On the Resolution of Secondary Phosphine Oxides via Diastereomeric Complex Formation: The Case of *tert*-Butylphenylphosphine Oxide

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Abstract: The secondary phosphine oxide, *t*-BuPhHP=O, the most prominent chiral member of this compound class, has been resolved in high yield and with excellent ee. This resolution discloses an efficient route to enantiopure phosphorus compounds.

Key words: secondary phosphine oxide, phosphinous acid, asymmetric catalysis, resolution, chiral ligand, P-chiral compounds

Trivalent chiral phosphorus compounds are of tremendous importance in organic chemistry, especially in asymmetric synthesis[2] and catalysis. Transition metal catalysis uses phosphorus-based ligands extensively[3] whereas phosphorus-based catalysts also play an important role in organocatalysis.[4]

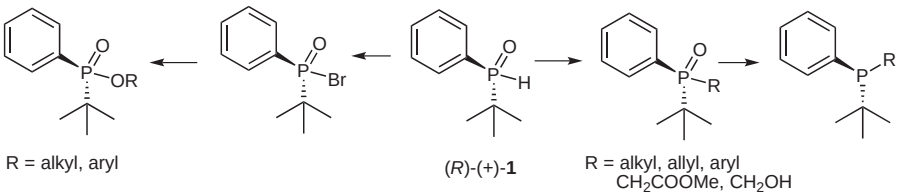
The synthesis of enantiopure P-chiral compounds, with chirality centered on phosphorus, is in general difficult to achieve.[5] Several successful approaches have nevertheless been developed over the years using chiral auxiliaries such as menthol or ephedrine, or chiral bases such as sparteine. These methods are frequently applied but require several synthetic steps, and the chiral pool sometimes provides only one enantiomer of the auxiliary. The resolution of tertiary phosphine oxides via diastereomeric complex formation (classical resolution)[6] has been reported a number of times as well.

Scheme 1 A secondary phosphine oxide (R^1, R^2 = alkyl or aryl) in equilibrium with its phosphinous acid. For the free compound only the phosphine oxide form is observed, but it tautomerizes to the phosphinous acid form upon complexation with a metal.

Secondary phosphine oxides,[7] (or phosphinous acids, Scheme 1), are important ligands in nonasymmetric transition metal catalysis, especially in cross-coupling reactions.[3,8] This class of ligands combines excellent coordinating properties with low oxidation sensitivity and is easily prepared, often in one step. These properties also make them in principle very good ligands in asymmetric catalysis;[9] secondary phosphine oxides have successfully been used in iridium-catalyzed imine hydrogenation,[10] iridium- and rhodium-catalyzed alkene hydrogenation,[11] palladium-catalyzed allylic substitution,[12] and platinum-catalyzed alkylidenecyclopropanation.[13]

Chiral enantiopure secondary phosphine oxides are also excellent starting materials for P-chiral phosphines and other derivatives (Scheme 2).[14] Alkylation of these compounds takes place with retention of stereointegrity, leading to tertiary phosphine oxides.[15] Subsequent deoxygenation affords the corresponding chiral phosphines.[16] The use of the corresponding borane complexes in a variety of applications has recently been described.[17]

The barrier in the application of chiral secondary phosphine oxides is the difficulty to obtain them enantiopure. Several strategies have been developed for the preparation of enantioenriched secondary phosphine oxides, mainly



Scheme 2 Secondary phosphine oxide **1** as a starting material for chiral enantiopure phosphorus compounds

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focusing on *t*-BuPhHP=O (**1**), the *primus inter pares* of this class.

Conversion of *rac*-**1** into the corresponding thiophosphoric acid, followed by resolution via diastereomeric complex formation and desulfurization has been developed on preparative scale and affords enantiopure **1** in high ee.[15,18] Preparative chiral HPLC of a series of secondary phosphine oxides has been successfully applied as well and afforded gram quantities of **1**.[10] Reaction of racemic *t*-BuPhPCl with (*R*)-α-methylbenzylamine led to diastereomeric aminophosphines that could be separated by distillation and subsequently hydrolyzed to **1**. However, the hydrolysis led to some racemization.[19] Recently, one of us reported the preparation of enantioenriched **1** via resolution of its borane complex, that is, phosphinous acid borane.[17] This work was followed by studies of the Buono group who reported a flexible synthesis of chiral secondary phosphine oxides using either menthol[20] or prolinol[21] as a chiral auxiliary. The enatiomeric excesses were in general excellent but did not exceed 91% for **1**. Very recently, the stereospecific alkylation of diastereomerically pure menthyl phosphinates was reported, which affords **1** in 95% yield and 99% ee.[22] Finally, the synthesis of enantiopure ferrocenyl-based secondary phosphine oxide ligands was recently reported in the patent literature using the addition of Grignard reagents to enantiopure ferrocenyl-PCl_2 derivatives followed by diastereoselective hydrolysis.[23]

