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New procedures for the resolution of chiral *tert*-butylphenylphosphine oxide and some of its reactions †

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Abstract

Racemic *t*-butylphenylphosphine oxide was resolved via formation of diastereoisomeric complexes with (+)-(*R*)-1,1′-binaphthalene-2,2′-diol and (+)-(*S*)-mandelic acid. With the latter complexing agent, separation of the essentially enantiopure (−)-(*S*)-enantiomer was achieved in a single complexation process. Addition of paraformaldehyde to this enantiomer gave α-hydroxymethyl-*t*-butylphenylphosphine oxide with high stereoselectivity and retention of configuration at phosphorus while its reaction with methyl bromoacetate in methanol/sodium methoxide resulted in the formation of methyl *t*-butylphenylphosphinate with inversion at phosphorus.

1. Introduction

Enantiomerically pure phosphorus compounds play an important role in asymmetric and stereoselective synthesis.[1] Of particular importance are P-chiral phosphine oxides since they are precursors of chiral phosphines which in turn serve as efficient ligands in homogeneous catalysis.[2] Among many substrates for the synthesis of a variety of enantiomerically pure phosphine oxides and other structurally related compounds, the enantiomeric forms of secondary *tert*-butylphenylphosphine oxide **1** are the most useful and promising ones. As was elegantly demonstrated by Haynes and his group[4–6] and by Okazaki and his co-workers,[7,8] the lithiated derivatives of **1**, (*R*)-Li-**1** and (*S*)-Li-**1**, are configurationally stable and react with various electrophilic reagents (alkyl halides, aldehydes, α,β-unsaturated carbonyl compounds) to give the corresponding P=O derivatives without loss of configurational integrity at phosphorus.

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† Dedicated to Professor R. Schmutzler (TU Braunschweig) on the occasion of his 65th birthday.

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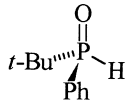
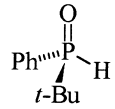
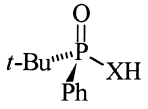


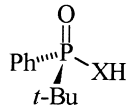
(*R*)-**1**



(*S*)-**1**

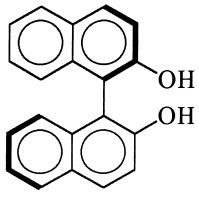


(*S*)-**2** X=S (*R*)-**2**
(*S*)-**3** X=Se (*R*)-**3**

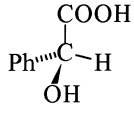


Similarly, addition of elemental sulfur and selenium to enantiomeric phosphine oxides **1** in the presence of triethylamine proceeds with a complete retention of configuration at phosphorus and gives the enantiomeric phosphinothioic acids **2** and phosphinoselenoic acids **3**, respectively.[9,10] The reverse reaction, i.e. hydrogenolysis of the optically active **2** and **3** with Raney nickel leads to **1** also with retention of configuration.[9,10] In fact, a multigram scale preparation of the enantiopure (*R*)-**1** and (*S*)-**1** elaborated by Haynes[3,11] is based on ultrasound-assisted desulfurization of the thioacid **2** with Raney nickel. However, this method is lengthy, time consuming and expensive because it involves at first the synthesis of racemic (±)-**1**, then its sulfurization to (±)-**2** followed by resolution into (−)-(*S*)-**2** and (+)-(*R*)-**2** and their final reductive desulfurization to enantiomeric phosphine oxides **1**.

The enantiomeric phosphinothioic acids **2** have recently attracted our interest as versatile chiral solvating agents for the NMR determination of the enantiomeric excesses (ees) of a large number of chiral organic and hetero-organic compounds.[12–14] The suitability of the enantiomeric phosphinoselenoic acids **3** for the same purpose is under current study in our laboratory. Since both optically active acids **2** and **3** are most conveniently prepared from enantiomeric phosphine oxides **1**, we were searching for a more efficient and shorter approach to the latter. Being stimulated by the observation of one of us that racemic **1** can be resolved via diastereoisomeric complexes with optically active (−)-dibenzoyltartaric acid,[15] we evaluated optically active (+)-2,2′-dihydroxy-1,1′-binaphthol **4** and (+)-mandelic acid **5** as resolving complexing agents and found that separation of the practically enantiopure (−)-(*S*)-**1** may be achieved with (+)-**5** in a single complexation process. The results of this study are reported herein.



