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Resolution of 3-methyl-3-phospholene 1-oxides by molecular complex formation with TADDOL derivatives

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Abstract—The antipodes of 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** were separated in good yield and in high enantiomeric excess (~99% ee) by resolution via formation of diastereomeric complexes with (4*R*,5*R*)-(−)- and (4*S*,5*S*)-(+)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane **2** (TADDOL) or (−)-(2*R*,3*R*)-α,α,α′,α′-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol **3**. The method was also suitable for the resolution of the 1-ethoxy-3-phospholene derivative **1b**, suggesting that our novel procedure may be of general value, both for the resolution of chiral phosphine oxides and phosphinates.

1. Introduction

Chiral phosphine oxides form an important class of phosphorus compounds, since they are precursors of the corresponding phosphines, which, in turn, may serve as ligands in transition metal complexes that can be applied in several highly efficient homogenous catalytic processes.[1,2] Since P-chiral organophosphorus compounds cannot be found in enantiomeric forms in the natural chiral pool,[3] the primary source of such compounds is resolution. Several methods described in the literature on the resolution of phosphorus compounds, are based on the formation of separable diastereomeric salts, diastereomeric transition metal complexes and molecular complexes.[1] In the sphere of P=O-compounds, diastereomeric salt formation may rely on the protonation of the weakly basic phosphoryl oxygen with an acid, such as (+)-bromocamphorsulfonic acid,[4] camphorsulfonic acid,[5] (−)-dibenzoyltartaric acid,[1] and (+)-mandelic acid.[6] The resolution of phosphonium salts can be accomplished by combining the racemate with the silver salt of a chiral acid.[7,1] A carboxylic acid derivative of a phosphine sulfide,[8] as well as a thiophosphinic acid[9] were resolved with either (+)- or (−)-1-phenylethylamine. Several transition metal complexes, such as Pd, Pt, Ni and Fe, were found to be useful in the separation of racemic phosphines.[10,1] Toda et al. reported the first enantiomeric separation of acyclic phosphine oxides and phosphinates via inclusion complex formation with 2,2′-dihydroxy-1,1′-binaphthol.[11] Later on, their method was extended to the resolution of an analogous phosphine oxide.[6]

Five-membered P-heterocycles, such as 1-substituted-3-phospholene 1-oxides, for example **1**, are of synthetic importance, as they can be used as starting materials in the preparation of a variety of five-, six-, seven-, and eight-membered P-heterocycles, including bridged derivatives.[12–15] Pietrusiewicz et al. reported several methods for the resolution of 1-phenyl-2- or 1-phenyl-3-phospholene 1-oxides and their epoxide derivatives based on dipolar cycloaddition,[16] enantioselective desymmetrization,[17–19] and quaternerization of their deoxygenated derivatives with a chiral reactant.[19] A practical procedure for the resolution of 1-substituted-3-methyl-3-phospholene 1-oxides **1** by the separation of the complexes formed by interaction with chiral hosts TADDOL[13] **2** or TADDOL analogue **3**[20] is described (Scheme 1).

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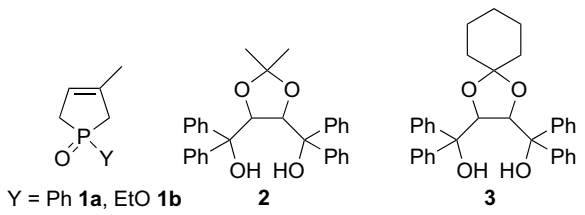