Summarizing the literature, the conclusion is that the routes to prepare enantiopure secondary phosphine oxides require a number of steps and often do not lead to enantiopure compounds, whereas racemic secondary phosphine oxides are readily available in one step. Therefore, resolution via diastereomeric complex formation seems to be a very attractive route to, for example, **1**. Remarkably, apart from one single example,[24] and contrary to the resolution of tertiary phosphine oxides, no reports on the resolution of secondary phosphine oxides via diastereomeric complex formation could be found in the literature.[25] In the aforementioned report, the resolution of **1** using mandelic acid was described. However, in later work,[26] problems with this resolution were encountered (also vide supra). The configuration and ee of **1** isolated in the complex were unpredictable, pointing at kinetic phenomena during the resolution.

As part of a program aiming at the preparation of P-stereogenic secondary phosphine oxides and phosphines we set out reinvestigating the resolution of **1**. We first optimized the synthesis of racemic **1**; the *t*-BuMgBr addition to dichlorophenylphosphine ($PhPCl_2$) followed by acidic hydrolysis, with a reported yield of 60%.[27] By performing the reaction at –10 °C to room temperature using an excess of Grignard reagent, and keeping a considerably shorter reaction time, an excellent 96% isolated yield was obtained on a preparative (0.4 mol) scale. The reaction afforded pure *rac*-**1** according to melting point and NMR spectrum.

A series of acidic resolving agents was selected for the resolution of **1** in various solvents (Figure 1). The varying results obtained using mandelic acid[24] were confirmed, as sometimes **1** crystallized from the solution, and sometimes complexes of **1** and mandelic acid were isolated with varying ee and absolute configuration for **1**. The use of the phosphoric acids Phencyphos, Anicyphos, and Chlocyphos[28] did not lead to complex formation whereas chalcone sulfonic acid[29] in butanone gave 30% of a complex with racemic **1**.

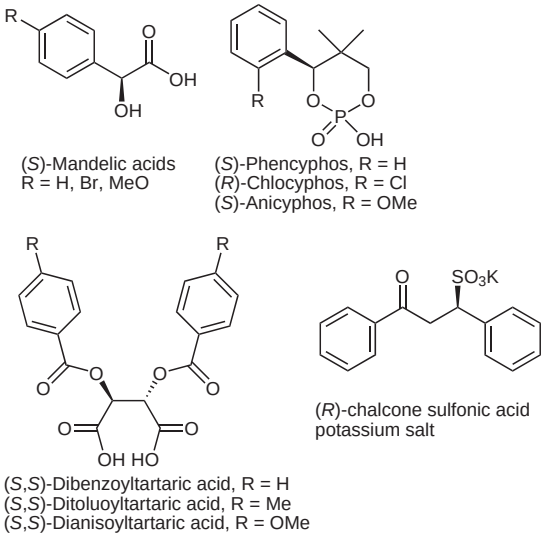
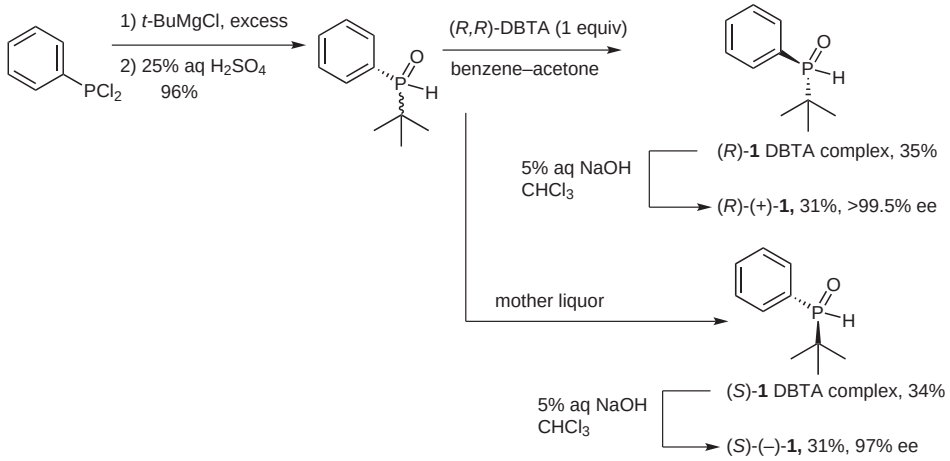


Figure 1 The resolving agents used in this study

Next, the application of mixtures of resolving agents, the so-called Dutch Resolution,[30] was performed. However, the M-mix (containing mandelic acid, *p*-bromomandelic acid and *p*-methoxymandelic acid), the P-Mix (containing the three aforementioned phosphoric acids) and the T-mix (dibenzoyl, ditoluoyl, and dianisoyltartaric acid) all gave oils in the resolution experiments or precipitated from the solution.

