SEPARATION OF THE ENANTIOMERS OF
P-CHIRAL CYCLIC PHOSPHORUS COMPOUNDS

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The antipodes of 1-aryl-, 1-alkyl- and 1-alkoxy-3-methyl-3-phospholene 1-oxides **1a-h** were separated in good yields and in high enantiomeric excesses (up to >99% ee) by resolution via formation of diastereomeric complexes with (−)-(4R,5R)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (−)-**2** (TADDOL) or (−)-(2R,3R)-α,α,α',α'-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol (−)-**3**. The resolution process of **1** with (−)-**3** was further examined in various mixture of solvents. Stereostructure of the supramolecular formations and absolute configuration of the resulting 3-phospholene oxides (−)-**1a**, (+)-**1e**, (+)-**1f** were elucidated by single crystal X-ray crystallography.[1-4] The method extended to the resolution of the 1-phenyl-3-methyl-3-phospholene 1-sulfide[2] **4**, 6-diethylamino-dibenzo[c.e][5,6]oxaphosphorine 6-oxide **5**, 1-[(1'R,2'S,5'R)-(−)-menthyl]-3-methyl-3-phospholene 1-oxide **6** and 3- and 5-methyl-1-phenyl-4-chloro-1,2-dihydro-phosphinine 1-oxide **7**, suggesting that our novel procedure may be of general value.

Keywords: P-chiral, resolution, diastereomeric complex, phospholene oxide,

Introduction

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.[5,6]

Resolution and asymmetric synthesis are the primary sources of P-chiral compounds. Despite the large number of enantioselective syntheses elaborated for the preparation of a single enantiomer to achieve industrial and scientific goals, resolution has not lost its significance.[7] There are several methods for chiral separation, based on induced crystallization,[8] resolution by diastereomeric salt formation,[9] diastereomeric complex formation,[10] separation by crystallization,[9] distillation,[11] supercritical fluid extraction[12] and membrane separation,[13] resolution with mixtures of resolving agents,[14] by formation of covalent diastereomers[9] and kinetic resolution.[15]

The methods described in the literature on the resolution of P(III) and P(V) phosphorus compounds are based on the formation of separable covalent diastereomers, diastereomeric salts, diastereomeric transition metal complexes and molecular complexes, as well as chemical and enzymatic kinetic resolution.[5] Direct acid-base resolutions of a carboxylic acid derivative of a phosphine sulfide,[16] with (+)- or (−)-1-phenylethyl-amine are known. The resolution of phosphonium salts can be accomplished by combining the racemate with the silver salt of a chiral acid.[17] Enantiomeric separation of P=O derivatives via inclusion complex formation with host compounds such as 2,2'-dihydroxy-1,1'-binaphthalene[18] was reported previously. Although these methods proved to be useful in some special cases, they did not turn out to be general. Several chiral transition metal complexes, such as Pd, Pt, Ni and Fe complexes were found to be useful in the separation of racemic phosphines.[19] Although, the resolution via transition metal complexes was found to be reasonably general and efficient, the cost of these reagents limited its usefulness.

An efficient and simple resolution process of 1-substituted-3-methyl-3-phospholene 1-oxides **1a-h** has been developed. Our resolution method suggested seems to be of general value for enantiomer separation of P-heterocycles. These P-chiral compounds can be ligands in transition metal complexes.

Experimental

*Resolution of 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** with TADDOL (–)-**2** in a mixture of ethyl acetate and hexane. Representative procedure.*

To 0.48 g (2.49 mmol) of racemic 1-phenyl-3-methyl-phosphol-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, colourless crystals of the complex started to appear immediately. After standing at room temperature for 2 hours without stirring, the crystals were separated by filtration to give 0.59 g (72%) of complex ((–)-**1a**·(–)-**2**); enantiomeric purity determined by HPLC (Daicel Chem. Ind., Chiralpack AD), 71% ee. The complex was further purified by two recrystallizations at room temperature from ethyl acetate–hexane (1 mL/5 mL) to afford complex (–)-**1a**·(–)-**2** in 54% yield with 87% ee and in 43% yield with 97% 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 purity, 97% ee, $[\alpha]_D^{25} = -37.0$ (*c* 1, CHCl$_3$).[2]

