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Highly Effective and Diastereoselective Synthesis of Axially Chiral Bis-sulfoxide Ligands via Oxidative Aryl Coupling

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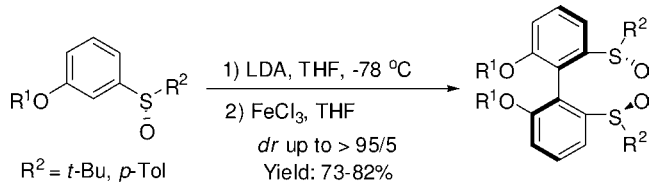
ABSTRACT



A series of axially chiral bis-sulfoxide ligands have been efficiently synthesized via oxidative coupling with high diastereoselectivities. The axial chirality is well controlled by the *tert*-butylsulfinyl or the *p*-tolylsulfinyl group. These axially chiral bis-sulfoxides proved to be remarkably efficient ligands for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to 2-cyclohexenone with 99% ee.

In the past decade, considerable efforts have been undertaken for using enantiopure sulfinyl groups as efficient chiral auxiliaries in asymmetric C−C and C−X bond formations.[1] The success and effectiveness of the sulfinyl group as a chiral controller lie in three basic factors: (i) its high optical stability, (ii) its efficiency as a carrier of the chiral information, and (iii) its accessibility in both enantiomeric forms. Therefore, much progress has been achieved in asymmetric synthesis employing enantiopure sulfoxides as chiral ligands.[1d,j,k,2] Despite the fact that axially chiral ligands are most commonly used for asymmetric transformations, limited optically pure sulfoxide ligands bearing axial chirality have hitherto been described.[3] Recently, Dorta et al. disclosed that axially chiral bis-sulfoxides, synthesized from racemic axial dibromides, can

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(1) (a) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (c) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (d) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (e) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (f) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z. H.; Han, Z. X.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93. (g) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (h) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559. (i) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993. (j) Pellissier, H. *Tetrahedron* **2007**, *63*, 1297. (k) Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129. (l) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (m) Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133.

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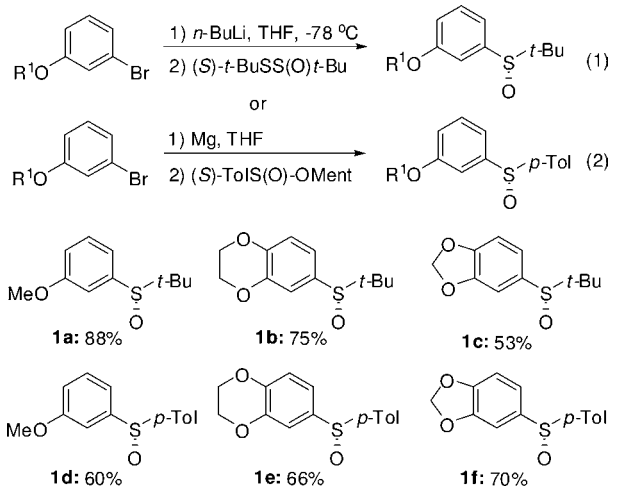
be used successfully as ligands in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to enones with excellent enantioselectivties.[3a,b] Thus, development of a simple and efficient method for the synthesis of optically pure axially chiral sulfoxide ligands is highly desirable. Herein, we report an efficient and highly diastereoselective synthesis of axially chiral bis-sulfoxide ligands via oxidative coupling.

On the basis of the preparation of chiral atropisomeric biaryl diphosphines through oxidative coupling with iron(III) chloride,[4] enantiopure sulfoxides **1** were first synthesized according to the literature procedure (Scheme 1).[2h] Standard

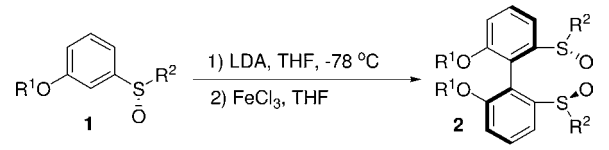
Scheme 1. Synthesis of Enantiopure Sulfoxides **1**

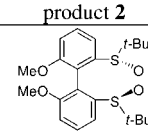
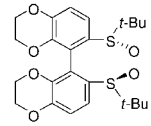
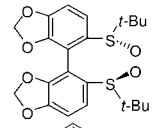
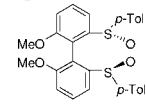
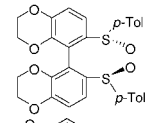
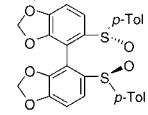


bromo−lithium exchange of bromo-arene derivatives proceeded at low temperature. After quench by thiosulfinate that is commercially available, the desired products **1a**−**1c** were obtained in moderate to high yields (53−88% yields, eq 1). The reaction of Grignard reagents (derived from aryl bromides) with enantiopure (S_S)-menthyl *p*-toluenesulfinate delivered their corresponding enantiopure sulfoxides **1d**−**1f** in good yields (60−70% yields, eq 2).

