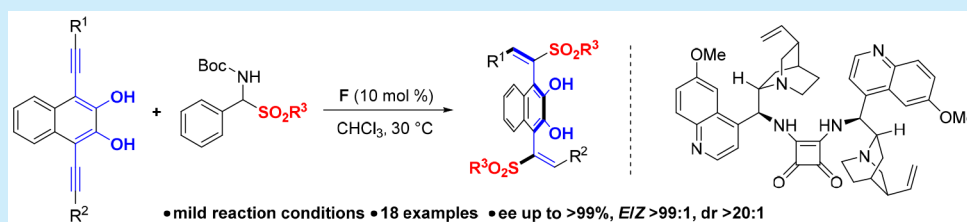


# Organocatalytic Asymmetric Atroposelective Construction of Axially Chiral 1,4-Distyrene 2,3-Naphthalene Diols

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**S** Supporting Information



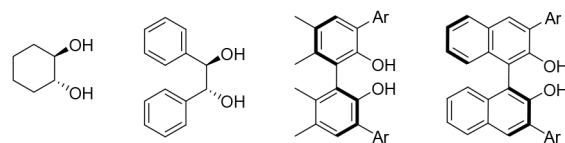
**ABSTRACT:** An efficient organocatalytic construction of enantioenriched axially chiral 1,4-distyrene 2,3-naphthalene diols through the nucleophilic addition of  $\alpha$ -amido sulfone to in situ generated vinylidene *o*-quinone methide is described. The reaction pathway was investigated by isolating reaction intermediates and performing a kinetic resolution process. Axially chiral 1,4-distyrene 2,3-naphthalene diol was used as the chiral ligand for the enantioselective addition of diethylzinc to naphthalene formaldehyde. The preliminary results revealed that these adducts could be potentially used as ligands in asymmetric synthesis.

Diols are prominent feature of a number of biologically active natural products such as Taxol, isolobophytolide, and TAN-1085.<sup>1</sup> In addition, chiral diols are also widely used as chiral ligands and auxiliaries in stereoselective synthesis such as cyclohexyl glycol, hydrobenzoin, and axially chiral diaryl diols.<sup>2</sup> As a result, synthetic approaches toward the construction of these scaffolds have attracted considerable attention, and many practical methods have already been achieved.<sup>3</sup> The chiral diols commonly used as catalysts or ligands are  $C_2$ -symmetric diols that bear two hydroxyl groups in a tunable dihedral angle to meet the coordination requirements and one rigid  $C_2$ -symmetric axis to play a fundamental cooperative role in the stereochemical control (Scheme 1a).<sup>4</sup> To our knowledge, chiral diols bearing two hydroxyl groups in a single plane (no angle) along with two chiral axes remain largely unaddressed, probably due to a lack of reliable synthetic routes to atroposelectively construct two contiguous enantioenriched chiral axes. Therefore, it is necessary to develop a synthetic approach to construct two chiral axes surrounding the diols to afford novel axial chirality compounds.

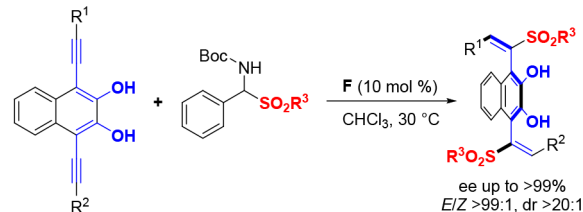
In order to develop new and practical organocatalytic atroposelective methods for the preparation of highly functionalized axially chiral styrene, we envisaged that two units of axially chiral styrene could be installed into the positions 1 and 4 of naphthalene 2,3-diols to accomplish the introduction of chiral circumvents to vicinal diols. The key to this scenario is the construction of the axially chiral styrene skeleton, which represents a formidable challenge in asymmetric synthesis due to the relatively low-rotation energy to racemization and the difficulty in controlling the enantioselectivity.<sup>5</sup> Consequently, few methods are available for their atroposelective synthesis in

