CHIRALITY 22:699–705 (2010)

A Practical and Efficient Method for the Resolution of 3-Phospholene 1-oxides via Coordination Complex Formation[1]

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ABSTRACT A simple, efficient, and economical method based on the combination of the exceptional behavior of *o*,*o*′-dibenzoyl- or *o*,*o*′-di-*p*-toluyl-(*2R*,*3R*)-tartaric acid in chiral recognition processes, and the coordination ability of calcium or magnesium ion was developed for the resolution of phospholene oxides **1**. The calcium or magnesium salt of (−)-*o*,*o*′-dibenzoyl-(*2R*,*3R*)-tartaric acid **2**,**4**-**6** or calcium hydrogen (−)-*o*,*o*′-di-*p*-toluyl-(*2R*,*3R*)-tartrate **3** may form crystalline diastereomeric coordination complexes with the appropriate antipode of substituted 3-phospholene oxides **1** that makes possible efficient resolutions. Optically active phospholene oxides **1** were prepared directly by simply crystallization and digestion of the corresponding diastereomeric complexes so formed. Thermal behavior of the crystalline diastereomeric complexes was studied by simultaneous TG/DTA. The novel method may be of more general value in respect of the resolution of tertiary phosphine oxides. *Chirality 22:699–705, 2010.*

KEY WORDS: coordinative resolution; P-chiral phospholene oxides; tartaric acid derivatives; solvent dependence

INTRODUCTION

In the last few years, our attention was focused on the preparation of chiral phosphines; since this area is a current challenge in synthetic organic chemistry because their transition metal complexes may provide high enantioselectivity in homogenous catalytic reactions.[2,3] From practical point of view, the preparation and resolution of racemic phosphine oxides followed by deoxygenation of the separated enantiomers is more appropriate than enantioselective synthesis.

Resolution of racemates via diastereomeric intermediates is the most frequently used method for the production of new compounds in enantiomerically pure form, applicable also on the industrial scale.[4,5] Depending on the type of interaction formed between the resolving agent and the enantiomer, the resolutions can be achieved via diastereomeric salts (involving ionic bonds), diastereomeric compounds (involving covalent bonds), diastereomeric coordination complexes (involving dative bonds), and diastereomeric molecular complexes (involving secondary interactions). Certainly, the resolving machinery is affected by weaker secondary interactions in all cases.[6,7]

Natural (2*R*,3*R*)-tartaric acid (TA) and its derivatives play an important role as resolving agents in the preparation of single enantiomers. The efficiency of TA derivatives in a wide range of chiral recognition processes is the consequence of the C_2 symmetry and relatively large number of functional groups of these molecules.[7] The resolution of racemic bases can be accomplished by diastereomeric salt formation with TA derivatives. The formation of ionic bonds between the racemic bases and TA or its derivatives is established readily and quantitatively.[8–10] Dibenzoyltartaric acid can also be used in silver salt formation for the resolution of phosphonium salts via diastereomeric salt formations.[11,12] Dibenzoyl-(2*R*,3*R*)-tartaric acid (DBTA) and di-*p*-toluyl-(2*R*,3*R*)-tartaric acid (DPTTA) can be used for the resolution of racemates without basic character, as they can result supramolecular formations with several chiral alcohols.[7,13] Noyori and coworkers[14] described the synthesis of optically active BINAP via resolution of its P-oxide with DBTA. The method has been used successfully for separation of the optical isomers of a number of bis(phosphine) oxides.[7] Combination of the exceptional behavior of DBTA in chiral recognition processes and the coordination ability of Ca^{2+}, Zn^{2+}, or Cu^{2+} was also applied in enantiomeric separations,[7] such as in the resolution of α-hydroxy-esters[15,16] and α-alkoxy-carboxylic acids[16] and in the enantiomeric enrichment of alcohols and α-alkoxyalkohols.[17]

Other methods were also described in the literature for the preparation of optically active P-compounds. These approaches, however, proved to be useful only in special cases.[12]

