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Enantiomerically Pure 2-Bromo-2′-diphenylphosphinyl-1,1′-binaphthyl as a Monophosphorus Template for Electrophilic Functionalization in Chiral MOP-Type Ligand Synthesis

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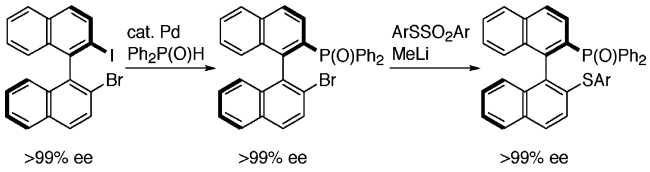

Pd-catalyzed monophosphinylation of (*R*)-2-bromo-2′-iodo-1,1′-binaphthyl with $Ph_2P(O)H$ afforded (*R*)-2-bromo-2′-diphenylphosphinyl-1,1′-binaphthyl in good yield with excellent chemoselectivity and no observable racemization. Subsequent lithiation in the presence of excess thiosulfonate furnished an enantiomerically pure sulfenylation product, which was reduced to afford a chiral S-MOP ligand.

Chiral ligand based on the 1,1′-binaphthalene scaffold is one of the most successful ligands in transition-metal-catalyzed enantioselective processes. BINAP has been the leading ligand in this class. In addition, since the pioneering work of the 2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl (MOP) ligand reported by Hayashi and Uozumi,[1] non-C_2-symmetrical monophosphine analogues of BINAP have also proven to be excellent ligands for asymmetric catalysis.[2] In the syntheses of the MOP-type ligands, enantiomerically pure monophosphorus templates of the general type **1** have found widespread application for further structural diversity due in part to the ease of replacement of the OTf group with nucleophiles.[1,3] However, electrophiles, which are useful complement of nucleophiles, cannot be employed in replacement of the OTf group due to the difficulty associated with the metalation of **1** to generate its carbanion intermediate (Scheme 1). For one to take full advantage of the MOP-type ligand architecture, a novel monophosphorus template for further functionalization by electrophiles has been needed which would provide more flexibility in the ligand synthesis. While oxides of BINAP have been evaluated as such templates, the synthetic route to the ligands entails the replacement of the large and expensive diphenylphosphinyl group by electrophiles.[4] In addition, a multistep synthesis as a result of the borane protection/deprotection of the phosphino group is required to prevent the inherent racemization of the axial chirality of the monolithio intermediate. Herein we report a synthetic study of (*R*)-2-bromo-2′-diphenylphosphinyl-1,1′-binaphthyl **2a** as a novel monophosphorus template and its electrophilic sulfenylation, realizing a straightforward route to the enantiomerically pure sulfur analogue of MOP (S-MOP) ligand **6**.

Pd-catalyzed phosphinylation reactions of aryl halides and triflates are powerful carbon−phosphorus bond-forming processes in the preparation of aryl-substituted phosphorus compounds. Actually, the preparation of **1** has been accomplished through the $Pd(OAc)_2$/dppb-catalyzed monophosphinylation reaction of binaphthyl ditriflate with $R_2P(O)H$. Thus, our efforts were focused on the development of the Pd-catalyzed monophosphinylation of enantiomerically pure binaphthyl dihalide with $Ph_2P(O)H$ (Table 1). First, we evaluated the readily available dihalides **3a** and **3b** as monophosphinylation substrates.[5] However, when the dibromide **3a** was employed, only a trace amount of the monophosphinylation product **2a** was obtained and **3a** was recovered in 75% yield (entry 1). Though the diiodide **3b** was more reactive to give the desired product **2b**,[4] dehalogenation of **2b** also occurred to give the byproduct **2c**[3i] in comparable yield, which diminished the yield of **2b** and made the purification of the products troublesome (entry 2).[6] To overcome this drawback, we next employed (*R*)-2-bromo-2′-iodo-1,1′-binaphthyl **3c** as an alternative monophosphinylation substrate with the expectation that the Pd catalyst would react with the iodide in preference to the bromide to afford the inert bromide-containing product **2a** which would better tolerate the dehalogenation than the iodide counterpart **2b**. (*R*)-2-Bromo-2′-iodo-1,1′-binaphthyl **3c** was readily prepared from **3a** in excellent yield (Scheme 2). As expected, the monophosphinylation reaction of **3c**

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(1) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887.
(2) For recent reviews, see: (a) Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213. (b) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809. (c) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.
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(6) While we investigated some other reaction conditions, only poor results were obtained. See the Supporting Information.