## Scheme 1. Reported $C_2$ -Symmetric Axis Diols and This Work

a) Reported structures:  $C_2$ -symmetric axis diols



b) This work: Double axes chiral diols



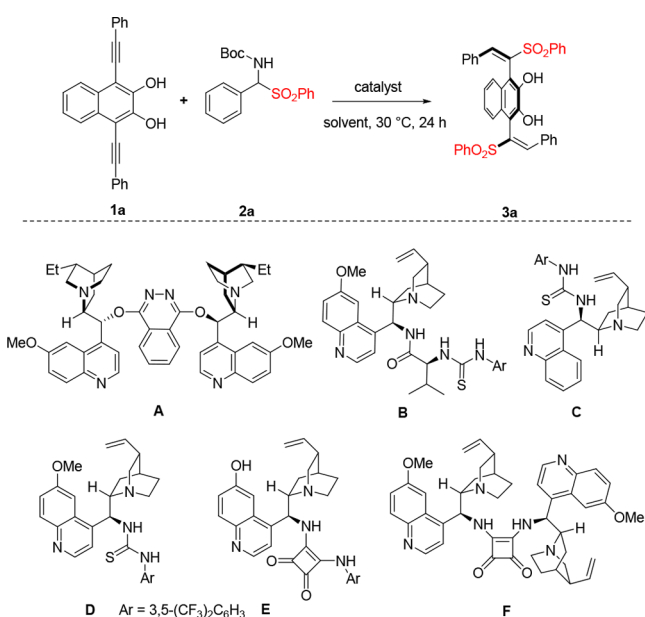
an operationally simple and scalable fashion. The current strategies include palladium-catalyzed enantioselective arylation of hydrazones and aryl bromide,<sup>6</sup> organocatalytic atroposelective direct Michael reaction of diones to alkynals,<sup>7</sup> and organocatalytic nucleophilic addition of the vinylidene *o*-quinone methide (VQM)<sup>8</sup> intermediate by sulfone. However, all of the reported methods afforded products bearing only a single chiral styrene axis. A method for constructing two continuous chiral styrene axes has not yet been reported. Our research group has been engaged in developing new and

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practical methods for the construction of axially chiral compounds based on VQM intermediate.<sup>8c–f</sup> We presumed that two moieties of VQM could be generated in one naphthalene, followed by a formal stereoselective nucleophilic addition to install two chiral styrene units. Thus, a new kind of chiral axis skeleton bearing two continuous chiral styrene axes arose. Herein, we describe an organocatalytic atroposelective synthesis of 1,4-distyrene compounds bearing a 2,3-diol motif allowing the construction of novel axial chiral scaffolds for the development of chiral ligands or catalysts for asymmetric synthesis.

Initially, we began our studies with 1,4-bis(phenylethynyl)-naphthalene 2,3-diol **1a** and  $\alpha$ -amido sulfone **2a** as model substrates. In the presence of dimeric cinchona alkaloid derivative catalyst **A**, the reaction proceeded smoothly with good yield, while the enantioselectivity (ee = 7%) (Table 1,

Table 1. Optimization of Reaction Conditions<sup>a</sup>



entry	catalyst	solvent	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	dr <sup>d</sup>
1	A	CHCl <sub>3</sub>	85	7	1:1
2	B	CHCl <sub>3</sub>	30	90	1:1
3	C	CHCl <sub>3</sub>	36	>99	10:1
4	D	CHCl <sub>3</sub>	50	>99	>20:1
5	E	CHCl <sub>3</sub>	75	>99	>20:1
6	F	CHCl <sub>3</sub>	88	>99	>20:1
7	F	CH <sub>2</sub> Cl <sub>2</sub>	77	>99	>20:1
8	F	toluene	79	>99	>20:1
9	F	CH <sub>3</sub> CN	72	99	>20:1
10	F	Et <sub>2</sub> O	<5		
11	F	THF	<5		

<sup>a</sup>Reaction conditions: **1a** (0.05 mmol), **2a** (0.1 mmol), catalyst (10 mol %) in solvent (1.0 mL) at 30 °C for 24 h, unless otherwise specified. <sup>b</sup>Isolated yield. <sup>c</sup>The ee value was determined by HPLC analysis. <sup>d</sup>Diastereomeric ratio (dr) was determined by <sup>1</sup>H NMR.