(+)-(*R*)-**4**



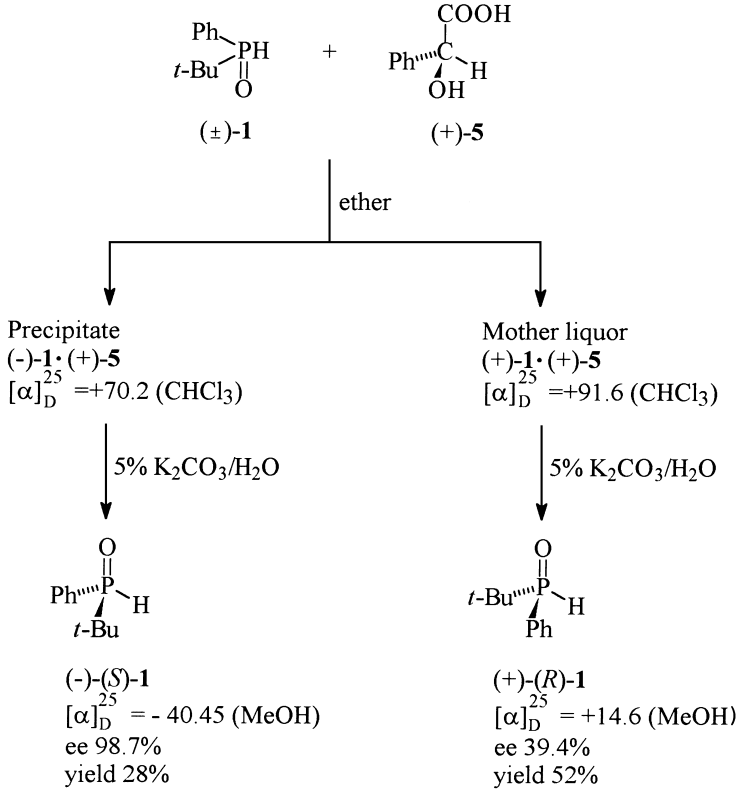
(+)-(*S*)-**5**

2. Results and discussion

Preliminary experiments showed that the racemic phosphine oxide **1** and binaphthol (+)-**4** readily formed diastereoisomeric complexes which were easily soluble in the majority of organic solvents such as ether, benzene, acetone and chloroform. However, they were very poorly soluble in water contrary to phosphine oxide **1**. This difference in solubility allowed the elaboration of a simple procedure for the resolution of the title compound **1**. Thus, a mixture of two equivalents of (±)-**1** dissolved in water

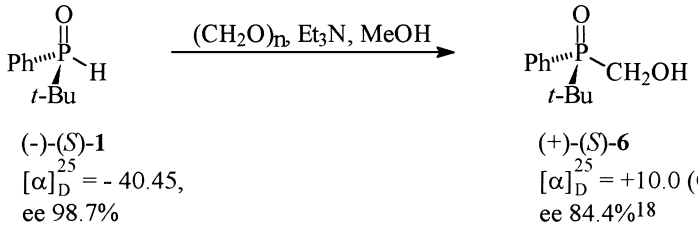
and one equivalent of (+)-**4** suspended in water was stirred at room temperature for ca. 15 h. The crystalline complex formed, $[\alpha]_D^{25}$=−19.7 ($CHCl_3$), was separated by filtration. The optically active (−)-(*S*)-**1**, $[\alpha]_D^{25}$=−21.5 ($CHCl_3$), ee 58%, was liberated from this complex by column chromatography on silica gel using chloroform as eluent. Extraction of the water solution with chloroform afforded the (+)-(*R*)-enantiomer of **1**, $[\alpha]_D^{25}$=+22.2 ($CHCl_3$), 60% ee. Repetition of the resolution procedure using the above sample of (+)-**1** allowed the recovery from the water phase of (+)-(*R*)-**1** with $[\alpha]_D^{25}$=+28.6, 77% ee.

