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Synthesis and Application of New Chiral Bidentate Phosphine, 2,7-Di-tert-butyl-9,9-dimethyl-4,5-bis(methylphenylphosphino)xanthene

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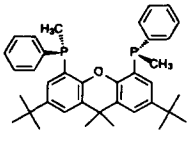
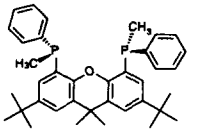
Abstract: New optically active bidentate phosphines, (*S,S*)- and (*R,R*)-2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(methylphenylphosphino)xanthenes ((*S,S*)-**1** and (*R,R*)-**1**), were prepared through resolution of the corresponding phosphine oxides using (*R,R*)-(-)-dibenzoyl-tartaric acid and a preliminary experiment on asymmetric synthesis using an allyl substrate proved the utility of the new bidentate phosphines.

Much effort has been devoted to development of chiral phosphines for catalytic asymmetric synthesis over the past few decades.[1,2] Most of the successful chiral phosphines are bidentate phosphines with two phosphines each bearing two phenyl substituents on the phosphorus atom, and the chirality usually occurs within the tethering carbon chain between the two phosphines. On the other hand, chiral bidentate phosphines with a stereogenic phosphorus atom(s) constitute a minor group because of their tedious synthesis and lack of reliable methods for their stereoselective synthesis.[3] While many chiral phosphines have been made, there is still a need for an entirely different phosphine for developing new transformations and improving the limitation of the known catalytic processes. We have engaged in the development of new chiral phosphine ligands for transition-metal catalyzed asymmetric synthesis.[4] As a part of the studies directed towards efficient ligands for catalytic processes we focused on the xanthene nucleus as a basic carbon backbone for the bidentate phosphine ligands which have two phosphines at positions 4 and 5 producing unique ligands with a wide bite angle. We report here the preparation, characterization and an application of the new optically active bidentate phosphines, (*S,S*)- and (*R,R*)-2,7-di-tert-butyl-9,9-dimethyl-4,5-bis(methylphenylphosphino)xanthenes ((*S,S*)-**1** and (*R,R*)-**1**) with stereogenic phosphorus centers and novel interconversion catalyzed by lithium aluminum hydride between the (*meso*)-bisphosphine oxide and the (*rac*)-one at the stereogenic phosphorus centers. This type achiral diphosphine has been known along with its X-ray crystal structure and has been used in hydroformylation.[5]



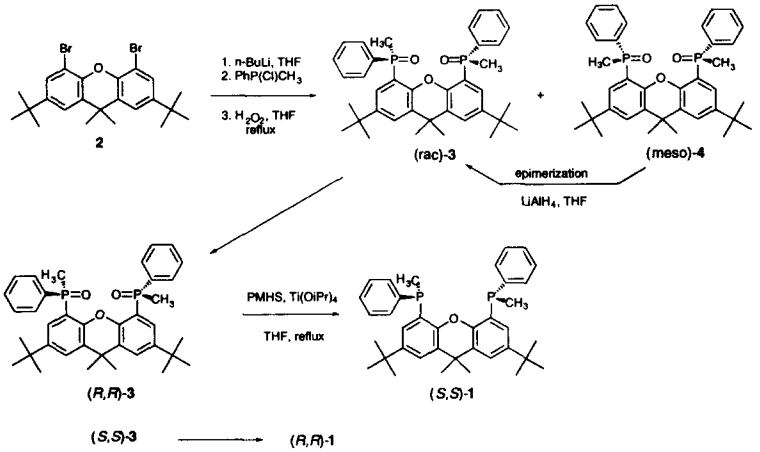
(*S,S*)-1



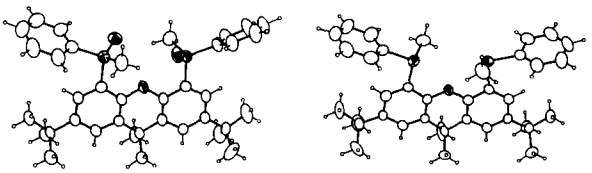
(*R,R*)-1

The preparation of **1** was carried out starting from the known dibromide **2**[6] which was readily obtained