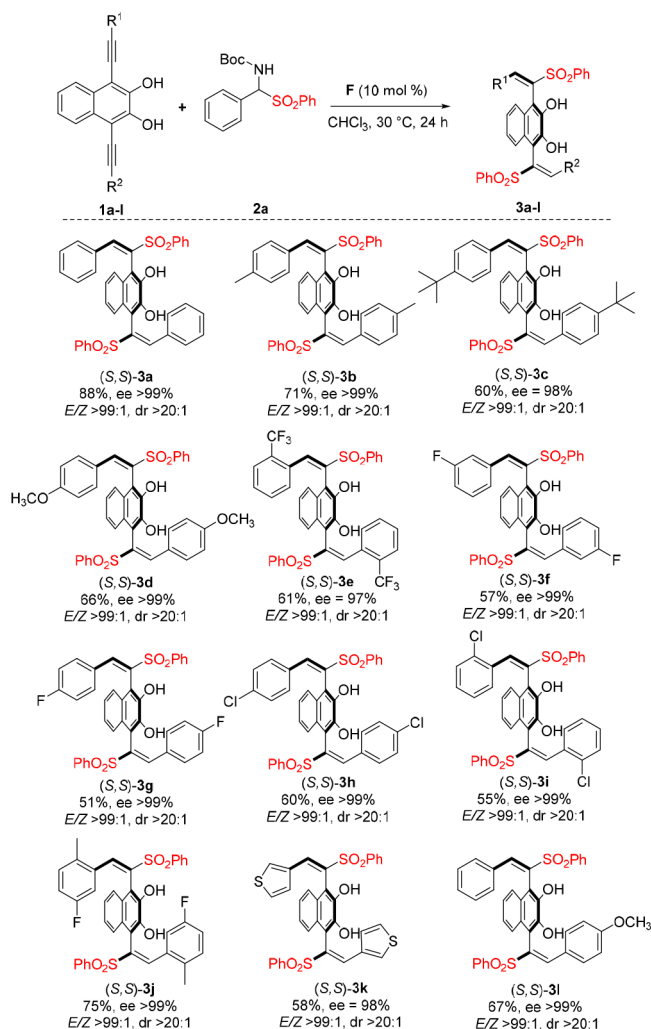
entry 1) and diastereoselectivity were quite poor (Table 1, entry 1). This might be ascribed to a lack of hydrogen-bonding donors. Therefore, we turned our attention to cinchona-derived catalysts with hydrogen-bonding donors. Thiourea-based catalysts **B–D** were selected for further screening. The enantioselectivities of the reactions were dramatically increased

compared to catalyst **A**. Both catalysts **C** and **D** showed excellent stereoselectivity. Nevertheless, the yields of reactions catalyzed by thiourea-based catalysts were generally low. Quinine-derived squaramides, which had a longer distance between the two donor hydrogen atoms than that of thioureas, had been successfully employed in a wide range of asymmetric reactions as hydrogen-bonding donor catalysts.<sup>9</sup> Cinchona squaramide catalysts **E** and **F** gave excellent enantiocontrol and afforded **3a** in higher yields. Eventually, bisquinona squaramide catalyst **F** afforded an improved chemical yield while retaining the stereoselectivity under the same conditions (88%, ee >99%, dr >20:1) (Table 1, entry 6). All of the solvents tested for the reaction were catalyzed by catalyst **F** (Table 1, entries 6–11), and chloroform was proven to be the optimal solvent with respect to enantioselectivity and yield (Table 1, entry 6). Finally, the reaction proceeded smoothly with retained enantioselectivity by using 10 mol % of catalyst **F** in chloroform at 30 °C.

After establishing the optimal catalyst **F** and experimental procedure, we expanded **1** toward the nucleophilic addition of **2a**. Substrates with electron-donating groups on the *para* position of the R group proceeded smoothly to give the desired adducts **3b**, **3c**, and **3d** in excellent stereoselectivity (ee up to 99%, dr >20:1) with moderate yields. The electron-withdrawing groups at different positions of R appeared to have a limited effect on stereoselectivity (**3e–i**) (Scheme 2). All of the substrates gave excellent enantioselectivities, and a significantly lower reaction rate was observed. The absolute configuration of product **3h** was determined by X-ray crystallographic analysis, while others were assigned by analogue. The substrate with 5-fluoro-2-methyl-disubstituted R also afforded the desired product **3j** with excellent stereocontrol (ee >99%) under the standard reaction conditions, demonstrating that the substrate scope was not limited to monosubstituted substrates. Changing the phenyl group into a more useful heterocyclic ring, such as thiophene, almost had no influence on the reaction stereoselectivity and still gave excellent results (**3k**) (Scheme 2). When the substrate was asymmetric (R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, R<sup>2</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>), the reaction also proceeded smoothly to afford the desired product with good results (**3l**) (Scheme 2).