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SCHEME 1. Structural Diversity of 1 in the Synthesis of MOP-Type Ligand

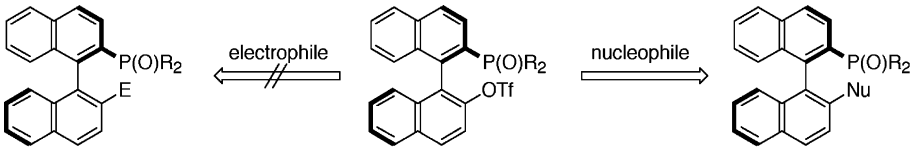

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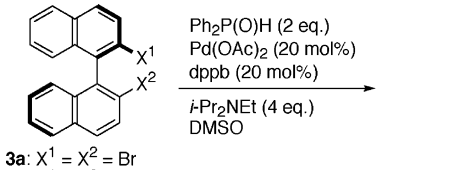
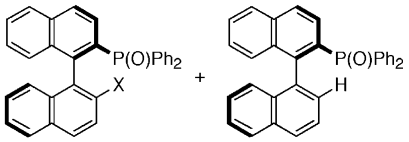
TABLE 1. Pd-Catalyzed Monophosphinylation Reaction of Binaphthyl Dihalide with $Ph_2P(O)H$[a]



3a: $X^1 = X^2 = Br$
3b: $X^1 = X^2 = I$
3c: $X^1 = Br$, $X^2 = I$

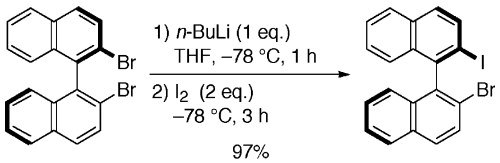


2a: X = Br
2b: X = I
2c

entry	dihalide	*T* (°C)	product, yield (%)	**2a** (or **2b**)/**2c**
1	**3a**	100	**2a**, trace; **2c**, trace[b]	
2	**3b**	100	**2b**, 28; **2c**, 18[b]	61:39
3	**3c**	100	**2a**, 61; **2c**, 21[b]	74:26
4	**3c**	90	**2a**, 70; **2c**, 5[c]	93:7
5	**3c**	80	**2a**, 14; **2c**, 6[b]	70:30

[a] The reaction times were in the range from 18 to 25 h. [b] Yield was estimated by ^1H NMR spectroscopy. [c] Isolated yield.

SCHEME 2



3a **3c**

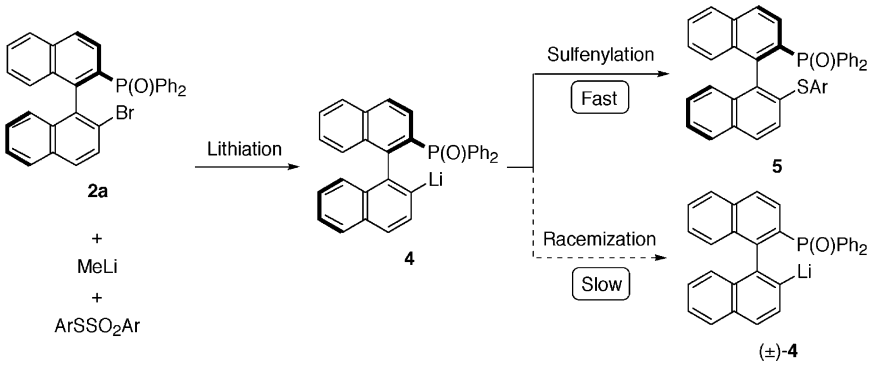
more efficiently controlled the unwanted dehalogenation to afford the enantiomerically pure **2a** as the major product in 61% yield without the observable formation of **2b** (entry 3). In addition, it is noteworthy that the iodide of **3c** is much more reactive than that of **3b**. Actually, the monophosphinylation products **2a** and **2c** were obtained in 82% combined yield when **3c** was used, in contrast to **3b** which provided the corresponding monophosphinylation products **2b** and **2c** in only 46% combined yield. Although precise explanation of the exceptional reactivity of the iodide of **3c** cannot be offered at this time, we believe that the less steric demand of a bromo group of **3c** relative to an iodo group of **3b** favors the reactivity of the iodide. Along with the halide substituents of the monophosphinylation substrate, it was found that the reaction temperature was also an important element of this reaction and the effective temperature range was very narrow. Actually, when the reaction was carried out at 90 °C, a ratio of **2a** to **2c** was significantly improved relative to that at 100 °C and the yield of **2a** also increased to 70% (entry 4). However, the Pd catalyst did not promote the reaction well at 80 °C, which is only 10 °C below the optimized temperature (entry 5).