Much better results were obtained with (+)-(*S*)-mandelic acid **5** as a resolving agent. In this case, equimolar amounts of (±)-**1** and (+)-**5** were dissolved in ether and the solution was stirred for ca. 70 h. The crystalline complex, $[\alpha]_D^{25}$=+70.2 ($CHCl_3$), 33.9% yield, precipitated and was filtered off. It turned out that a single diastereoisomeric complex was isolated as evidenced by ^{1}H NMR spectra (one doublet for the *t*-Bu-P protons). Dissolution of this complex in a 5% aqueous solution of potassium carbonate and extraction with chloroform gave practically enantiomerically pure (−)-(*S*)-**1**, $[\alpha]_D^{25}$=−40.45, ee 98.7%,[16] in 28.4% yield. Evaporation of the mother liquor afforded a mixture of two diastereoisomeric complexes in a 7:3 ratio (NMR assay: two doublets for the *t*-Bu-P protons) from which (+)-(*R*)-**1**, $[\alpha]_D^{25}$=+14.6, ee 39.4%, was released and isolated in 52% yield. The procedure is shown in Scheme 1.



Scheme 1.

With optically active **1** in hand, two reactions were carried out. The first was the addition of paraformaldehyde to (−)-(*S*)-**1** in the presence of triethylamine. In spite of rather forced reaction conditions (2 h reflux in methanol) the corresponding α-hydroxymethylphosphine oxide (+)-(*S*)-**6** was obtained with high stereoselectivity (Eq. 1).[18] Due to the presence of the hydroxy group it may be used in further studies.

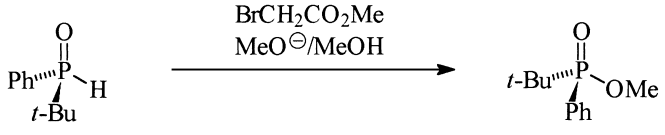


(-)-(*S*)-**1**
$[\alpha]_D^{25}$ = - 40.45,
ee 98.7%

(+)-(*S*)-**6**
$[\alpha]_D^{25}$ = +10.0 ($CHCl_3$),
ee 84.4%[18]

(1)

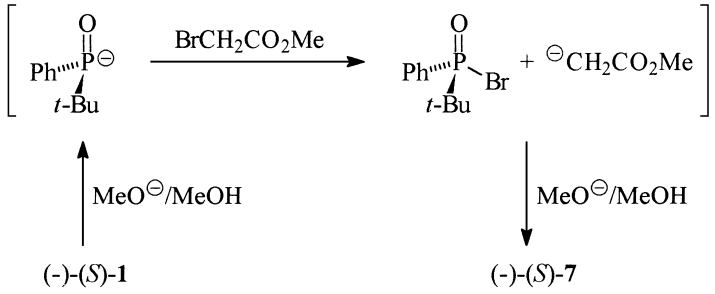
The second reaction between the sodium salt of (−)-(*S*)-**1** and methyl bromoacetate in methanol gave, however, not the expected alkylation product but (−)-(*S*)-methyl *t*-butylphenylphosphinate **7**[17] with inversion of configuration (Eq. 2). Taking into account the fact that bromine is a highly polarizable (soft) atom and behaves in some reactions as a so-called 'electropositive halogen',[19] it is reasonable to assume that the nucleophilic attack of the phosphine oxide **1** anion is directed towards bromine and not carbon in bromoacetate. Then, the phosphinoyl bromide formed as a reactive intermediate undergoes nucleophilic attack at phosphorus by the methoxy anion to form the phosphinate **7** with inversion of configuration (Scheme 2).



(-)-(*S*)-**1**
$[\alpha]_D^{25}$ = - 36.7 (MeOH)
ee 87.4%

(-)-(*S*)-**7**
$[\alpha]_D^{25}$ = - 51.5 ($CHCl_3$),
ee 76%[18]

(2)



Scheme 2.

