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Synthesis and Crystal Structure of a New C_2-Symmetric Chiral Bis-sulfoxide Ligand and Its Palladium(II) Complex

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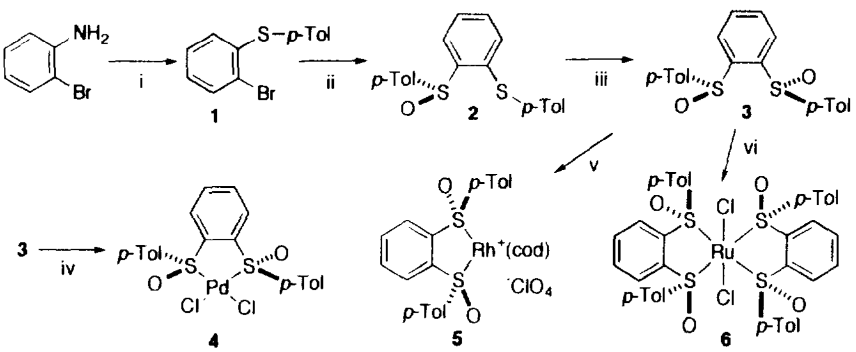
Abstract: A new chiral bis-sulfoxide ligand (*S,S*)-1,2-bis(*p*-tolylsulfinyl)benzene (BTSB), which possesses S,S-bidentate chelating donor atoms on an aromatic ring, was synthesized. Pd, Rh, and Ru readily gave adducts with this ligand. The crystal structure of $PdCl_2$[btsb-*S,S'*]•2(C_6H_6) showed that this ligand had C_2-symmetric S-coordination. Moderate asymmetric induction was observed in the Pd-catalyzed allylic substitution using BTSB as a ligand.

Various C_2-symmetric chiral ligands have been developed, and they play a significant role in catalytic asymmetric synthesis. They can be classified into two types, which carry their chirality either in their backbones or in the coordinating atom itself. The latter type usually involves a chiral phosphorus atom, and much less attention has been paid to the chiral sulfur atom. Only a few studies have examined the use of chiral sulfoxide as a ligand for a transition metal catalyst.[1] In this report, we describe a new C_2-symmetric bis-sulfoxide ligand, its transition metal complexes, and its application to an asymmetric allylic substitution reaction.

Sulfoxides are known to act as ambidentate ligands, which coordinate to metals via either oxygen (O) or sulfur (S) according to electronic and steric factors. Due to this flexible coordination of sulfoxide, careful design is important to obtain the S,S-coordinating bis-sulfoxide ligand. Based on the bite angle and the ring size of the resulting metal chelates, we designed (*S,S*)-1,2-bis(*p*-tolylsulfinyl)benzene (BTSB) (**3**). Synthesis of **3** was readily achieved in a three-step sequence starting from 2-bromoaniline, as shown in Scheme 1.[2] First, 2-bromoaniline was converted into the tolylthioether **1** in 55% yield.[3] Next, an optically active sulfinyl group was introduced to **1** using (-)-menthyl (*S*)-*p*-toluenesulfinate according to the method of Anderson *et al.*[4] to give (-)-**2** in 51% yield [$[\alpha]^{24}_D$ -231° (*c* 0.38, $CHCl_3$)]. The optical purity of (-)-**2** (>99%) was confirmed by HPLC analysis using a chiral phase column (Daicel Chiralcel OJ, *i*PrOH-hexane = 1/9). Finally, oxidation of (-)-**2** with MCPBA gave the desired optically active bis-sulfoxide (-)-**3** in 46% yield [$[\alpha]^{26}_D$ -316° (*c* 2.40 $CHCl_3$)]. Although meso-sulfoxide (30%) and sulfone-sulfoxide (24%) were also formed, these byproducts were readily separated by flash column chromatography. Final confirmation of the structure of **3** was achieved by X-ray analysis (Fig. 1).[5]

To investigate how this ligand coordinates to transition metals, we prepared Pd, Rh, and Ru complexes of (-)-**3**. [(*S,S*)-1,2-Bis(*p*-tolylsulfinyl)benzene-*S,S'*]dichloro palladium(II) ($PdCl_2$[(*S,S*)-btsb]) (**4**) was readily prepared in a quantitative yield by treating (-)-**3** with $PdCl_2(CH_3CN)_2$ (1 eq) in ethanol [$[\alpha]^{24}_D$ -252° (*c* 0.50, CH_2Cl_2)]. The resulting yellow Pd complex (-)-**4** was stable in air and in most organic solvents. A cationic Rh complex, $[Rh((S,S)\text{-btsb})(cod)]^+ClO_4^-$ (**5**), was obtained by reacting