In transition-metal-catalyzed enantioselective processes, the trans effect generally serves as a powerful control element for chiral non-C_2-symmetrical bidentate ligands containing strong and weak donor heteroatom pairs. Among such ligands, thioether-containing ligands have recently attracted growing attention because catalysts bearing them have the ability to generate an extra chiral center at the sulfur upon coordination as an additional control element in asymmetric catalysis.[7] While the synthesis of S-MOP ligands was reported by Gladiali and co-workers in their asymmetric hydrogenation reaction,[3j] their synthetic sequence is not amenable to the preparation of S-MOP ligand containing an *S*-aryl substituent, which can be regarded as the monosulfur counterpart of BINAP. Thus, we focused our efforts on the development of the electrophilic sulfenylation of **2a** with diaryl thiosulfonate ($ArSSO_2Ar$) via the monolithio intermediate **4**. Hayashi and Shimada also prepared the intermediate **4** by lithiation of the dioxide of BINAP in their synthetic study of MOP-type ligands and found its facile racemization of the axial chirality even at low temperature.[4,8] Thus, any attempt to incorporate **4** into the synthetic sequence must consider potential erosion of the enantiopurity of the product. A prospective solution of this problem would be an in situ lithiation of **2a** in the presence of the thiosulfonate. The premise of this strategy rests on the proposition that if the thiosulfonate would quench the monolithio intermediate **4** before its racemization, the sulfenylation product **5** would be obtained with retention of the axial chirality (Scheme 3). To a solution of **2a** and 4 equiv of phenyl benzenethiosulfonate in THF was initially added 2 equiv of MeLi at −70 °C.[9] After being stirred for 2 h, 2 equiv of the thiosulfonate and the same amount of MeLi were sequentially added to the reaction mixture and stirred for additional 2 h. Then, this operation was repeated five times until the reaction was completed (Scheme 4).

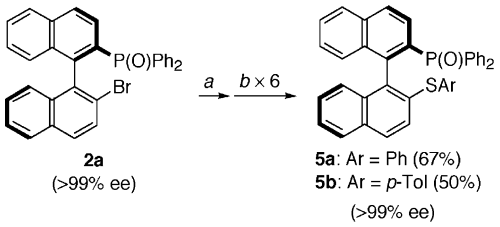
(7) For some recent examples of chiral mixed phosphorus/sulfur ligands, see: (a) Nakano, H.; Takahashi, K.; Suzuki, Y.; Fujita, R. *Tetrahedron: Asymmetry* **2005**, *16*, 609. (b) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc*. **2004**, *126*, 456. (c) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed*. **2004**, 43, 3944. (d) Arrayás, R. G.; Mancheño, O. G.; Carretero, J. C. *Chem. Commun*. **2004**, 1654. (e) Zhang, W.; Xu, Q.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3161. (f) Evans, D. A.; Michael, F. E.; Tedrow, J. S. Campos K. R. *J. Am. Chem. Soc*. **2003**, *125*, 3534. (g) Mancheño, O. G.; Priego, J.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *J. Org. Chem*. **2003**, *68*, 3679. (h) Tu, T.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X.; Dong, X.-C.; Yu, Y.-H.; Sun, J. *Organometallics* **2003**, *22*, 1255. (i) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed*. **2003**, *42*, 2054.

(8) We also observed the drastic decrease in enantiopurity of the sulfenylation product **5b** when the standard sulfenylation procedure was carried out in which lithiation of **2a** was followed by substitution of the resultant **4** with *p*-tolyl *p*-toluenethiosulfonate. See the Supporting Information for details.