3. Conclusions

The resolution procedures described above simplify the approach to *t*-butylphenylphosphine oxide in both enantiomeric forms, and consequently, make this compound available more readily for synthetic and stereochemical studies.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 200 spectrometer at 200 MHz. All optical rotation measurements were done on a Perkin–Elmer MC 241 photopolarimeter. Reactions were monitored by TLC chromatography (Merck Kieselgel 60 F_{254}). Column chromatography was conducted on Merck silica gel (70–230 mesh).

4.2. Resolution of racemic t-butylphenylphosphine oxide **1** with enantiomerically pure (+)-1,1′-binaphthalene-2,2′-diol **4**

A heterogeneous mixture of racemic *t*-butylphenylphosphine oxide **1** (0.1472 g, 0.8 mmol) and (+)-(*R*)-**4** (0.116 g, 0.4 mmol) in 3.5 ml of water was stirred at room temperature for 15 h. The white crystals formed were separated by filtration. The isolated complex of the phosphine oxide **1** and the binaphthol **4** (0.152 g, ~50% yield) had $[\alpha]_{589}^{25}$=−19.7 (c=1.14, $CHCl_3$) and the following spectroscopic data: ^{1}H NMR ($CDCl_3$) δ=1.123 (d, J=16.72 Hz, 9H); 5.83 (bs, 3H); 7.00–8.00 (m, 17H); ^{31}P NMR ($CDCl_3$) δ 48.64 (s). Column chromatography of this complex (0.09 g) on silica gel (5 g) gave after elution with a 1:1 mixture of ethyl ether and petroleum ether enantiomerically pure (+)-(*R*)-**4**. Further elution with chloroform afforded optically active *t*-butylphenylphosphine oxide (−)-**1** (0.030 g): $[\alpha]_{589}^{25}$=−21.5 (c=1.18, $CHCl_3$); ee=58%. The ^{1}H and ^{31}P NMR spectral data fully supported its structure. In order to isolate the non-complexed phosphine oxide **1**, the water phase was extracted with chloroform (3×5 ml). The chloroform solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo gave the analytically pure phosphine oxide (+)-**1** [(0.068 g, 45%); $[\alpha]_{589}^{25}$=+22.2 (c=1.34, $CHCl_3$); ee=59.7%].

Repetition of the resolution procedure of this sample of (+)-**1** using 0.05 g of (+)-(R)-**4** gave, after extraction from the water phase, the non-complexed phosphine oxide (+)-**1** (0.0448 g) with $[\alpha]_{589}^{25}$=+28.6 (c=2.24, $CHCl_3$); ee=77%.

4.3. Resolution of racemic t-butylphenylphosphine oxide **1** with enantiomerically pure (+)-(S)-mandelic acid **5**

Racemic *t*-butylphenylphosphine oxide **1** (1.84 g, 0.01 mol) was dissolved in ethyl ether (10 ml). Compound (+)-(*S*)-**5** (1.52 g, 0.01 mol) was added slowly to this solution. After addition of each portion the solid acid disappeared rapidly. A few minutes after the addition of the last portion of the acid the colourless crystals of the complex started to appear. The reaction mixture was left at room temperature for 72 h. The complex formed was filtered off (1.01 g, 33.9%). It had $[\alpha]_{589}^{25}$=+70.2 (c=2.14, $CHCl_3$) and the following spectroscopic data: ^{1}H NMR ($CDCl_3$) δ=1.116 (d, J=16.97 Hz, 9H); 5.153 (s, 1H); 7.01 (d, J=463.74 Hz, 1H); 7.25–7.75 (m, 10H); ^{31}P ($CDCl_3$) δ=49.77 (s). The ^{1}H NMR data indicated that the isolated complex contained only a single diastereoisomer. In order to isolate enantiomerically pure *t*-butylphenylphosphine oxide, the isolated complex (500 mg) was dissolved in 4 ml of 5% aqueous solution of K_2CO_3 and the water phase was extracted with $CHCl_3$ (4×5 ml). The combined chloroform solutions were dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the virtually pure *t*-butylphenylphosphine oxide (−)-**1** (0.261 g, 28.4%) with $[\alpha]_{589}^{25}$=−40.45 (c=1.78, MeOH) and $[\alpha]_{589}^{25}$=−36.6 (c=1.38, $CHCl_3$). The spectral and analytical data (^{1}H, ^{31}P and HRMS) fully supported its structure. Evaporation of the mother liquor gave an oil (2.190 g, 65.2%) with $[\alpha]_{589}^{25}$=+91.55 (c=3.1