Contract grant sponsor: Hungarian Scientific Research Fund (OTKA); Contract grant numbers: T075236, T067679.
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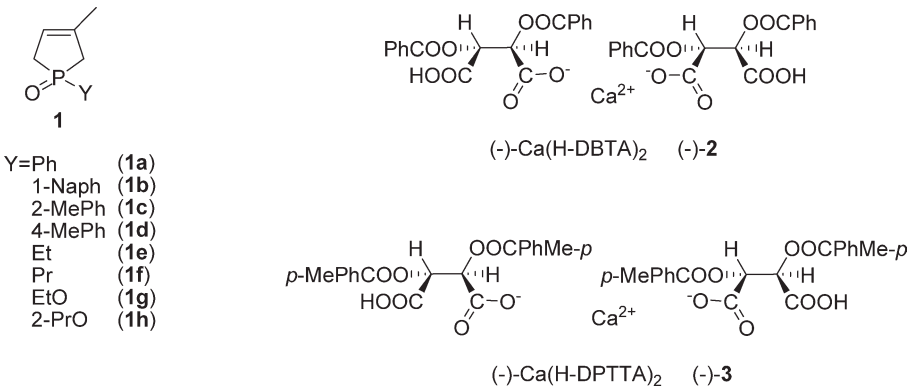
Received for publication 20 May 2009; Accepted 28 October 2009
DOI: 10.1002/chir.20821
Published online 8 February 2010 in Wiley InterScience (www.interscience.wiley.com).



Scheme 1. The phospholene oxides **1** and the resolving agents (−)-**2** and (−)-**3**.

The exceptional behavior of TA derivatives prompted us to use them in the resolution of phospholene oxides **1**. Recently, we have described that substituted 3-phospholene 1-oxides **1** can be resolved via molecular complex formation with (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (TADDOL)[18] or its spiro derivative, (−)-(2*R*,3*R*)-α,α,α′,α′-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol.[19–21] In contrast, TA and its *o*,*o*′-dibenzoyl- (DBTA) or *o*,*o*′-di-*p*-toluyl- (DPTTA) derivatives did not form molecular complex with phospholene oxides **1**. However, we have found that using calcium hydrogen (−)-*o*,*o*′-dibenzoyl-(*2R*,*3R*)-tartrate [(−)-Ca(H-DBTA)$_2$, (−)-**2**] or calcium hydrogen (−)-*o*,*o*′-di-*p*-toluyl-(*2R*,*3R*)-tartrate [(−)-Ca(H-DPTTA)$_2$, (−)-**3**], 1-aryl-3-phospholene 1-oxides **1a** and **1b** can be resolved via diastereomeric coordination complex formation.[1] This method is based on the coordination ability of Ca^{2+} ion toward the oxygen atom of the P=O moiety.[1] In addition, the *o*,*o*′-dibenzoyltartrate or *o*,*o*′-di-*p*-toluyltartrate units play an important role in the formation of complexes that crystallize well.[7] In this article, we study if this novel resolution method can be extended to any 3-phospholene oxides having, for example, 1-aryl-, 1-alkyl-, or 1-alkoxy substituents (Scheme 1).

MATERIALS AND METHODS

The ratio of ligands in the diastereomeric complexes were determined by ^{1}H NMR. The ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 500 MHz in DMSO. The enantiomeric excess (ee) values were determined by chiral HPLC (Chiralpack AD-H column 250 × 4.6 mm ID, Daicel Chem. Ind., using hexane/isopropanol 85/15 as the eluent with a flow rate of 0.8 ml/min, T = 20°C, UV detector λ = 254 nm) or by chiral GC (was carried out on Agilent 4890D instrument equipped with a BETA DEX^{TM} 120 column, 30 m × 0.25 mm, 0.25 μm film, FID detector, nitrogen as carrier gas, injector 240°C, detector 300°C, head pressure: 15 psi, at 1:100 split ratio). Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Simultaneous thermogravimetric (TG) and differential thermal analytical (DTA) measurements were carried out on a STD 2960 Simultaneous DTA-TGA apparatus (TA Instruments Inc., New Castle, DE).