SCHEME 3. In Situ Lithiation of 2a in the Presence of $ArSSO_2Ar$

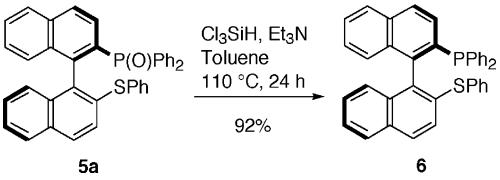


SCHEME 4[a]



[a] Reagents and conditions: (a) $ArSSO_2Ar$ (4 eq.), MeLi (2 eq.), THF, −70 °C, 2 h; (b) $ArSSO_2Ar$ (2 eq.), MeLi (2 eq.), THF, −70 °C, 2 h.

SCHEME 5



During the course of this reaction, nucleophiles (**4** and/or MeLi) in the reaction mixture were exposed to more than 2 equiv of the thiosulfonate to effectively quench the intermediate **4**. As expected, the sulfenylation product **5a** was obtained in 67% yield without observable racemization. The enantiomerically pure *p*-tolyl thioether **5b** was also obtained in 50% yield. Finally, $HSiCl_3/Et_3N$ reduction of **5a** afforded the enantiomerically pure S-MOP ligand **6** in 92% yield (Scheme 5).

In conclusion, we have developed (*R*)-2-bromo-2′-diphenylphosphinyl-1,1′-binaphthyl **2a** as a monophosphorus template for electrophilic sulfenylation access to the enantiomerically pure S-MOP ligand containing *S*-phenyl substituent **6**. The preparation of **2a** was effected via chemoselective monophosphinylation of (*R*)-2-bromo-2′-iodo-1,1′-binaphthyl **3c**. We also found the importance of the in situ generation of the monolithio intermediate **4** in the presence of excess thiosulfonate in order to obtain the sulfenylation product **5** in enantiomerically pure form. Further work for the syntheses of other MOP-type ligands is underway in our laboratory. Study toward the development of enantioselective processes catalyzed by transition-metal complexes bearing S-MOP ligands is also ongoing.

(9) In the lithiation of **2a**, the use of MeLi is essential for the selective cleavage of the C−Br bond to generate the intermediate **4**. When more reactive *n*-BuLi was used as a lithiation reagent, the cleavage of the C−P bond also took place. The weak nucleophilicity of MeLi is also an important element of the in situ lithiation of **2a** in the presence of the *highly electrophilic* thiosulfonate.

Experimental Section

Representative Procedure for Sulfenylation Reaction of (*R*)-2-Bromo-2′-diphenylphosphinyl-1,1′-binaphthyl 2a. To a solution of **2a** (>99% ee) (250 mg, 0.469 mmol) in THF (2.5 mL) was added a THF solution of $PhSSO_2Ph$ (618 μL, 3.04 M, 1.88 mmol). The mixture was cooled to −70 °C, and then an Et_2O solution of MeLi (957 μL, 0.98 M, 0.938 mmol) was added. After being stirred for 2 h, a THF solution of $PhSSO_2Ph$ (0.94 mmol) and an Et_2O solution of MeLi (0.94 mmol) were sequentially added to the reaction mixture and stirred for 2 h, and this operation was performed additionally five times until the reaction was completed. The reaction mixture was quenched by saturated $NH_4Cl_{(aq)}$, diluted with AcOEt, and washed twice with water and once with brine. The combined aqueous solutions were extracted with AcOEt, and the combined organic solutions were dried over Na_2SO_4 and concentrated in vacuo. The crude reaction mixture was purified by silica gel chromatography eluting with 2:3 hexane/AcOEt to give **5a** (177 mg, 0.315 mmol) in 67% yield and >99% ee as a white solid: mp 93−95 °C; R_f = 0.15 (3:2 hexane−AcOEt); $[\alpha]^{20}_D$ +48.6 (*c* 0.96, $CHCl_3$); HPLC analysis indicated an enantiomeric excess of >99% [Chiralcel AD-H column; flow: 0.5 mL/min; hexane/*i*-PrOH, 90:10; 320 nm; minor enantiomer (*S*)-**5a**, t_R = 52.2 min; major enantiomer (*R*)-**5a**, t_R = 67.0 min]; ^1H NMR (270 MHz, $CDCl_3$) δ 6.84 (d, *J* = 8.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 7.08−7.38 (m, 15H), 7.40−7.60 (m, 6H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.67−7.78 (m, 1H), 7.88−8.02 (m, 2H). Anal. Calcd for $C_{38}H_{27}OPS$: C, 81.11; H, 4.85. Found: C, 80.89; H, 4.79.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds of **2a**, **3c**, **5b**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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