Next, we studied the oxidative homocoupling reactions of enantiopure sulfoxides **1** using $FeCl_3$ as the oxidant (Table 1). Deprotonation of **1a** with LDA generated the ortholithiated intermediate, which could be oxidized by $FeCl_3$ to provide bis-sulfoxide **2a** with high diastereoselectivity (>95:5) and good yield (76%, entry 1). Recrystallization from EtOAc and CH_2Cl_2 gave optically pure **2a** as a colorless crystalline solid, and its absolute configuration was assigned as (*M*,*S*,*S*) by X-ray crystallographic analysis (Figure 1).

Table 1. Atropo-diastereoselective Oxidative Coupling Reaction with a *tert*-Butyl and a *p*-Tolylsulfinyl Group as Chiral Auxiliary



entry	1	product 2	yield (%)[a]	dr[b]
1	**1a**		76 (**2a**) *t*-Bu-MeO-BipheSO	> 95:5 (*M*,*S*,*S*)[c]
2	**1b**		76 (**2b**) *t*-Bu-MeO-SynSO	94:6
3	**1c**		78 (**2c**) *t*-Bu-MeO-SegSO	> 95:5
4	**1d**		73 (**2d**) *p*-Tol-MeO-BipheSO	92:8
5	**1e**		81 (**2e**) *p*-Tol-MeO-SynSO	> 95:5
6	**1f**		82 (**2f**) *p*-Tol-MeO-SegSO	> 95:5

[a] Mixture of both diastereomers. [b] Determined by ^{1}H NMR on the crude mixture. [c] The absolute configuration of major diastereomer of **2a** was determined by X-ray analysis. Other products' absolute configurations were assigned as (*M*,*S*,*S*) by analogy to **2a**.

The oxidative coupling reaction was quite general. Several aryl sulfoxides **1** bearing *tert*-butyl or *p*-tolyl sulfinyl group all delivered their corresponding axially chiral bis-sulfoxides **2b**−**2f** in good yields with excellent diastereoselectivities (entries 2−5). Fortunately, the minor diastereomer (*P*,*S*,*S*)-**2d** was obtained after repeated recrystallization from mother liquor of **2d**. Following the nomenclature for MeO-Biphep, ligand **2a** was named as *t*-Bu-MeO-BipheSO [2,2′-dimethoxy-6,6′-bis(*tert*-butylsulfinyl)biphenyl].

To further understand the origin of the high diastereoselectivities during the oxidative coupling, a computational

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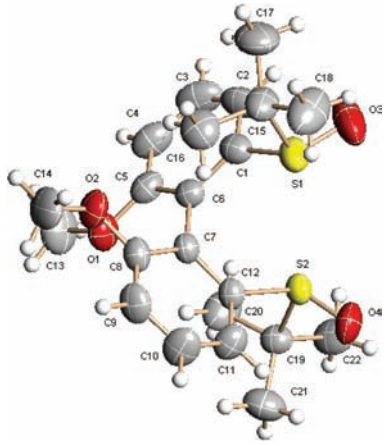


Figure 1. X-ray structure of chiral compound (*M*,*S*,*S*)-**2a**.

study concerning two diastereomers of **2a** was performed at the B3LYP/6-311+G** level (Figure 2). The calculation

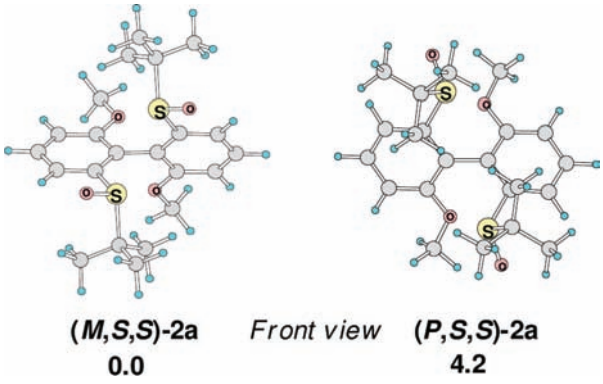


Figure 2. Optimized structures of (*M*,*S*,*S*)-**2a** and (*P*,*S*,*S*)-**2a**. The calculations have been performed at the B3LYP/6-311+G** level, and the relative free energies ΔG (298 K) are in kcal/mol.

results indicate that the major diastereomer (*M*,*S*,*S*)-**2a** is more stable than (*P*,*S*,*S*)-**2a** owing to the absence of the repulsion between two *tert*-butyl groups observed in (*P*,*S*,*S*)-**2a**.