$CHCl_3$). The ^1H NMR spectrum indicated that the oil contained two diastereoisomers in a ratio ~7:3. To isolate enantiomerically enriched *t*-butylphenylphosphine oxide, the oil was dissolved in 20 ml of 5% aqueous solution of K_2CO_3 and the water phase was extracted with chloroform (3×20 ml). The chloroform solution was dried over magnesium sulfate. Evaporation of the solvent gave the virtually pure phosphine oxide (+)-**1** with $[\alpha]_{589}^{25}$=+14.6 (c=1.68, MeOH); ee=39.4%.

*4.4. Reaction of (−)-(S)-t-butylphenylphosphine oxide **1** with paraformaldehyde: preparation of (+)-hydroxymethyl-t-butylphenylphosphine oxide **6***

A solution of (−)-(*S*)-**1** [0.261 g, 1.5 mmol; $[\alpha]_{589}^{25}$=−40.45 (MeOH), ee=98.7%] and paraformaldehyde (0.2 g) in triethylamine (2 ml) was refluxed for 2 h. Then, chloroform (50 ml) was added and the chloroform solution was washed with 5% H_2SO_4 and water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave virtually pure (^1H and ^{31}P assay) hydroxymethylphosphine oxide (+)-**6** (0.184 g, 60%); $[\alpha]_{589}^{25}$=+10.0 (c=1.41, $CHCl_3$). The ^{31}P NMR spectrum of this sample recorded in the presence of (+)-(*R*)-*t*-butylphenylthiophosphinic **2** acid as a chiral solvating agent indicated that the phosphine oxide **6** obtained has ee=88.4% [by integration of the resonance signals at δ=49.935 ppm (major diastereoisomer) and δ=49.477 ppm (minor diastereoisomer)].

*4.5. Reaction of the sodium salt of (−)-(S)-t-butylphenylphosphine oxide **1** with methyl bromoacetate: preparation of (−)-methyl t-butylphenylphosphinate **7***

(−)-(*S*)-*t*-Butylphenylphosphine oxide **1** [0.368 g, 2 mmol; $[\alpha]_{589}^{25}$=−36.7 (c=1.77, MeOH), ee=90.4%] was added to a solution of sodium methoxide (0.002 mol) generated in situ in 10 ml of methanol. The specific rotation of this solution was found to be unchanged during two weeks. After that time methyl bromoacetate was added at room temperature and the reaction was monitored by polarimetry. The rotation of the reaction mixture changed from $[\alpha]_{589}^{25}$=−1.2 to $[\alpha]_{589}^{25}$=−2.3 during 24 h and remained constant during the following 72 h. After that time the reaction mixture was poured into water (100 ml) and the aqueous solution was extracted with chloroform (2×30 ml). The organic solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the analytically pure (−)-(*S*)-methyl *t*-butylphenylphosphinate (0.360 g, 75%) with $[\alpha]_{589}^{25}$=−51.5 (c=1.84, $CHCl_3$). Its spectral and analytical data (^1H, ^{13}C, ^{31}P NMR, HRMS) fully supported the structure. The ^1H NMR spectrum of this sample recorded in the presence of (+)-(*R*)-*t*-butylphenylthiophosphinic acid **2** as a chiral solvating agent indicated that the prepared ester had an ee=76% [the OMe signals at δ=3.625 ppm (for major diastereoisomer) and δ=3.615 ppm (for minor diatereoisomer)].

Acknowledgements

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