Although dianisoyltartaric acid in butanone gave a complex containing racemic **1**, we were pleased to observe that (*R*,*R*)-*O*,*O*-dibenzoyltartaric acid [(*R*,*R*)-DBTA] gave 20% yield and 12% ee when applied in water with a small amount of acetonitrile. All the more so because both enantiomers of DBTA are commercially available. The breakthrough came when EtOAc or water–acetonitrile (1:1) were used as the solvent, which led to 28% yield and 90% ee. After some optimization, 32% yield of a complex containing a 1:1 ratio of DBTA and **1** was obtained with an ee for **1** of 97%! One recrystallization afforded the complex with >99% ee, thereby excluding end-solid solution behavior.[31] Performing the method of 'half quantities',[25d] applying 0.6 equivalent of DBTA gave a small but significant improvement of the ee to 99%. Finally, using benzene–acetone as the solvent, 35% yield was obtained with an ee of >99.5%, making recrystallization unnecessary. Liberation of **1** from the complex by washing a chloroform solution with aqueous $NaHCO_3$ or 5% aqueous NaOH afforded pure **1** without erosion of the ee.



Scheme 3 The resolution of *rac*-**1** with (*R*,*R*)-DBTA

It is noteworthy that, contrary to most resolutions via diastereomeric complex formation, this procedure affords large colorless crystals, with a diameter of up to 1 cm regardless of the solvent. To assure that this resolution was a thermodynamic and robust process, several control experiments were carried out. The resolution was reproduced seven times, using both enantiomers of DBTA and at two different locations, without any failure. In addition, in one experiment the resulting suspension was stored for several weeks, to conclude that the composition of the precipitated complex did not change.

When the mother liquor of the crystallization in benzene–acetone was concentrated in vacuo and dissolved in hot benzene, the other diastereomer of the complex was obtained in 34% yield and 97% ee for **1**. So, both enantiomers of **1** were obtained in one resolution in high yield and excellent ee without recrystallization. The developed resolution protocol is summarized in Scheme 3.

Finally, the resolutions were scaled up starting with 53 g of *rac*-**1** using benzene–acetone, and 1 equivalent of (*R*,*R*)-DBTA [(*R*,*R*)-(–)-dibenzoyltartaric acid, (–)-2,3-dibenzoyl-L-tartaric acid] affording, after liberation of **1** from the complex, 16 grams (31%) of (*R*)-**1** with an ee of >99.5% and after crystallization of the residue of the filtrate from benzene, 16 g (31%) of (*S*)-**1** with an ee of 97%. The resolution in EtOAc was carried out starting with 15 grams of *rac*-**1** and 0.6 equivalent of (*R*,*R*)-DBTA; it afforded (*R*)-**1** in 21% yield and 97% ee. Crystallization of the residue obtained from the filtrate of the latter experiment gave complexes with a considerable lower ee.

The use of (*R*,*R*)-DBTA afforded invariably crystals containing (*R*)-(+)-**1**. This was deduced from the optical rotation and chiral HPLC of liberated **1**, as the absolute configuration of **1** is known.[26] To confirm this, and to get insight into the interactions between DBTA and **1** in the solid phase, single crystals of both the less soluble [(*R*,*R*),*R*] complex (**A**) and the more soluble [(*R*,*R*),*S*] complex (**B**) were obtained and subjected to X-ray diffraction (Figures 2 and 3) (see experimental for details).

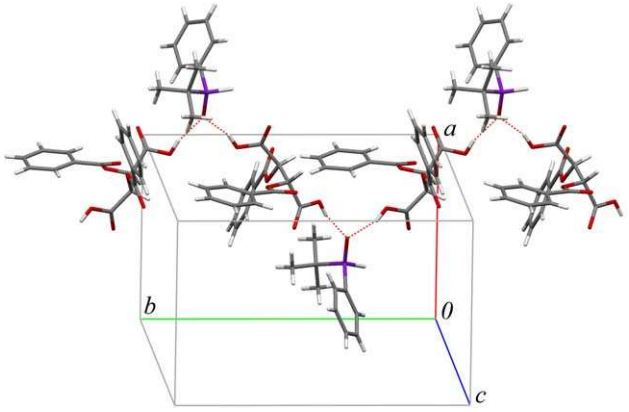


Figure 2 Hydrogen-bonded polymeric ribbons in **A**, running along the [010] direction; hydrogen bonds are drawn as dashed lines