Scheme 1. i) $NaNO_2$, cHCl, 0 °C, then *p*-Tol-SNa, aq.NaOH, reflux; ii) *n*-BuLi, THF -78 °C, then (*S*)-Mentyl-*p*-toluenesulfinate, rt; iii) MCPBA, CH_2Cl_2, -30 °C; iv) $PdCl_2(CH_3CN)_2$, EtOH, rt; v) $[Rh(cod)Cl]_2$, $AgClO_4$, acetone, rt; vi) $RuCl_2(dmso)_4$, $CHCl_3$, reflux;

(-)-**3** with a cationic complex prepared from $[Rh(cod)Cl]_2$.[6] The bimetallic complex, $[Rh(cod)Cl]_2$, was first treated with $AgClO_4$ (2 eq) in acetone, and (-)-**3** (1 eq to Rh) was then added to the mixture after AgCl was removed by filtration. Concentration of the reaction mixture after stirring at 23 °C for 12 h gave the desired **5** in a quantitative yield. The bis-BTSB complex of Ru(II) **6** ($RuCl_2[(S,S)$-btsb$]_2$) was obtained in 54% yield by refluxing $RuCl_2(dmso)_4$[7] and 2 eq of (-)-**3** in $CHCl_3$ for 2 days. Simple ^{1}H-NMR spectra revealed the C_2-symmetric structure of these complexes. Early work on sulfoxide complexes led to the empirical observation that coordination to a metal center via oxygen generally leads to a decrease in the frequency of the band assigned as ν(S=O),[8] whereas coordination via sulfur generally leads to an increase in frequency. The IR spectra of all of these complexes indicate coordination via sulfur (**3**: 1057 cm^{-1}; **4**: 1072 cm^{-1}; **5**: 1092 cm^{-1}; **6**: 1114 cm^{-1}).

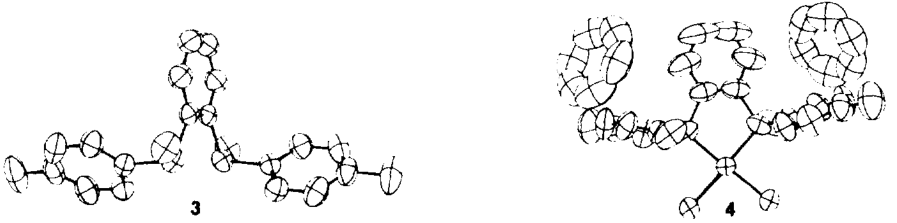
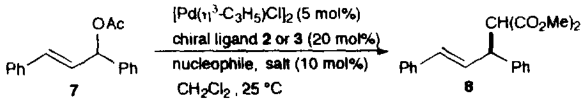


Figure 1. ORTEP diagram of **3 and 4**. Selected distances (Å) and angles (deg) are; **3**: S-O 1.481(4), S-C(tol) 1.805(4), S-C(Ph) 1.821(6), O-S-C(tol) 106.3(2), O-S-C(Ph) 105.5(2), C(tol)-S-C(Ph) 96.6(2). **4**: S-O 1.461(12), S-C(tol) 1.755(4), S-C(Ph) 1.789(7), Pd-S 2.223(2), Pd-Cl 2.302(2), S-Pd-S 90.57(1), S-Pd-Cl 87.58(1), Cl-Pd-Cl 94.68(1).

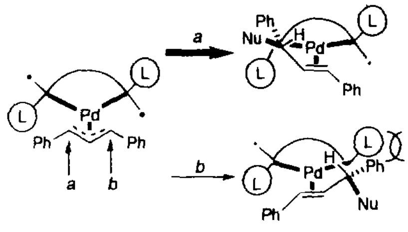
Final structural confirmation of **4** was achieved by X-ray crystal structure analysis (Fig 1).[5] The small differences in S-O bond lengths between **3** and **4** (0.020 Å) deserve comment. In the case of $PdCl_2(dmso)_2$, the S-O bond length is 0.055 Å shorter than that in DMSO,[8] suggesting an increase in the π-bonding character and a change in the localization of an electron from oxygen to sulfur. The relatively small shortening of the bond length in $PdCl_2$(btsb) implies that the electron deficiency of the sulfur atom may be compensated for by the aryl π-electron of BTSB or by π-backdonation from the metal, rather than by the electron of the oxygen. As a result, the electron density of the oxygen in **4** is relatively high, suggesting the possibility of additional positive interaction between the sulfoxide oxygen and the substrate.