Results and Discussion

*Resolution of racemic 3-phospholene 1-oxides **1***

Five-membered P-heterocycles, such as 1-substituted-3-phospholene 1-oxides **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. We assumed that the 1-substituted-3-methyl-3-phospholene 1-oxides **1**, which have neither acidic nor basic functional groups, could be resolved via molecular complex formation.[1] Therefore racemic phospholene oxide **1a** was attempted to be resolved via diastereomeric complex formation by adding half equivalent of tartaric acid, *O,O'*-dibenzoyl-tartaric acid, TADDOL[20] **2** or its derivative[20] **3**, ephedrine, 2,2'-dihydroxy-1,1'-binaphthalene, menthol, phenylalanin,

prolin and ascorbic acid. We found that only TADDOL **2** and its derivative **3** could form co-crystalls with the phospholene oxides **1a-h**. The use of other chiral auxiliaries did not afford crystallizing disteromers.

Enantiomerically pure 1-substituted-3-methyl-3-phospholene oxides **1a-h** were prepared by molecular complex formation with chiral host (–)-**2** or (–)-**3** *Fig 1* and *Table 1*. To a solution of racemic phospholene 1-oxide **1a-h** and half equivalent of (–)-TADDOL **2** or its analogue (–)-**3** in hot ethyl acetate was added hexane where upon a **1**·(–)-**2** or a **1**·(–)-**3** crystalline complex precipitated.

Complexes **1a-d**·(–)-**2** and **1a-d**·(–)-**3** were analyzed by chiral HPLC (Chiralpack AD), while species **1e-h**·(–)-**2** and **1e-h**·(–)-**3** by chiral GC (BetaDEC^{TM}, after decomp.). The enantiomeric purities of **1a-h** obtained were 10-96% ee Table 1. Recrystallization of these complexes from a mixture of ethyl acetate–hexane significantly improved the enantiomeric excesses of the complexes **1**·(–)-**2** and **1**·(–)-**3**, up to >99% ee in most cases Table 1. After flash column chromatography, 3-phospholene 1-oxides **1a-h** were recovered quantitatively without the loss of chirality.

In most cases, the 1:1 complexes of **1**·(–)-**2** or **1**·(–)-**3** were formed. In the instance of 1-propyl-3-phospholene oxide **1f** and resolving agent (–)-**3**, a 1:2 complex of (+)-**1f**·(–)-**3** was obtained as shown by the ^{1}H NMR spectrum. For this, the resolution of **1f** was achieved with the use of 1 equivalent of (–)-**3**. Interestingly, in all cases but two, the resolving agents (–)-**2** and (–)-**3** preferred the complex formation with the same enantiomer of the given 3-phospholene oxides **1a-e**, **h**. In case of **1f** and **1g**, (–)-**2** and (–)-**3** formed complexes with opposite antipodes.

The separation of the covalent diastereomers of 1-[(1'*R*,2'*S*,5'*R*)-(–)-menthyl]-3-methyl-3-phospholene 1-oxide **6** has not been investigated. Using resolving agent (–)-**3** to the separation of covalent diastereomer was successful (90% de in 45% yield).