from commercially available xanthone. The reaction of **2** with *n*-butyllithium followed by treatment of chloromethylphenylphosphine[7] produced, after treatment of hydrogen peroxide, a mixture of the (*rac*)-diphosphine oxide **3** and (*meso*)-one **4**.[8] The desired (*rac*)-**3** was easily separated by column chromatgraphy or crystallization in 35 % yield along with 46 % of the undesired (*meso*)-**4**. Disappointingly, this process unsurprisingly gave the undesired **4** as the major product. Fortunately, however, Mislow has observed racemization[9] of an optically active phosphine oxide by treatment of lithium aluminum hydride in which racemization occurs prior to reduction. We envisaged that the racemization procedure might be applied for interconversion between (*rac*)-**3** and (*meso*)-**4**. The reaction of the (*meso*)-**4** with 0.5 equivalent of lithium aluminum hydride in tetrahydrofuran at room temperature for 14 h proceeded along with some reduction of the substrate and afforded the (*rac*)-**3** in 61 % yield together with recovery of the starting (*meso*)-**4** in 34 % yield after oxidation of the crude product with hydrogen peroxide and chromatographic purification.[10] To our knowledge, this epimerization for preparation of the P-chiral bisphosphine is unprecedented in terms of the practical use and provides a practical solution of the inherent problem between the reaction of the dianion from the bishalide with the racemic phosphorus electrophile.



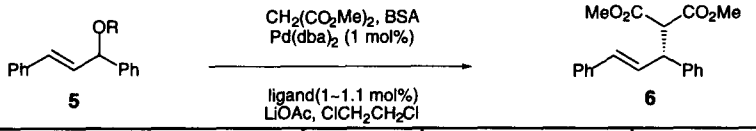
Resolution of (*rac*)-**3** was carried out by the diastereomeric salt formation with (*R,R*)-(-)-dibenzoyltartaric acids ((-)-DBTA). Treatment of (*rac*)-**3** with (-)-DBTA (0.6 eq) in chloroform-ethyl acetate and repeated recrystallization of the resulting crystals from benzene gave the (+)-**3**·(-)-DBTA with 99.6 % ee as colorless crystals in 37 % yield. The combined mother liquor was treated with aqueous ammonia. The obtained (-)-**3** enriched material was subjected to salt formation and recrystallization to afford the (-)-**3**·(+)-DBTA with 99.4 % ee in 39 % yield. The free phosphine oxide was obtained by treatment of the salt with aqueous ammonia without the loss of stereogenic integrity. Their optical purities were unequivocally confirmed by chiral HPLC analysis.[11] Reduction of the phosphine oxide function with titanium tetraisopropoxide and polymethyl hydrosiloxane (PMHS)[12] smoothly proceeded with complete retention of the phosphorus chirality to give the corresponding phosphine[13] in high yield. The phosphine without loss of optical purity was clearly confirmed by HPLC analysis of the corresponding phosphine oxides derived from hydrogen peroxide oxidation of (+)-**1** and (-)-**1**. In order to determine absolute stereochemistry, X-ray analyses of (+)-**3** and (+)-**1** were carried out disclosing the (*S,S*)- and (*S,S*)-configurations, respectively, by comparison with the R factors of a pair of the enantiomers.[14]

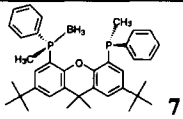
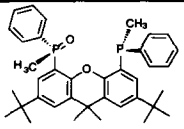


(*S,S*)-(+)-**3** (*S,S*)-(+)-**1**

Figure 1. Molecular structures of (*S,S*)-(+)-**3** and (*S,S*)-(+)-**1**.

In order to examine the utility of (+)-**1**, we focused on the asymmetric allylic substitution reaction between 1,3-diphenyl-2-propenyl acetate and dimethyl malonate.[15,16] With 1 mol % bis(benzylideneacetone) palladium and 1.1 mol % (*S,S*)-(+)-**1**, the reaction in the presence of lithium acetate in 1,2-dichloroethane (-15 ℃, 1 h then room temperature, 6 h) efficiently proceeded to afford the (*R*)-product with 85 % ee in 96 % yield.[17]



(*S,S,*)-(+)-**1**	R = Ac	-15 ℃,1h; rt, 6 h	96 %, 85 % ee(*R*)
(*S,S*)-(+)-**1**	R = Piv	rt, 3.5 d	99 %, 79 % ee(*R*)
 **7**	R = Piv	rt, 18 h	100 %, 76 % ee(*S*)
 **8**	R = Piv	rt, 2 d	76 %, 20 % ee(*S*)

Interestingly, the monophosphine borane **7** served as the same efficient ligand as **1** for the asymmetric allylic substitution reaction while the corresponding monophosphine oxide **8** was a poor ligand. The above results indicate that either **7** might be converted to the corresponding free phosphine in the reaction media or the phosphine borane part as well as the phosphine one might function as a chelating ligand for the palladium.