Table 1.



entry	ligand	nucleophile [a]	salt	time (h)	yield (%)	ee (%)
1	(*S*) - **2**	A	AcOK	114	77	49
2	(*S*) - **2**	A	AcONa	68	82	49
3	(*S*,*S*) - **3**	A	AcOK	140	0	-
4	(*S*,*S*) - **3**	A	AcONa	228	40 (80)[b]	64[c]
5	(*S*,*S*) - **3**	B	AcOK	168	17 (95)	20
6	(*S*,*S*) - **3**	B	AcONa	168	70 (89)	62
7	(*S*,*S*) - **3**	B	$(AcO)_3La$	120	64 (88)	50
8	(*S*,*S*) - **3**	B	$^nBu_4NOAc$	76	25 (85)	25

a) A: $CH_2(CO_2Me)_2$ (3 eq), BSA (3 eq), B: $TMSO(MeO)C=CHCO_2Me$ (3 eq),
b) yield on the basis of recovered starting material, c) $[\alpha]^{25}_D$ -10.1° (c 1.0 EtOH)



Scheme 2.

To test the effectiveness of (-)-**3** as a chiral ligand, we used it in an asymmetric allylic substitution reaction (Table 1). Under standard conditions[9] (5 mol % of [Pd(η^3-C_3H_5)Cl]$_2$, 20 mol % of **3**, and a mixture of *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of acetate salt), racemic **7** reacted with dimethyl malonate to give the optically active substitution product **8**. The enantioselectivity of this reaction was determined by HPLC analysis using a chiral phase column (Daicel Chiralpak AD *i*PrOH-hexane = 1/20). The absolute configuration was determined to be (*S*) by comparing the optical rotation with literature values.[10] C_2-symmetric BTSB **3** gave better asymmetric induction than unsymmetric monosulfoxide ligand **2** (entries 2 and 4). However, the chemical yield of **8** from the reaction using **3** was low because of deactivation of Pd-catalyst, probably owing to the generation of *N*-(trimethylsilyl)acetamide. In fact, this problem was solved by using the ketene trimethylsilyl acetal of dimethyl malonate (entry 6).[11] Also in this case, a catalytic amount of acetate salt appears to give a low concentration of the metal salt of dimethyl malonate *in situ*. Although the ee of the product is still not satisfactory, the asymmetric induction observed here is, to our knowledge, the highest among those observed in reactions using ligands with only sulfoxide chirality. It is also interesting that the counter cation of the nucleophile greatly affects the chemical and optical yield. Furthermore, the absolute configuration of the product was opposite that of what we expected. Nucleophiles normally prefer to attack at carbon ***a*** to avoid steric interaction between the phenyl group and a large substituent (L) of the ligand in the transition state (Scheme 2).[12] In the case of (*S,S*)-BTSB, however, the dominant product was (*S*), suggesting a predominant attack at carbon ***b***. These results may imply some secondary interaction between the sulfoxide oxygen and the nucleophile.

In conclusion, we have synthesized and characterized a novel C_2-symmetric chiral bis-sulfoxide ligand **3** and its sulfur-bound complexes with Pd(II), Rh(I), and Ru(II). The crystal structure of the Pd complex clearly shows that this ligand coordinates to Pd(II) through the sulfur atom, and that the complex has C_2-symmetry. Preliminary results in allylic alkylations demonstrate the potential of this novel type of the chiral sulfoxide ligand. Further studies on various catalytic asymmetric reactions using this ligand and its derivatives are in progress.