To clarify the absolute configuration of (–)-**1a**, (+)-**1e** and (+)-**1f**, the supramolecular formations (–)-**1a**·(–)-**2** acetone, (+)-**1e**·(–)-**3** and (+)-**1f**·(–)-**2** were subjected to single crystal X-ray analysis. The absolute configuration of the P atom in (–)-**1a**, (+)-**1e** and (+)-**1f** was found to be *S*,[1] *R*[2] and *R*,[2] respectively.[1-4]
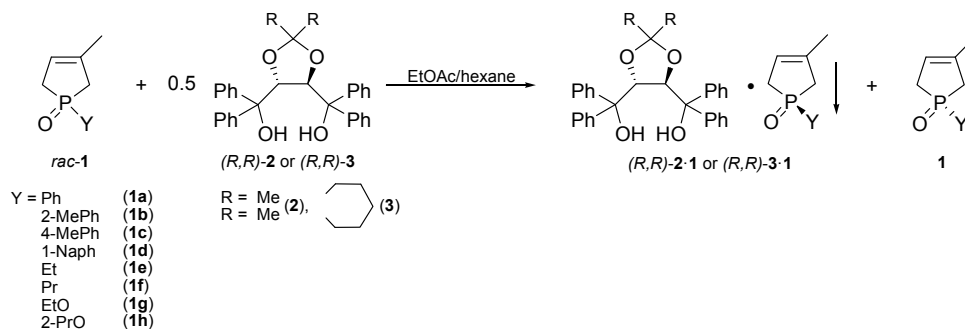

Figure 1: Resolution of 3-phospholene 1-oxides **1** with TADDOL derivatives (–)-**2** and (–)-**3**

Table 1: Resolution of 1-aryl-, 1-alkyl- and 1-alkoxy-3-methyl-3-pholene 1-oxides 1a-h with chiral host 2 and 3.[2]

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Table 1: Resolution of 1-aryl-, 1-alkyl- and 1-alkoxy-3-methyl-3-phospholene 1-oxides **1a-h** with chiral host **2** and **3**.[2]

	Complex forming agents							
	1·(−)-2				1·(−)-3			
subst.	ee[a] (%)	yield (%)	S[b]	[α]$_D$[c]	ee[a] (%)	yield (%)	S[b]	[α]$_D$[c]
1a	97 (71) [S][d]	44	0.43		>99 (53) [S]	29	0.29	− 37.0
1b	57 (31) [S]	49	0.28		>99 (48) [S][e]	41	0.41	− 28.6
1c	69 (29) [S]	42	0.29		>99 (11) [S][e]	30	0.30	− 39.1
1d	70 (25)	42	0.29		>99 (27)	55	0.55	− 40.9
1e	24 (10) [R]	36	0.09		58 (23) [R][d]	45	0.26	+ 8.7
1f	95 (68) [R][d]	35	0.33	+ 13.4	89 (29)[f] [S]	30	0.27	
1g	44 (20) [S]	25	0.11		95 (58) [R][e]	50	0.48	− 10.6
1h	>99 (89) [R]	5	0.05		>99 (96) [R][e]	37	0.37	− 15.6

[a]The enantiomeric purities were determined by chiral HPLC (Chiralpack AD) or chiral GC (BetaDEC[TM]) after two recrystallizations (and after crystallization).

[b]Resolving capability, also known as the Fogassy parameter (S = yield*enantiomeric purity).

[c]Specific rotation of the regenerated enantiomer (*c* 1, CHCl$_3$).

[d]Absolute configuration was determined by X-ray analyses.

[e]Absolute configuration was determined by CD spectroscopy.

[f]One equivalent of **3** was used.

Single crystal X-ray analysis of (−)-*1a·*(−)-*2 and* (+)-*1e·*(−)-*3*

Final structure models are shown in *Figs 2* and *3* with the basic H-bridges indicated.[1,2] The resulting crystal structure models are well ordered and contain in all cases, with 1:1 stoichiometry, the associated forms of the resolving agents with either one of the phospholene target guest molecules as in **1a·2** and **1e·3**. The crystal structure of (−)-**1a·**(−)-**2** contains an acetone molecule, so, in this case, a ternary complex (−)-**1a·**(−)-**2·**acetone is formed Fig. 2. 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**.[1]