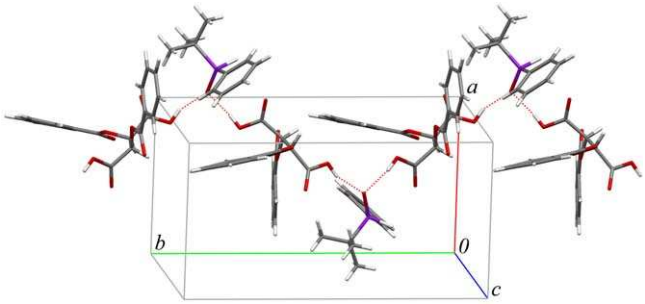


Figure 3 Hydrogen-bonded polymeric ribbons in **B**, running along the [010] direction; hydrogen bonds are drawn as dashed lines

The melting points of the crystals obey the rule that the less soluble complex has a higher melting point (176–178 °C) than the more soluble complex (137 °C).[25d] In both cases, the oxygen of **1** forms hydrogen bonds with carboxylic acid residues of two DBTA molecules. The tetrahedral arrangement around phosphorus in both molecules of **1** is deformed, the valency angles in complex **A** and **B** ranging from 103(1) to 113.6(1)° and 100(2) to 112.9(2)°, respectively. The positions of the P=O bonds in relation to the phenyl rings are identical in **A** and **B**. Over-

all, the origin of the difference in solubility of **A** and **B** is not clear from the X-ray structures alone.

Whereas secondary phosphine oxides tend to decompose slowly at room temperature, the corresponding DBTA complexes were found to be perfectly stable at room temperature, a characteristic reminiscent to the method of Netheton and Fu for the handling of air sensitive phosphines.[32]

In conclusion, it has been shown that *tert*-butylphenylphosphine oxide (**1**), the most prominent chiral secondary phosphine oxide, can be resolved via diastereomeric complex formation. Enantiopure **1** has been prepared in two steps, namely synthesis of the racemate in 96% yield and resolution with dibenzoyltartaric acid in 31% yield (max. 50%), >99.5% ee for one enantiomer and 31% yield, 97% ee for the other enantiomer. The starting materials and the resolving agent are commercially available, the procedure has been carried out on preparative (>50 g) scale and recrystallization is not necessary. As **1** is a versatile ligand itself and an excellent starting material for the preparation of P-chiral phosphines and other phosphorus compounds, their preparation is strongly facilitated this way.

$PhPCl_2$, *tert*-butyl chloride and all resolving agents were used as received. NMR spectra were recorded using $CDCl_3$ as solvent. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). The enantiomeric excess of **1** was determined by HPLC on a Chiralpak AD column (Daicel), solvent: *n*-heptane–propan-2-ol (90:10), flow: 0.5 mL/min, UV-detection: 216 nm, (*S*)-**1** = 9.2 min, (*R*)-**1** = 12.4 min, or was approximated by comparison of the optical rotation values.

tert-Butylphenylphosphine Oxide (*rac*-1)

A 2 L round-bottomed flask equipped with a stirring bar, dropping funnel, condenser, and thermometer was charged with Mg turnings (38.8 g, 1.6 mol), a crystal of I_2 and anhyd Et_2O (200 mL). Under N_2, *t*-BuCl (148 g, 1.6 mol) was added dropwise over 5 h. Subsequently, the temperature was decreased and kept between –10 and –15 °C. $PhPCl_2$ (71.2 g, 0.4 mol) in anhyd Et_2O (100 mL) was added dropwise and after 1 h at that temperature, stirring was continued for 1 h at r.t. Subsequently, 25% aq H_2SO_4 (600 mL) was added carefully. After phase separation, the aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL) and the combined organic layers were dried ($MgSO_4$). The solvents were removed under vacuum and the crude product was distilled at 105–110 °C/0.1 mm Hg to give 70 g (96%) of **1** as white crystals; mp 46 °C. NMR data were as reported in the literature.[18]