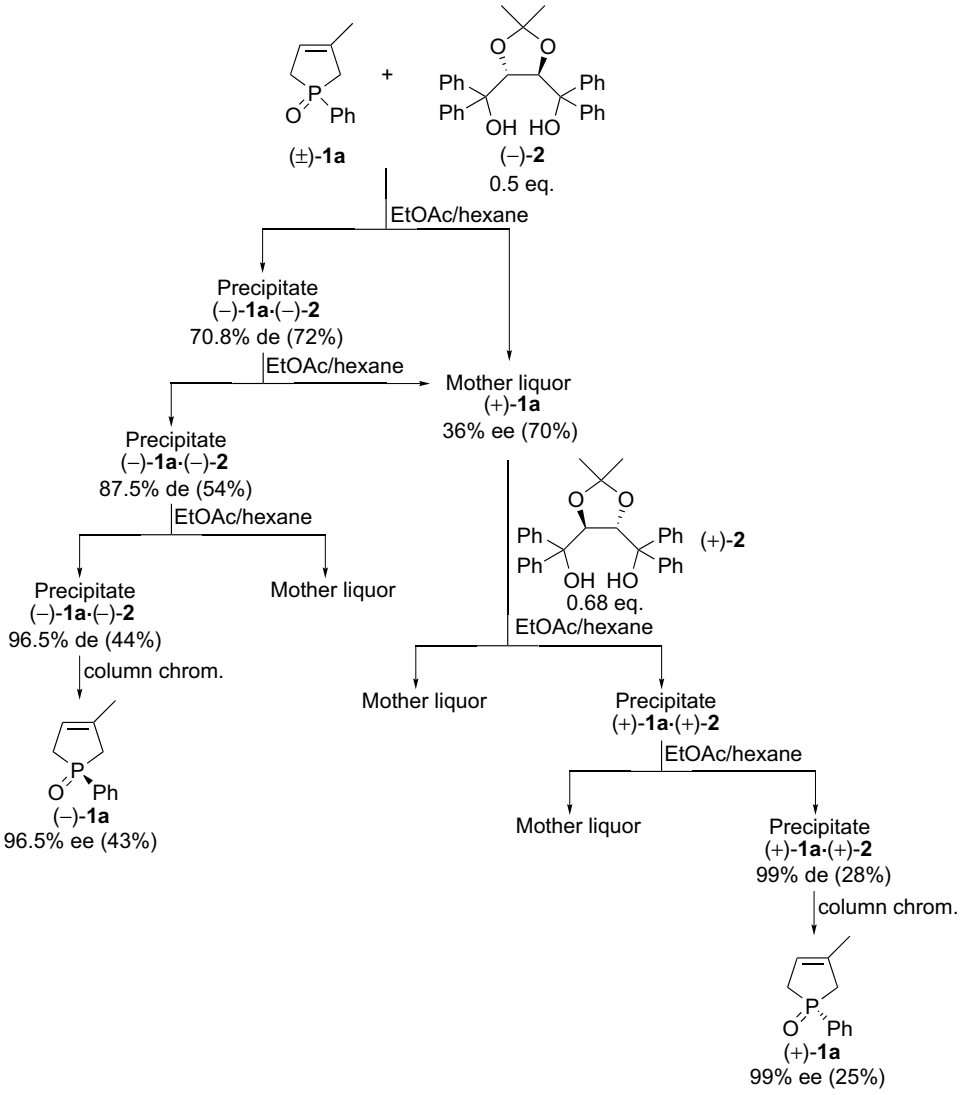
Scheme 1.

2. Results and discussion

Racemic 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** was resolved by adding half equivalent of (−)-TADDOL **2** to its hot ethyl acetate solution and precipitating a 1:1 crystalline complex (−)-**1a**·(−)-**2** by the addition of hexane.[21] Complex (−)-**1a**·(−)-**2** was analyzed on a chiral HPLC column (Chiralpack AD) showing that the enantiomeric excess of (−)-**1a** regenerated was 70.8%. Two recrystallizations of the complex from a 1:5 mixture of ethyl acetate–hexane gave complex (−)-**1a**·(−)-**2** with an excellent enantiomeric excess of 96.5% in 44% yield based on **1a**. After flash chromatography on a silica gel, 96.5% ee of (−)-**1a** was recovered in 43% yield (Scheme 2).

To obtain the enantiomerically pure (+)-**1a**, the mother liquors of the crystallization and the first recrystallization were combined and purified by column chromatography using silica gel to give (+)-**1a** in 70% yield with an enantiomeric excess of 36%. From the solution of phenyl-methylphospholene oxide (+)-**1a** thus obtained and 0.68 equiv of (+)-TADDOL **2** in hot ethyl acetate, crystals of complex (+)-**1a**·(+)-**2** were obtained by the addition of hexane that were recrystallized from a 1:5 mixture of ethyl acetate–hexane to afford the complex (+)-**1a**·(+)-**2** with a 99% de, in 28% yield. After flash column chromatography using silica gel, (+)-**1a** of 99% ee was obtained in 27% yield (Scheme 2).