During the radical coupling reaction, the two *tert*-butyl groups should point in opposite directions to avoid repulsions (Figure 3). In addition, the lithium cation will coordinate with oxygen atoms of the sulfinyl groups, keeping the two S═O bonds on the same side, which may also have some effects on the chiral induction.[5] Therefore, the chiral induction possibly originates from the repulsion between the two *tert*-butyl groups and the coordination of metal ion with the sulfinyl groups. Product (*M*,*S*,*S*)-**2a** is a more favorable diastereoisomer with respect to both thermodynamics and kinetics according to this propose.

(5) Sugiyarna, S.; Kido, M.; Satoh, T. *Tetrahedron Lett.* **2005**, *46*, 6771.

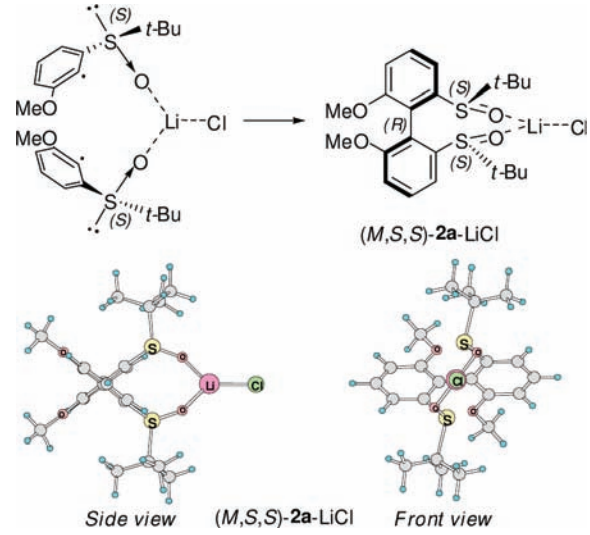
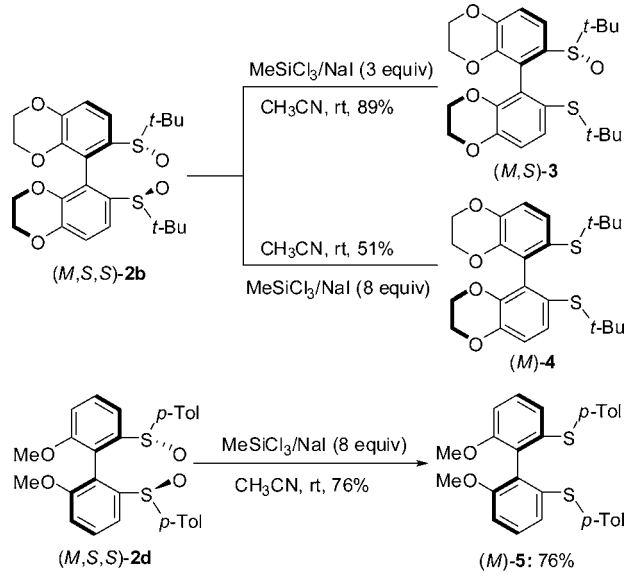


Figure 3. Possible mechanism of the chiral induction.

Some potentially useful sulfur-based ligands could be readily obtained by the reduction of axially chiral bis-sulfoxides **2** (Scheme 2). The deoxygenation of sulfoxide

Scheme 2. Synthesis of Sulfur-Based Ligands from Chiral Bis-sulfoxides **2**



(*M*,*S*,*S*)-**2b** to the corresponding monosulfoxide (*M*,*S*)-**3** and disulfide (*M*)-**4** was conveniently carried out at ambient temperature by using trichloromethylsilane/sodium iodide in acetonitrile.[6] However, no semireduction product of (*M*,*S*,*S*)-

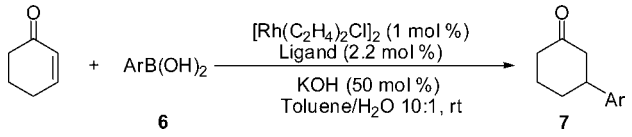
(6) Olah, G. A.; Husain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.

(7) For reviews on Rh-catalyzed asymmetric 1,4-addition reactions, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

2d was observed under the above conditions even with a reduced amount of trichloromethylsilane/sodium iodide.