In summary, new bidentate phosphine ligands, (*S,S*)-(+)-**1** and (*R,R*)-(-)-**1**, have been synthesized and their application to the asymmetric allylic substitution reaction has been demonstrated. As described above, we found the novel interconversion from unutilized (*meso*)-bisphosphine oxide to (*rac*)-bisphosphine oxide, which provides a practical access to the synthesis of chiral bisphosphine ligands with stereogenic phosphorus centers. Further investigations of (*S,S*)-(+)-**1** and (*R,R*)-(-)-**1** are in progress.

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8. To a cooled (-78 ℃), stirred solution of **2**[6] (8.46 g, 17.6 mmol) in THF (160 mL) under an argon atmosphere was added a *n*-butyllithium solution (44 mmol), and the resulting mixture was stirred at -78 ℃ for 30 min. A solution of chloromethylphenylphosphine (6.99 g, 44 mmol) in THF (10 mL) was successively added at -78 ℃. After being stirred at the same temperature for 30 min, the resulting mixture was allowed to warm to room temperature and stirred for 12 h. Hydrogen peroxide (30 %, 50 mL) was slowly added at 0 ℃, and the whole was refluxed for 2 h. The reaction mixture was concentrated in vacuo, the residue was extracted with CH_2Cl_2 (100 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give (*rac*)-**3** (3.66 g, 35 %) and (*meso*)-**4** (4.60 g, 44 %).
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10. To a cooled (0 ℃), stirred solution of (*meso*)-**4** (89 mg, 0.149 mmol) in THF (3 mL) was added $LiAlH_4$ (1 M in THF, 0.075 mL, 0.075 mmol), and the resulting mixture was stirred at room temperature for 14 h. The reaction mixture was carefully treated with 30 % H_2O_2 (1 mL) at 0 ℃ and stirred at room temperature for 14 h. The mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (20 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to give (*rac*)-**3** (54 mg, 61 %) and (*meso*)-**4** (30 mg, 34 %).
11. The optical purity was determined by HPLC analysis with Daicel Chiralcel OD using *n*-hexane-*i*-propanol (9 : 1) as an eluant.
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13. To a stirred suspension of (*S,S*)-**3** (365 mg, 0.61 mmol) in THF (1 mL) under an argon atmosphere was added PMHS (1 g) and $Ti(O\text{-}i\text{-}Pr)_4$ (540 μL, 1.83 mmol), and the resulting mixture was refluxed overnight. Dry hexane (15 mL) was added to the mixture. After refluxing for 2 h, the mixture was allowed to cool, filtered, and washed with dry hexane. The insoluble solids were recrystallized from $CHCl_3$-MeOH to give (*R,R*)-**1** (272 mg, 79 %). (*S,S*)-(+)-**1**: mp 226-227°C; $[\alpha]^{26}_D$ +43.9 (c 0.64 $CHCl_3$). Anal. Calcd for $C_{37}H_{44}OP_2$: C, 78.42; H, 7.83. Found: C, 78.30; H, 7.82. (*R,R*)-(-)- **1**: mp 226-227°C; $[\alpha]^{24}_D$-43.7 (c 0.64, $CHCl_3$). Anal. Calcd for $C_{37}H_{44}OP_2$: C, 78.42; H, 7.83. Found: C, 78.15; H, 7.83.
14. Crystal data for (*S,S*)-(+)-**3**: formula $C_{37}H_{44}O_3P_2$, F.W. 598.7, monoclinic, space group $P2_1$, a = 10.126(2)Å, b = 15.533(5)Å, c = 10.879(2)Å, V = 1707.2(9)Å^3, Z = 2, Enraf-Nonius CAB-4, Mo Kα, R = 0.0587, Rw = 0.0603. Crystal data for (*S,S*)-(+)-**1**: formula $C_{37}H_{44}OP_2$, F.W. 566.7, monoclinic, space group $P2_1$, a = 10.198(2)Å, b = 15.634(5) Å, c = 10.284(2)Å, V = 1632.5(13)Å^3, Z = 2, Enraf-Nonius CAB-4, Mo Kα, R = 0.0541, Rw = 0.0553.
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17. The enantiomeric excess was determined by HPLC analysis with Daicel Chiralcel OD using *n*-hexane-*i*-propanol (99 : 1) as an eluant.

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