The resolution of phenyl-methylphospholene oxide **1a** with half equivalent of TADDOL **2** was also accomplished from a 1:5 mixture of acetone–pentane. Crystallization and two



Scheme 2. The optical resolution of 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** with TADDOL **2**.

recrystallizations of **1a** with (−)-TADDOL **2** followed by flash column chromatography led to enantiomerically pure (−)-**1a** with a 98.6% ee in 39% yield.

To establish the absolute configuration of (−)-**1a**, (−)-**1a**·(−)-**2**·acetone was subjected to single crystal X-ray analysis.[22] The absolute configuration of (−)-**1a** was found to be (*S*) (Fig. 1).

The crystal structure reveals a complementary H-bridging assisted fit of **1a** arranged around the screw axis at $\{0, y, 0\}$ to the spiralling columnar stacks of self-complementary **2** around the screw axis at $\{1/2, y, 1/2\}$ while acetone guest molecules fill an infinite channel at $\{1/2, y, 0\}$. Thus acetone acts not only as a co-solvent but is also essential in sustaining a closely packed crystal made up of semi-rigid molecules **1a** and **2**.

It can be seen that the oxygen atom of the P═O group plays an important role in the complex formation.

TADDOL analogue (−)-**3** could also form a molecular complex with **1a**, but the resolution sequence was less effective than with TADDOL **2**. Two recrystallizations of the complex formed from P-heterocycle **1a** and half an equivalent of (−)-**3** using the same procedure described above led, after flash column chromatography, to (−)-**1a** with a >99% ee in 29% yield.

After the successful resolution of cyclic phosphine oxide **1a**, that of 1-ethoxy-3-methyl-3-phospholene 1-oxide **1b** was also attempted. The use of half equivalent of (−)-TADDOL analogue **3** was more appropriate than that of (−)-TADDOL **2**, as after two recrystallizations from 1:10 ethyl acetate–hexane followed by chromatography, the ee values were 93.3 and 44.2, respectively. It is noteworthy that the use of **3** and **2** led to different antipodes (−)-**1b** and (+)-**1b**, respectively. In these instances, the yields have not yet been optimized.

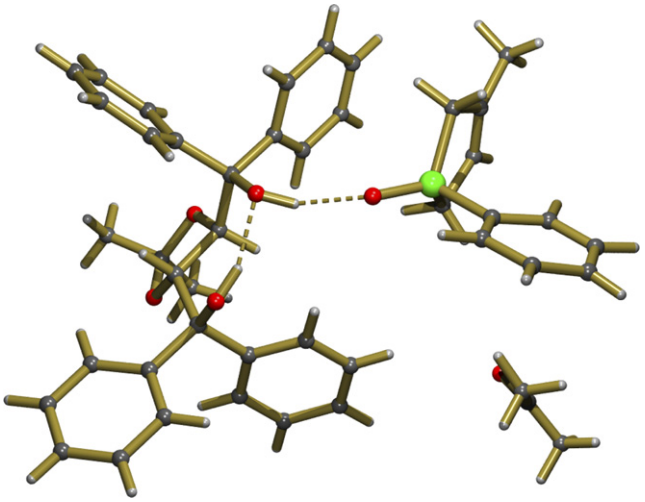


Figure 1. X-ray structure of the 1:1:1. coordinato-clathrate inclusion of (−)-1-phenyl-3-methyl-3-phospholene 1-oxide **1a** with (−)-TADDOL **2** and acetone (−)-**1a**·(−)-**2**·acetone.

3. Conclusion

We have developed a resolution procedure that is the first example of the enantiomeric separation of a cyclic phosphine oxide or a phosphinate via inclusion complex formation. Crystallization with TADDOL **2**, the recrystallization of the complex and the regeneration of **1** form a simple and convenient method for the preparation of both enantiomers with high enantiomeric purity. The resolving agent is relatively inexpensive and easily available.

The method introduced may be suitable for the resolution of other P-heterocycles with P═O function as well.