To further evaluate the substrate scope, we then investigated a series of substitution groups on the sulfone moiety of  $\alpha$ -amido sulfones. The results are outlined in Scheme 3. Regardless of the type of substituents on the aromatic rings of sulfone, bearing electron-donating (**3m**) (Scheme 3) or electron-withdrawing (**3n–p**) (Scheme 3) groups on the *para* position, the reactions of these  $\alpha$ -amido sulfones gave axially chiral distyrene diols with high stereoselectivities and good reactivities. Notably, 3-chloro-4-methyl-disubstituted  $\alpha$ -amido sulfone also led to the desired adduct with excellent stereoselectivity and good yield (**3q**) (Scheme 3). An aliphatic substitution group on the sulfone moiety also is tolerated to our reaction system. A high enantioselectivity of 99% ee was also obtained, although the diastereoselectivity and chemical yield were decreased.

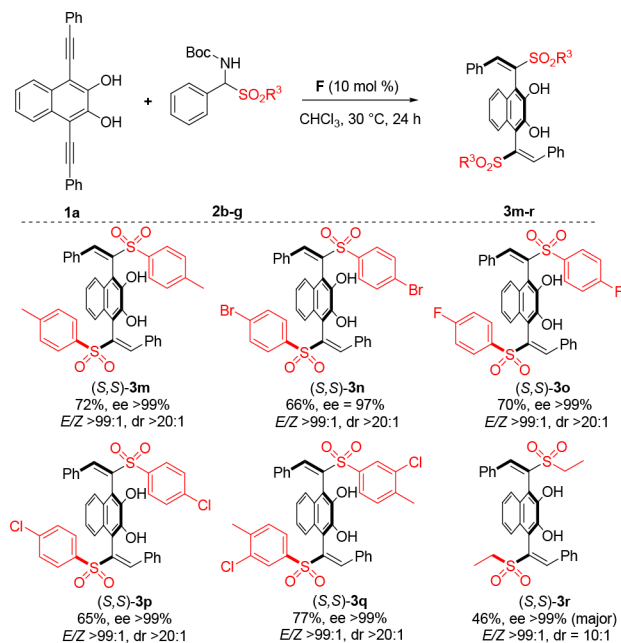
In order to gain insight into the reaction process, we performed an experiment to monitor the reaction with thin-layer chromatography (TLC). We found that, at an early stage of the reaction, two new spots appeared simultaneously. At the beginning of the reaction, intermediate (*S*)-**3aa** with high enantioselectivity (ee = 97%) was isolated, and product (*S,S*)-**3a** was also formed with excellent enantioselectivity (ee >99%)

Scheme 2. Substrate Scope<sup>a</sup>

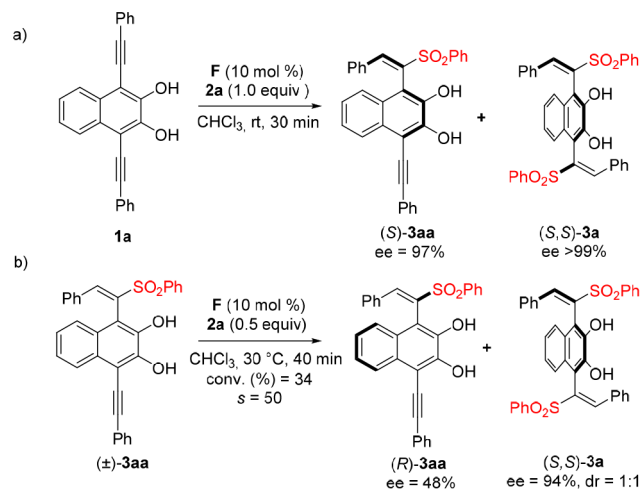
<sup>a</sup>Reaction conditions: 1 (0.2 mmol), 2a (0.4 mmol), F (10 mol %) in CHCl<sub>3</sub> (2.0 mL) at 30 °C for 24 h, unless otherwise specified.

(Scheme 4a). In the later stage, the reaction experienced a change in two different trends. The intermediate (S)-3aa disappeared with the increase in final product (S,S)-3a. To further understand the reaction process of the second step, we performed a kinetic resolution reaction with racemic (±)-3aa as substrate. As shown in Scheme 4b, the racemic (±)-3aa was treated with 0.5 equiv of 2a under the standard reaction conditions. After 40 min, optically pure (S,S)-3a (ee = 94%) was successfully formed. The *s* value of this kinetic resolution process was 50 (see the Supporting Information (SI) for details). This observation indicated that this reaction could be explored as a kinetic resolution process. Our catalytic system has a strong stereocontrol even in the second reaction step.

Mechanistically, we assume a stepwise process initiated by a conjugate addition of the in situ generated sulfone anion to the VQM which is generated through an enantioselective prototropic rearrangement (tautomerization) in the presence of quinine-derived squaramide catalyst F (Scheme 5). The activation of the α-amido sulfone with quinine-derived squaramide catalyst F appears necessary for increasing its nucleophilicity and facilitating the conjugate addition. Next, repeating the above-mentioned reaction pathway gives the final product (S,S)-3a with excellent enantioselectivity.

