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

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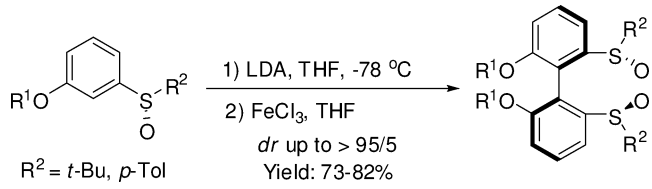
ABSTRACT



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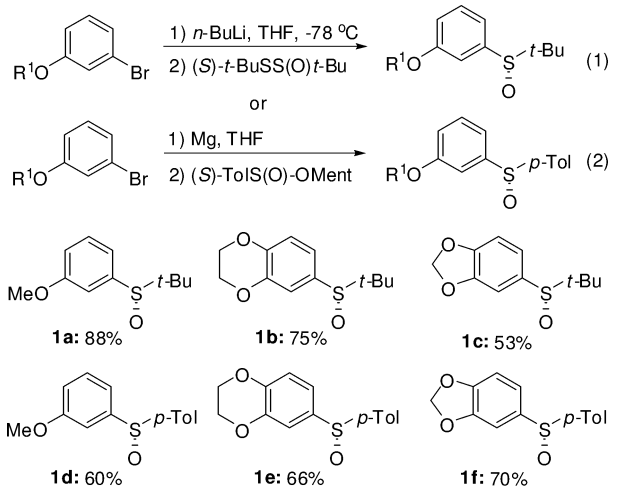
be used successfully as ligands in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to enones with excellent enantioselectivties.[3a,b] Thus, development of a simple and efficient method for the synthesis of optically pure axially chiral sulfoxide ligands is highly desirable. Herein,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

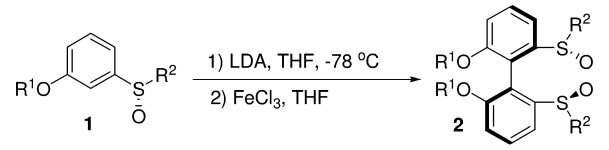
Scheme 1. Synthesis of Enantiopure Sulfoxides **1**

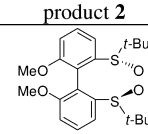
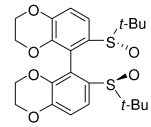
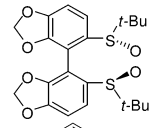
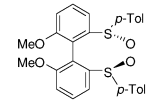
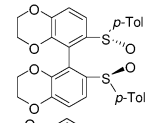
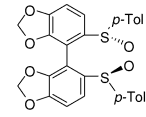


bromo−lithium exchange of bromo-arene derivatives proceeded at low temperature. After quench by thiosulfinate that is commercially available, the desired products **1a**−**1c** were obtained in moderate to high yields (53−88% yields, eq 1). The reaction of Grignard reagents (derived from aryl bromides) 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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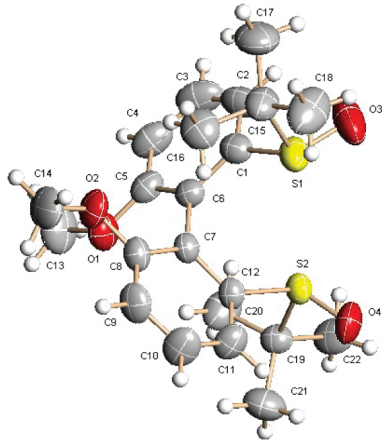


Figure 1. X-ray structure of chiral compound (*M*,*S*,*S*)-**2a**.

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

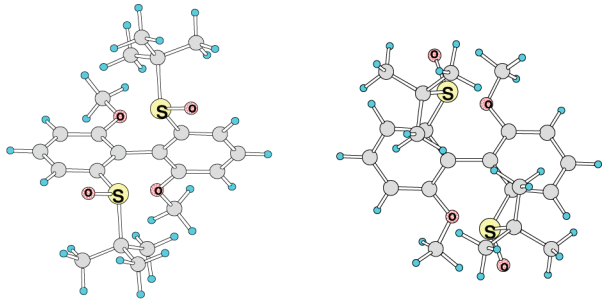


Figure 2. Optimized structures of (*M*,*S*,*S*)-**2a** and (*P*,*S*,*S*)-**2a**. The calculations have been performed at the B3LYP/6-311+G** level, and the relative free energies ΔG (298 K) are in kcal/mol.

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.

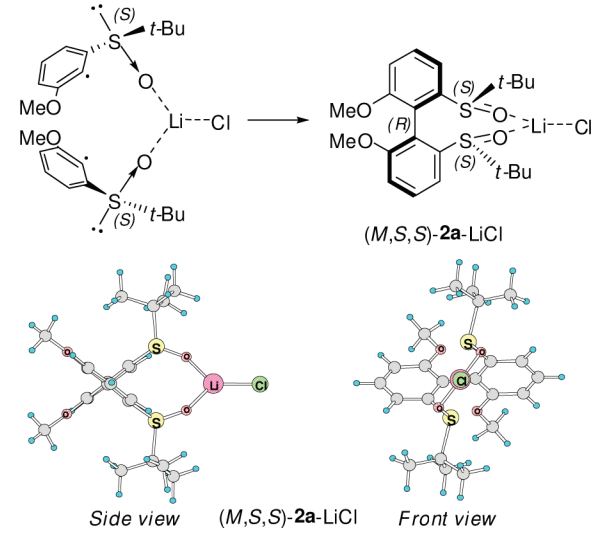
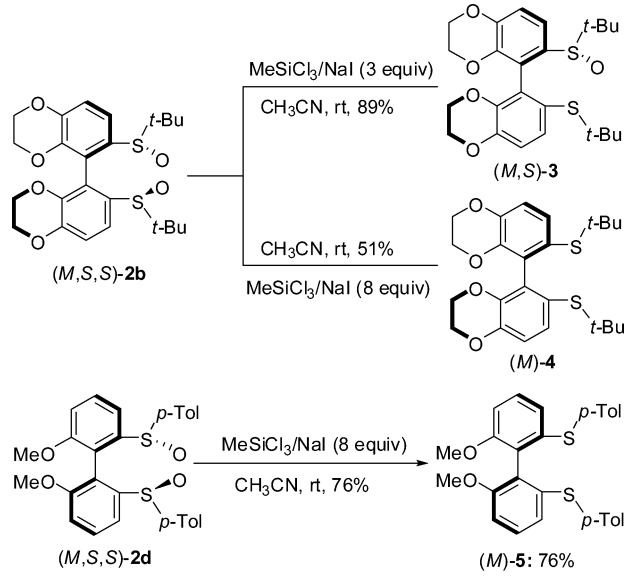


Figure 3. Possible mechanism of the chiral induction.

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*)-

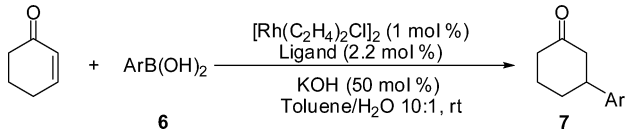
(6) Olah, G. A.; Husain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.

(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.

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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.