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21. *Resolution of 1-phenyl-3-methyl-3-phospholene 1-oxide* **1a** *with TADDOL* **2** *in a mixture of ethyl acetate and hexane—a sample procedure*. To 0.48 g (2.49 mmol) of racemic 1-phenyl-3-methylphosphol-3-ene 1-oxide **1a** and 0.58 g (1.245 mmol) of (−)-TADDOL **2** in 1 mL of hot ethyl acetate was added 5 mL of hexane. After the addition, colorless crystals of the complex started to appear immediately. After 30 min, the crystals were separated by filtration to give 0.59 g (72%) of complex (−)-**1a**·(−)-**2**; enantiomeric excess (determined by HPLC), 70.8% ee. The complex was further purified by two recrystallizations from ethyl acetate–hexane [(1) 0.53 mL/2.64 mL, (2) 0.26 mL/1.3 mL] to afford complex (−)-**1a**·(−)-**2** in 54% yield with 87.2% ee and in 43% yield with 96.5% ee, respectively. Column chromatography (silica gel, chloroform) of the complex regenerated 96 mg (40%) of the enantiomerically pure (−)-(*S*)-1-phenyl-3-methyl-3-phospholene 1-oxide {(−)-**1a**; enantiomeric excess, 96.5% ee, $[\alpha]_D^{25} = -34.4$ (*c* 1, $CHCl_3$)}. Phenyl-phospholene oxide **1a** was separated from the combined mother liquors of the crystallization and the first recrystallization by column chromatography (silica gel, chloroform). To 0.17 g (0.94 mmol) of phenyl-methylphospholene oxide **1a** (36% ee) and 0.30 g (0.64 mmol) of (+)-TADDOL **2** in 0.33 mL of hot ethyl acetate was added 1.66 mL of hexane. After 30 min, the crystals that precipitated were separated to afford 0.30 g of complex (+)-**1a**·(+)-**2**. The complex was further purified by recrystallization from a mixture of 0.20 mL ethyl acetate and 1.00 mL hexane to give 0.23 g (28%) of (+)-**1a**·(+)-**2** (99% ee, mp: 139 °C, $[\alpha]_D^{20} = +56.0$ (*c* 1, $CHCl_3$), Anal. Calcd for $C_{42}H_{43}O_5P$ (658.76): C, 76.58; H, 6.58. Found: C, 76.65; H, 7.00). Column chromatography (silica gel, chloroform) of the complex recuperated 60 mg (25%) of the enantiomerically pure (+)-(*R*)-1-phenyl-3-methyl-3-phospholene 1-oxide (+)-**1a**; 99.0% ee; $[\alpha]_D^{25} = +36.6$ (*c* 1, $CHCl_3$).
22. Crystal data for **1a** were collected on a Rigaku R-Axis RAPID IP diffractometer using standard procedures of a graphite monochromator with Mo-Kα radiation at 135(2) K: $C_{31}H_{30}O_4 \cdot C_{11}H_{12}OP \cdot C_3H_6O$, Fwt.: 716.81, colorless block, size: $0.79 \times 0.72 \times 0.62$ mm, monoclinic, space group $P2_1$, $a = 9.464(1)$ Å, $b = 9.965(1)$ Å, $c = 20.999(3)$ Å, $\alpha = 90.00°$, $\beta = 99.773(5)°$, $\gamma = 90.00°$, $V = 1951.7(4)$ Å^3, $T = 135(2)$ K, $Z = 2$, $D_C = 1.220$ Mg/m^3, numerical absorption correction ($T_{max}/T_{min} = 0.937/0.953$). 98,323 reflections, 16,786 unique [$R_{int} = 0.0467$, completeness 99.9%]; and 13,533 $> 2\sigma(I)$, initial structure model by direct methods, hydrogens either calculated from assumed geometries or located from difference density maps and kept riding, model refined by least-squares, final $R_1 = 0.0623$ and $wR_2 = 0.1207$ for all (16,786) intensity data, number of parameters = 637, goodness-of-fit = 1.095, absolute structure parameter Flack $x = 0.00(5)$. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 613425. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223336033 or e-mail: deposit@ccdc.cam.ac.uk].