Scheme 3. Substrate Scope<sup>a</sup>

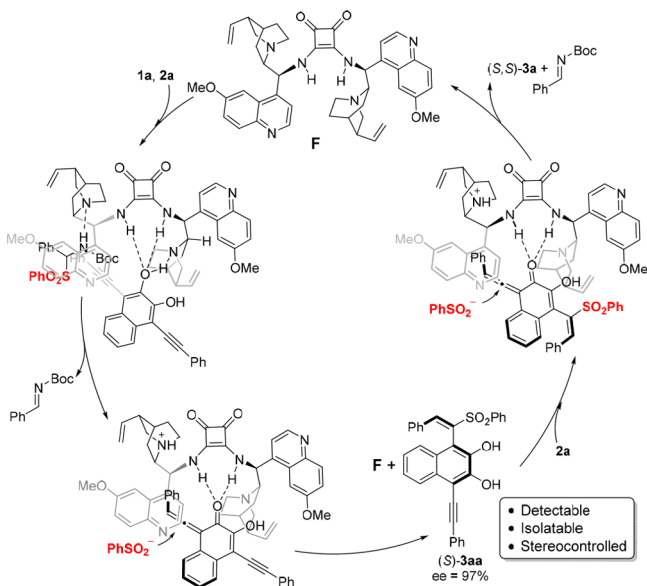
<sup>a</sup>Reaction conditions: 1a (0.2 mmol), 2 (0.4 mmol), F (10 mol %) in CHCl<sub>3</sub> (2.0 mL) at 30 °C for 24 h, unless otherwise specified.

Scheme 4. Mechanistic Experiments<sup>a</sup>

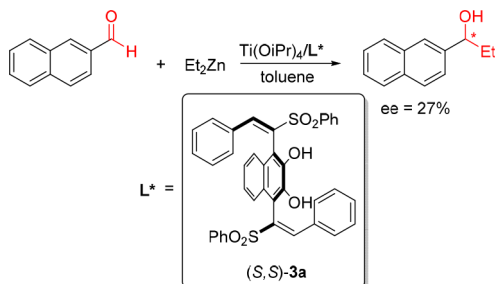
<sup>a</sup>For reaction conditions, see the SI. The ee value was determined by HPLC analysis.

Additionally, to further demonstrate the utility of the obtained chiral 1,4-distyrene 2,3-naphthalene diols in synthesis, especially used as organocatalysts or ligands, we first performed a scaled-up experiment (see the SI for details). The reaction proceeded smoothly to give the product on gram scale without the loss of stereoselectivity and yield. Next, we tested the configurational stability of the product by heating a solution of (S,S)-3a in DCE at 80 °C for 24 h. Chiral HPLC analysis showed that the ee was unaffected (see the SI for details). Thus, we further investigated the obtained chiral 1,4-distyrene 2,3-naphthalene diol (S,S)-3a as a ligand for the enantioselective addition of diethylzinc to naphthalene formaldehyde, which was considered to be one of standard reactions to test the reactivity and enantioselectivity of newly designed chiral ligands.<sup>10</sup> As a result, product (S,S)-3a showed

## Scheme 5. Proposed Mechanism



the role as ligand in this reaction and gave chiral *sec*-alcohols with an enantiomeric excess of 27% under unmodified reaction conditions (Scheme 6).

Scheme 6. Preliminary Application in Addition of Diethylzinc to Aldehyde<sup>a</sup>

<sup>a</sup>For reaction conditions, see the SI. The ee value was determined by HPLC analysis.

In conclusion, we have developed an organocatalytic atroposelective approach for the construction of axially chiral 1,4-distyrene 2,3-naphthalene diols with excellent stereoselectivities (ee up to 99%, dr >20:1). The reaction proceeded through nucleophilic addition of  $\alpha$ -amido sulfone to VQM and gave 1,4-distyrene 2,3-naphthalene diols with high atroposelectivity. The reaction process was demonstrated by isolating and identifying the reaction intermediates and performing kinetic resolution experiments. The preliminary investigation indicated the potential of axially chiral 1,4-distyrene 2,3-naphthalene diols as ligands for asymmetric synthesis.

## ■ ASSOCIATED CONTENT

## S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03398.

Experimental procedures and characterization data for all of the products (PDF)

## Accession Codes

CCDC 1864091 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](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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