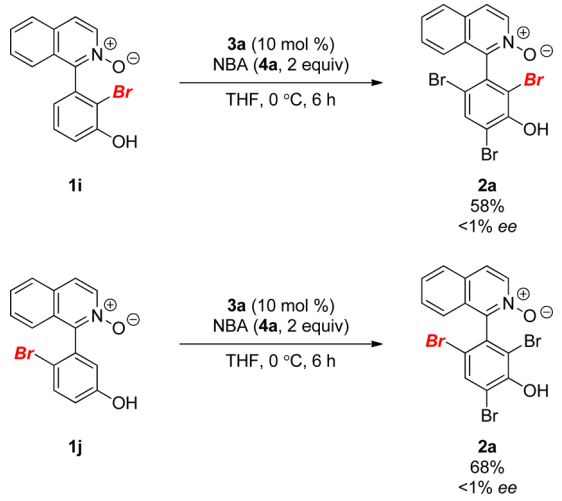
Scheme 2. Reactions of Substrates with Substituted Phenols



Scheme 3. Reactions of Monobrominated Substrates

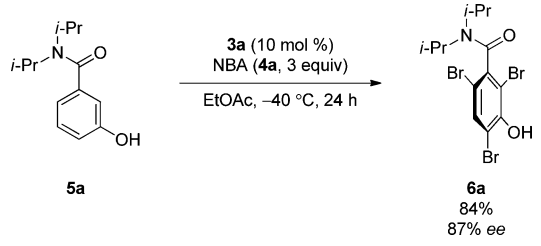


results imply that the bromination at an ortho position of the axis is the enantiodetermining step in this reaction, and once one of the ortho positions is brominated, no racemization occurs by bond rotation during the course of further bromination.[7]

In addition, this protocol could also be applied to the synthesis of an axially chiral benzamide (Scheme 4),[3g] indicating the feasibility of this method with the use of this bifunctional organocatalyst. By using 10 mol % **3a** and 3 equiv **4a** with EtOAc at −40 °C, benzamide **5a** was tribrominated to afford optically active benzamide **6a** in high yield and enantioselectivity.[8]

In summary, we present a novel, highly enantioselective synthesis of axially chiral isoquinoline *N*-oxides using bifunctional organocatalysts. This method efficiently produces axially chiral *N*-oxides, which are promising chiral catalysts in organic synthesis. Notably, this is the first example of the use of simple bifunctional organocatalysts for the asymmetric synthesis of axially chiral biaryls. In addition, good-to-excellent enantioselectivities were accomplished with a range of substrates. Thus, this methodology demonstrates utility for further application in the synthesis of various axially chiral compounds. Further studies regarding the detailed clarification of the reaction mechanism and application of this methodology to the construction of other axially chiral structures are currently underway and will be reported in due course.

Scheme 4. Asymmetric Synthesis of Benzamide



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures including spectroscopic and analytical data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04151.

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Notes

The authors declare no competing financial interest.

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(6) Catalysts **3a**−**3e** were prepared according to previous studies (see the SI for details): for **3a**−**3d**, see ref 1c; for **3e**, see ref 1a. Catalyst **3f** was purchased from Aldrich; see: Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

(7) The reaction conducted using 1 equiv of NBA (**4a**) afforded a mixture of multiple products including monobromide **1i**, while a small amount of **1j** was generated; the ee of **1i** was >95% ee (see the SI for details). Thus, we currently consider that the bromination at the ortho position of the hydroxy group occurs before the bromination at the para position of the hydroxy group.

(8) The reaction of 3-hydroxy-*N*,*N*-dicyclohexylbenzamide (**5b**) afforded the corresponding tribromide, 2,4,6-tribromo-*N*,*N*-dicyclohexyl-3-hydroxybenzamide (**6b**) in 99% yield with 79% ee; the absolute configuration of **6b** was determined by X-ray analysis (see the SI for details).

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