The resolving machinery is affected by the interplay of the anchoring and identical primary O–H···O hydrogen bridges to the guest P=O functions, as well as by a series of weaker C–H···O interactions. Such weak stabilizing C–H···O interactions can be formed between the oxygen atom of one of the hydroxy groups of TADDOL (−)-**2** and the C4 atom of the P-heterocycle, and the oxygen atom of one of the hydroxy groups of TADDOL (−)-**2** and the C4' carbon of the phenyl ring in the crystal structure of (−)-**1a·**(−)-**2·**acetone.[3]

Other weak interactions, such as the one between the oxygen atom of the P=O function and the C2 carbon of the P-heterocycle, and another one between the oxygen atom of one of the hydroxy groups of TADDOL derivative (−)-**3** and the suitable hydrogen atom of the P-species stabilise the crystal structure of (+)-**1e·**(−)-**3** Fig. 3.
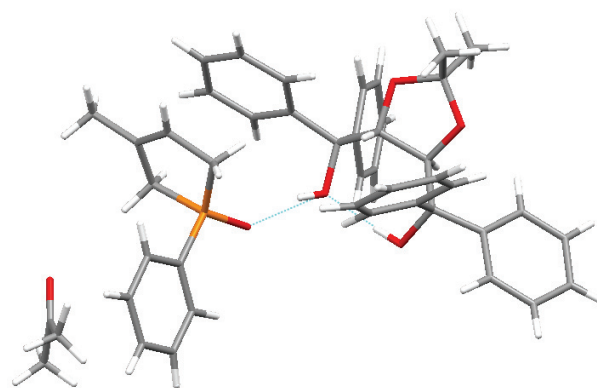

Figure 2: X-ray structure of the 1:1:1 coordinato-clathrate inclusion of 1-phenyl-3-methyl-3-phospholene 1-oxide (−)-**1a** with TADDOL (−)-**2** and acetone with the basic H-bridge interactions indicated by blue lines for (−)-**1a·**(−)-**2·**acetone.[1]
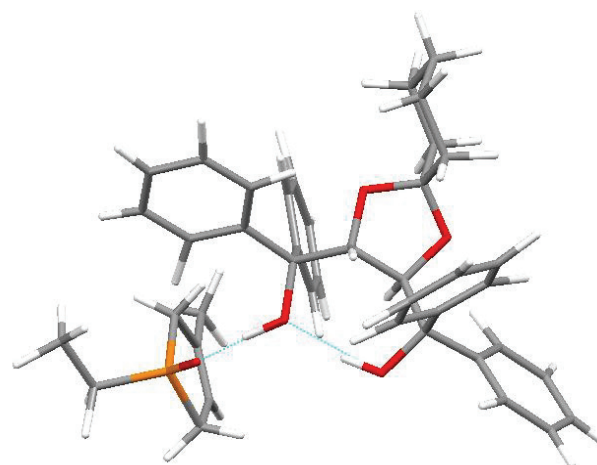

Figure 3: X-ray structure of the 1:1 inclusion of 1-ethyl-3-methyl-3-phospholene 1-oxide (+)-**1e** with TADDOL derivative (−)-**3** with the basic H-bridge interactions indicated by blue lines for (+)-**1e·**(−)-**3**.[2]

Solvent dependence of the resolution

Although, the resolution of phospholene oxides **1** with (–)-**2** and (–)-**3** were accomplished in ethyl acetate-hexane mixture, the single crystals could only be obtained from acetone-pentane mixture. The presence of acetone influences the formation of the crystal structures of the complexes. In the case of the complex (–)-**1a**·with (–)-**2**, the acetone was incorporated to the crystal structure and a ternary complex was grown. Into the crystal structure of (+)**1e**·(–)-**3** and (+)-**1f**·(–)-**2** acetone was not incorporated. In the course of growing a single crystal of (–)-**1b-d** with (–)-**3,** the acetone displaces the phospholene oxides from the crystals completly, because acetone may be a more suitable H acceptor for the H bridges than the phospholene oxides. The presence of acetone effected significantly the structures of the single crystals, suggesting that the acetone could effect the efficiency of the resolution as well. The results of the resolution of phospholene oxides **1a-h** with (–)-**3** from a mixture of acetone-hexane is summarized in *Table 2*. It can be seen that the efficiency of the resolutions was improved in all cases.