Resolution of *rac*-1 in Benzene–Acetone

To a round-bottomed flask containing benzene–acetone (4:1, 780 mL) at reflux was added **1** (53 g, 0.291 mol) and (–)-(*R*,*R*)-dibenzoyltartaric acid (110.5 g, 0.291 mol). After complete dissolution, the mixture was allowed to cool down to r.t. and kept for 17 h. The large white crystals formed were isolated by filtration and washed with benzene–acetone (4:1, 50 mL). After drying, 57 g (35%) of DBTA/**1** complex (**A**) was obtained; mp 176–178 °C; $[\alpha]_D$ –66.6 (*c* = 2.5, MeOH). The crystals were dissolved in $CHCl_3$ (50 mL) and the solution was washed with 5% aq NaOH (3 × 300 mL) followed by H_2O (200 mL). After drying ($MgSO_4$) and evaporation of the solvent, 16 g (31%) of (*R*)-**1** was obtained; mp 48 °C; $[\alpha]_D$ +41.8 (*c* = 2.5, MeOH); >99.5% ee. Spectral data were identical with those in the literature. The remaining filtrate of the crystallization was taken and solvents were removed under vacuum. After dissolution in hot benzene (500 mL), cooling down to r.t., and keeping for 24 h, the large white crystals formed were isolated by filtration and washed with benzene (50 mL). After drying, 56 g (34%) of DBTA/**1** complex (**B**) was obtained; mp 137 °C; $[\alpha]_D$ –87.8 (*c* = 2.5, MeOH). The crystals were dissolved in $CHCl_3$ (50 mL) and the solution was washed with 5% aq NaOH (3 × 300 mL) followed by H_2O (200 mL). After drying ($MgSO_4$) and evaporation of the solvent, 16 g (31%) of (*S*)-**1** was obtained; mp 48 °C; $[\alpha]_D$ –40.4 (*c* = 2.5, MeOH); >97% ee. Spectral data were identical with those in the literature.

X-ray Crystal Structures of Compounds A and B[33]

Structures of the compounds **A** [DBTA/**1** (*R*,*R*),*R* complex] and **B** [DBTA/**1** (*R*,*R*),*S* complex] were determined by single-crystal X-ray diffraction at ambient temperature. Intensity data for the crystal of **A** were collected using an Enraf-Nonius CAD4 diffractometer[34] and graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å). The measurements for **B** were performed on a Kuma KM-4 κ-axis diffractometer[35] with graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å). The structures were solved by direct methods using the SHELXS-97 program.[35]All non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F^2 using the SHELXL-97 program,[36] and the complete set of reflections. The final geometrical calculations were carried out with the PLATON program.[37] Figures were drawn using the Mercury program.[38] In **A** and **B**, hydrogens attached to P1 atoms were located in a difference Fourier map and their positions and displacement parameters were refined freely. Remaining hydrogen atoms were placed in their calculated positions, assigned isotropic thermal parameters (1.2 or 1.5 times that of the atom attached to) and allowed to ride on their respective parent atoms.

Figures 2 and 3 show a stereoscopic view of the molecular packing in the unit cell for complexes **A** and **B**. In both structures the molecules are connected by O4–H4···O1 and O5–H5···O1 hydrogen bonds, which run along the *b* axis of the unit cell, resulting in a $C_2^1(9)$ graph-set motif.[39] The two O4–H4···O1 [–x + 1, y – 0.5, –z + 1] and O5–H5···O1[x + 1, y, z] hydrogen bonds in the complex**A** are 1.81 and 1.82 Å with the angles O4–H4···O1 and O5–H5···O1 165 and 161°; distances O4···O1 and O5···O1 are 2.610(3) and 2.605(2) Å. Analogous hydrogen bonds are observed in the complex **B**, where O4–H4···O1 [x, y – 1, z + 1] and O5–H5···O1 [–x, y – 0.5, –z + 1] are 1.80 and 1.84 Å with the angles O4–H4···O1 and O5–H5···O1 of 158 and 167°; distances O4···O1 and O5···O1 are 2.577(4) and 2.641(4) Å.

Resolution of *rac*-1 in EtOAc

A round-bottomed flask was charged with (–)-(*R*,*R*)-dibenzoyltartaric acid monohydrate (18.61 g, 0.049 mol, 0.6 equiv), **1** (15 g, 0.082 mol, 1.0 equiv), and EtOAc (375 mL). The mixture was heated at reflux until complete dissolution, subsequently allowed to cool down to r.t. and kept for 24 h. The mother liquor was decanted, the crystals were washed with Et_2O (50 mL) and dried to give 9.79 g (22%) of the complex. To isolate **1**, the crystals were suspended in sat. aq $NaHCO_3$ (200 mL) and Et_2O (200 mL). After stirring for 20 min, the organic phase was separated and the aqueous phase extracted with Et_2O (4 × 200 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was evaporated under vacuum to give 3.087 g (21%) of (*R*)-**1** with an ee of 97%.

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