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2. Selected spectral data for **1**-**6**:
   1: colorless solid. ^{1}H-NMR δ (400 MHz, $CDCl_3$; all J in Hz) 2.39 (3H, s), 6.81 (1H, dd, J = 1.5, 8.0), 6.98 (1H, ddd, J = 1.5, 8.0, 8.0), 7.10 (1H, ddd, J = 1.5, 8.0, 8.0), 7.22 (2H, d, J = 8.0), 7.40 (2H, d, J = 8.0), 7.53 (1H, dd, J = 1.5, 8.0). IR (cm^{-1}, neat) 1489, 1426. EI-MS (m/z) 280, 278 (M^+). HR-MS calcd for $C_{13}H_{11}{}^{81}BrS$ 279.9745, found 279.9738. mp = 60 °C
   2: colorless prism (recrystallized from AcOEt - hexane). ^{1}H-NMR δ (400MHz, $CDCl_3$) 2.32 (3H, s), 2.35 (3H, s), 7.07 (4H, s), 7.15 (1H, dd, J = 1.5, 8.0), 7.20 (2H, d, J = 8.0), 7.32 (1H, ddd, J = 1.5, 8.0, 8.0), 7.48 (1H, ddd, J = 1.5, 8.0, 8.0), 7.62 (2H, d, J = 8.0), 8.10 (1H, dd, J = 1.5, 8.0). ^{13}C-NMR δ (67.8MHz, $CDCl_3$) 21.0, 21.4, 124.6, 126.3, 128.2, 129.8, 130.1, 130.5, 131.2, 131.4, 132.5, 134.2, 137.8, 141.6, 141.9, 146.3. IR (cm^{-1}, neat) 1056. EI-MS (m/z) 338 (M^+). HR-MS calcd for $C_{20}H_{18}OS_2$ 338.0800, found 338.0805. mp = 115 °C
   3: colorless prism (recrystallized from CH_2Cl_2). ^{1}H-NMR δ (400MHz, $CDCl_3$) 2.38 (6H, s), 7.28 (4H, d, J = 8.0), 7.62 (2H, dd, J = 3.2, 5.8), 7.64 (2H, d, J = 8.0), 7.98 (2H, dd, J = 3.2, 5.8). ^{13}C-NMR δ (67.8MHz, $CDCl_3$) 21.4, 124.4, 125.6, 130.3, 132.2, 140.8, 142.4, 143.9. IR (cm^{-1}, KBr) 1057. EI-MS (m/z) 355(M^++1). HR-MS calcd for $C_{20}H_{18}O_2S_2$ 354.0749, found 354.0756. mp = 178-180 °C
   4: pale brown plate (recrystallized from CH_3CN-benzene). ^{1}H-NMR δ (400MHz, $CDCl_3$) 2.37 (6H, s), 7.36 (4H, d, J = 8.5Hz), 7.73 (4H, s), 7.77 (4H, d, J = 8.5). ^{13}C-NMR δ (67.8MHz, $CDCl_3$) 21.7, 126.0, 127.3, 131.0, 137.0, 138.1, 142.9, 146.0. IR (cm^{-1}, KBr) 1072. mp = 168-170 °C
   5: yellow solid. ^{1}H-NMR δ (270MHz, $CDCl_3$) 2.49 (6H, s), 2.4-2.7 (8H, br), 5.00 (2H, br), 5.80 (2H, br), 7.52 (4H, d, J = 8.0), 7.73-7.82 (4H, m), 7.85 (4H, d, J 8.0). IR (cm^{-1}, KBr) 1092
   6: yellow solid. ^{1}H-NMR δ (400MHz, $CDCl_3$) 2.40 (12H, s), 7.09 (8H, d, J 8.0), 7.56 (8H, d, J 8.0), 7.57 (4H, m), 7.68 (4H, m). IR (cm^{-1}, KBr) 1114
3. W. E. Truce, D. P. Tate, D. N. Burdge, *J. Am. Chem. Soc.*, **1960**, *82*, 2872. Separation of **1** from *p*-Tol-SH is crucial to obtain **2** with high ee in the next step. **1** was also prepared from 1,2-dibromobenzene without contamination of *p*-Tol-SH ((i) Mg, Et_2O, reflux, then *p*-Tol-SO_2Me, rt. (ii) Cl_3SiH, Et_2O, 0 °C. 26% in two steps).
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5. X-ray analysis was carried out using single crystals of (±)-**3** (recrystallized from AcOEt-CH_2Cl_2) and (±)-**4** (recrystallized from CH_3CN-benzene) because unfortunately (-)-**3** and (-)-**4** did not give X-ray grade single crystals.
   Crystal data for **3**. $C_{20}H_{18}O_2S_2$, Mr = 354.48, Monoclinic, Space group $C2/c$, a = 19.431(1), b = 7.782(1), c = 12.133(1)Å, ß = 107.46(1)°, V = 1750.20(4)Å^3, Z = 4, Dc = 1.345 Mg/m^3, F(000) = 744.
   Crystal data for **4**. $C_{20}H_{18}O_2S_2Cl_2Pd{\bullet}2C_6H_6$, Mr = 688.02, Monoclinic, Space group $C2/c$, a = 16.774(1), b = 10.431(1), c = 20.521(1)Å, ß = 118.80(1)°, V = 3146(1)Å^3, Z = 4, Dc = 1.453 Mg/m^3, F(000) = 1400.
   Crystallographic Measurements and Structure Analyses : The intensity data for both compounds were collected by 2θ/ω scan technique using graphite-monochromated CuKα radiation on a four-circle diffractometer (Rigaku/AFC5R) at 293K°. The empirical (ψ-scan) absorption corrections were applied as Tmax = 1.0, Tmin = 0.80 for **3**, Tmax = 1.0, Tmin = 0.60 for **4**, respectively. The total numbers of reflections collected for **3** and **4** were 1488 and 2682, respectively, of which 1399 and 2399 were significant ($|Fo| \geq 2.667\sigma(|Fo|)$). Both structures were solved by direct method using SHELXS-86[13] and were refined by the full matrix least-squares methods. The weighting schema used in the final refinement cycles were $\sqrt{w} = 1/\sigma(|Fo|)$. The final R and Rw values were 0.065 and 0.071 for **3**, and 0.070 and 0.074 for **4**. GOF values were 10.50 for **3** and 2.30 for **4**. All of the atomic coordinates, bond lengths and angles, and the thermal parameters have been deposited at the Cambridge Crystallographic Data Center.
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