Table 2: Resolution of 1-aryl-, 1-alkyl- and 1-alkoxy-3-methyl-3-phospholene 1-oxides **1** with chiral host (–)-**3** in acetone-hexane

	Complex forming agents		
	1·(–)-**3**		
subst.	enantiomeric purity[a] (% ee)	S[b]	Abs. config.
1a	97	0.81	[*S*]
1b	88	0.42	[*S*]
1c	27	0.25	[*S*]
1d	71	0.23	
1e	55	0.42	[*S*]
1f	38	0.34	[*S*]
1g	93	0.67	[*R*]
1h	>99	0.56	[*R*]

[a]The enantiomeric purities were determined by chiral HPLC (Chiralpack AD) or chiral GC (BetaDEC[TM]) after crystallization.
[b]Resolving capability, also known as the Fogassy parameter (S=yield*enantiomeric purity).

In the next part of the work, resolution processes of **1a** with (–)-**3** were further tested in various other solvents or solvent mixtures, but no crystals were obtained. Therefore, the resolution process of **1a** was further examined in ethyl acetate-hexane mixture adding another solvent as an additive (2 eq., based on the racemate of **1a)**. The results are summarized in *Table 3*.

Sakai and co-workers examined the effect of the solvent(s) on the resolution process via diastereomeric salt formation. They observed that the efficiency of the resolution via diastereomeric salt formation was dependent on the dielectric constant (ε) of the solvents used. They called this phenomenon dielectrically controlled resolution process (DCR).[21,22] We found that the resolution of (–)-**1a**·with (–)-**3** via diastereomeric complex formation

took place with a good efficiency only when the additive used had a dielectric constant (ε) of lower than 40 *Fig. 4*.

Table 3: Resolution of 1-phenyl-3-methyl-3-pholpholene 1-oxides **1a** with chiral host (–)-**3** in ethyl acetate-hexane in the presence of additive

	(–)-**1a**·(–)-**3**		
Additive 2 eq.	Dielectrically constant (ε)	enantiomeric purity[a] (% ee)	S[b]
acetone	20.7	86	0.60
DMSO	46.7	25	0.32
DMF	36.7	71	0.63
acetonitrile	37.5	63	0.49
acetic acid	6.2	75	0.47
water	78.5	12	0.11
MEK	18.5	74	0.52
MIBK	13.1	73	0.55
ethanol	24.6	78	0.57

[a]The enantiomeric purities were determined by chiral HPLC (Chiralpack AD) after crystallization.
[b]Resolving capability, also known as the Fogassy parameter (S=yield*enantiomeric purity).
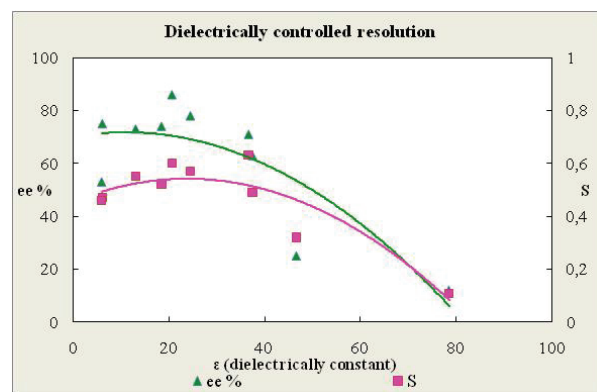

Figure 4: Dependence of the resolution on the dielectric constant of the additive

Dutch resolution

The efficiency of a resolution can be improved in the presence of a chiral or achiral, structurally similar derivative of the substrate or the resolving agent (e.g. Dutch resolution).[23,24] We found that the result of the resolution of 1-phenyl-3-methyl-3-phospholene oxide (**1a**) with chiral host (–)-**3** was improved in the presence of impurities. The resolution of pure **1a** with (–)-**3** led to the corresponding complex (–)-**1a**·(–)-**3** of 53% diastereomeric excess in 87% yield. We obtained the best results when we used crude **1a**. In this case the diastereomeric excess of the complex (–)-**1a**·(–)-**3** formed was 79% de in 71% yield.