With ligands **2**−**5** in hand, their catalytic performance in the asymmetric 1,4-addition of arylboronic acids to 2-cyclohexenone was investigated using $[Rh(C_2H_4)_2Cl]_2$ as the metal precursor (Table 2).[7,8] Surprisingly, ligands (*M*,*S*,*S*)-**2a**, -**2b**, and -**2c** bearing *tert*-butylsulfinyl groups showed no activity toward the enantioselective addition of phenylboronic acid **6a** to 2-cyclohexenone (entries 1−3), whereas (*M*,*S*,*S*)-**2d**, -**2e**, and -**2f** with *p*-tolylsulfinyl groups emerged as efficient ligands for this addition with respect to yields and enantioselectivites (99% ee, entries 4−6). This interesting phenomenon was probably ascribed to a mismatched binding mode of (*M*,*S*,*S*)-**2a**, -**2b**, and -**2c** with the dimeric rhodium precursor, which was supported by the inertness of (*P*,*S*,*S*)-**2d** in this reaction (entry 7).[3b] To our disappointment, ligands **3**−**5** were not effective (entries 8−10). After the evaluation of the ligands, the scope of asymmetric 1,4-addition of arylboronic acids to 2-cyclohexenone was explored using $[Rh(C_2H_4)_2Cl]_2$/(*M*,*S*,*S*)-**2e** as the catalyst. In general, arylboronic acids bearing either electron-withdrawing or electron-donating groups at the *para*-position all delivered the addition products in excellent enantioselectivities (up to >99% ee) and high yields (entries 11−13). The use of 3-methoxybenzene-boronic acid **6e** resulted in a decrease of yield (59%) but the retention of enantioselectivity (99% ee, entry 14).

Table 2. Asymmetric 1,4-Addition of Boronic Acids to 2-Cyclohexenone Catalyzed by Rhodium Complexes[a]



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entry	Ar in **6**	ligand	yield (%)[b]	ee (%)[c]
1	Ph (**6a**)	(*M*,*S*,*S*)-**2a**	trace	N/A
2	Ph (**6a**)	(*M*,*S*,*S*)-**2b**	trace	N/A
3	Ph (**6a**)	(*M*,*S*,*S*)-**2c**	trace	N/A
4	Ph (**6a**)	(*M*,*S*,*S*)-**2d**	98	99
5	Ph (**6a**)	(*M*,*S*,*S*)-**2e**	89	99
6	Ph (**6a**)	(*M*,*S*,*S*)-**2f**	87	99
7	Ph (**6a**)	(*P*,*S*,*S*)-**2d**	trace	N/A
8[d]	Ph (**6a**)	(*M*,*S*)-**3**	trace	N/A
9[d]	Ph (**6a**)	(*M*)-**4**	trace	N/A
10[d]	Ph (**6a**)	(*M*)-**5**	trace	N/A
11	4-$CF_3C_6H_4$ (**6b**)	(*M*,*S*,*S*)-**2e**	96	>99
12	4-MeC_6H_4 (**6c**)	(*M*,*S*,*S*)-**2e**	95	97
13	4-$MeOC_6H_4$ (**6d**)	(*M*,*S*,*S*)-**2e**	82	96
14	3-$MeOC_6H_4$ (**6e**)	(*M*,*S*,*S*)-**2e**	59	99

[a] The reaction was carried out with 2-cyclohexenone (0.30 mmol), arylboronic acid (0.45 mmol), $[Rh(C_2H_4)_2Cl]_2$ (0.003 mmol), ligand (0.0066 mmol, 1.1 equiv to Rh), and 0.75 M aq KOH (0.20 mL) in toluene (2.0 mL) at room temperature for 3−6 h. [b] Isolated yield based on 2-cyclohexenone. [c] Determined by HPLC analysis. [d] At 40 °C.

In conclusion, we have developed an efficient and highly diastereoselective synthesis of axially chiral bis-sulfoxide ligands via oxidative coupling. The axial chirality is well controlled by the *tert*-butylsulfinyl or the *p*-tolylsulfinyl group. This methodology provides easy access to various potentially useful sulfur-based ligands. These axially chiral bis-sulfoxides proved to be remarkably efficient ligands for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to 2-cyclohexenone with up to >99% ee. Further exploration of the applications of these ligands in various asymmetric reactions is currently underway, and related results will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of National Natural Science Foundation of China (20921092 and 20872140), National Basic Research Program of China (2010CB833300), and Chinese Academy of Sciences.

Supporting Information Available: Experimental, spectroscopic, computational, and crystallographic details including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For recent literatures on Rh-catalyzed asymmetric 1,4-addition reaction of arylboronic acids to enones, see: (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Kuriyama, M.; Nagai, K.; Yamada, K.; Miwa, Y.; Taga, T.; Tomioka, K. *J. Am. Chem. Soc.* **2002**, *124*, 8932. (c) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (d) Ma, Y. D.; Song, C.; Ma, C. Q.; Sun, Z. J.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871. (e) Shintani, R.; Duan, W. L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (f) Duan, W. L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130. (g) Feng, C. G.; Wang, Z. Q.; Shao, C.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2008**, *10*, 4101. (h) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J. P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (i) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387. (j) Hu, X. C.; Zhuang, M. Y.; Cao, Z. P.; Du, H. F. *Org. Lett.* **2009**, *11*, 4744. (k) Jana, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 971.