It was also interesting that the resolution 1-phenyl-3-methyl-3-phospholene oxide **1a** with 0.25 equiv. of (–)-**2** and 0.25 equiv. of (–)-**3** proved to be more efficient than with either 0.5 equiv. of (–)-**2** or with 0.5 equiv. of (–)-**3**. Diastereomeric excesses of the complexes (–)-**1a**·

(−)-**2**·(−)-**3**, (−)-**1a**·(−)-**2** and (−)-**1a**·(−)-**3**, were 77%, 71% and 53%, respectively. The (−)-**1a**·(−)-**2**·(−)-**3** complex contained 40% of (−)-**2** and 60% of (−)-**3** based on ^{1}H NMR.
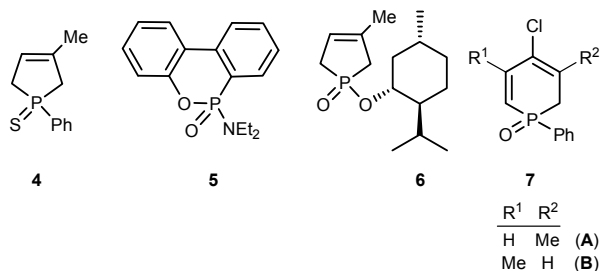
The experiments for the separation of the enantiomers of 1-phenyl-3-methyl-3-phospholene sulfide **4** with (−)-**3** were puzzling at first. The resolution of the pure racemic compound **4** with (−)-**3** was not too efficient (24% de). When substrate **4** contained 4% of 1-phenyl-3-methyl-2-pholene sulfide, the enantiomeric purity of the complex (+)-**4** [(−)-**3**]$_2$ was quite similar (20% de). The efficiency of the resolution was, however, improved significantly by using the crude product of the synthesis of **4**. In this case, the diastereomeric excess of the complex (+)-**4** [(−)-**3**]$_2$ formed was 65% after crystallization and >99% after recrystallization ([α]$_D^{20}$= –65.2 (c 1, CHCl$_3$)). The ^{1}H NMR spectrum suggested a 1:2 stochiometry of (+)-**4** and (−)-**3**. The 1-phenyl-3-methyl-3-phospholene sulfide was regenerated by column chromatography ([α]$_D^{20}$= +7.8 (c 1, CHCl$_3$)).[2]

Resolution of other P-heterocycles

Our resolution method was tested on other P-heterocycles to prove that our novel procedure may be of general value for the resolution of P-chiral cyclic compounds.

The resolution of 6-diethylamino-dibenzo[c.e][5,6]-oxaphosphorine 6-oxide **5** with (−)-**3** was not efficient (51% de).

In the course of preparation of 3- and 5-methyl-4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxide **7**, two double-bondisomers were obtained[25] that could not be separated. Therefore an 1:3 mixture of dihydro-phosphinine oxides **7** was resolved with (−)-**3**. The ratio of the double-bondisomers remained the same after crystallization and recrystallization of the diastereomers. After the resolution, dihydrophosphinine-oxides **7A** and **7B** with (−)-**3,** the diastereomers were obtained with 90% ee and in 33% yield.

	R^1	R^2	
	H	Me	(**A**)
	Me	H	(**B**)

Conclusion

An efficient and simple resolution process of 1-substituted-3-methyl-3-phospholene 1-oxides **1a-h** was developed. In our resolution method of **1a-h** were resolved with half equivalent of (−)-**2** or (−)-**3**. We found that the efficiency of the resolution is highly dependent on the solvents or the additives. The method suggested seems to be of general value for enantiomer separation of P-heterocycles.

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