The 3-phospholene 1-oxides **1a-h** were synthesized as described earlier.[20,22–25] (−)-*o*,*o*′-Dibenzoyl-(*2R*,*3R*)-tartaric acid and (−)-*o*,*o*′-di-*p*-toluyl-(*2R*,*3R*)-tartaric acid were purchased from Aldrich Chemical Co.

Resolution of 1-Propyl-3-methyl-3-phospholene 1-oxide 1f with Calcium hydrogen o,o′-dibenzoyl-(2R,3R)-tartrate (−)-2 Representative Procedure A

To 0.46 g (0.61 mmol) of (−)-**2** in 1.6 ml of a 10:1 mixture of ethanol–water was added 0.20 g (1.23 mmol) of *rac*-**1f**. After the addition, colorless crystals appeared immediately. After standing at room temperature for 4 h, the crystals were filtered off to give 0.41 g (74%) of Ca[((*S*)-**1f**)(H-DBTA)$_2$(H_2O)] with a de of 37%. The complex was taken up in 1.6 ml of a 10:1 mixture of ethanol–water and the suspension was stirred at 60°C for 24 h. The crystals were filtered off to give 0.23 g (42%) of Ca[((*S*)-**1f**)(H-DBTA)$_2$(H_2O)] with a de of 78% as colorless crystals. The digestion was repeated and 0.10 g (18%) of Ca[((*S*)-**1f**)(H-DBTA)$_2$(H_2O)] with a de of 96% was obtained (mp. 152°C, dec.). The phospholene oxide (*S*)-**1f** was recovered by treatment of the chloroform solution (2 ml) of the complex with 2 ml of a 10% aqueous ammonia. The organic phase was washed with 0.5 ml of water, dried (Na_2SO_4), and concentrated to give 17 mg (0.11 mmol, 17%) of (*S*)-1-propyl-3-methyl-3-phospholene 1-oxide (*S*)-**1f** with an ee of 96%; $[\alpha]^{25}_D = -13.9$ (c 0.6, $CHCl_3$).

The resolutions of 1-substituted-3-methyl-3-phospholene 1-oxides **1a-h** with resolving agents (−)-**2** or (−)-**3** were carried out according to the representative procedure A. The conditions and the results of the resolutions are shown in Tables 1 and 2. Retention times by chiral HPLC: 9.3 min for (*R*)-**1a** and 10.9 min for (*S*)-**1a**; 11.2 min for **1b**, and 13.5 min for **1b**; 11.5 min for (*R*)-**1c** and 15.5 min for (*S*)-**1c**; 10.5 min for (*R*)-**1d**, and 12.7 min for (*S*)-**1d**. Retention times by chiral GC (program for **1e-g**: 2 min at 140°C, 20°C/min to 190°C, then kept at 190°C): 12.1 min for (*R*)-**1e** and 12.3 min for (*S*)-**1e**; 13.9 min for (*R*)-**1f** and 14.2 min for (*S*)-**1f**; 9.1 min for (*S*)-**1g** and 9.3 min for (*R*)-**1g**. Retention times by chiral GC (program for **1h**: 25 min at 140°C): 21.8 min for (*S*)-**1h**, 22.2 min for (*R*)-**1h**.

TABLE 1. Optimized conditions for the resolution of *rac*-3-phospholene 1-oxides 1 using 0.25 equiv. of resolving agent (–)-2

Subst.	Coordination complex[a]	Solvents	Yield[b] (%)	Ee[c] (%)	S[d]	Abs. config.[e]	Mp[f] (°C) Dec.
1a	Ca[(**1a**)$_2$(H-DBTA)$_2$(H_2O)]	EtOAc-EtOH 1:1[g] [4] EtOH-Water 10:1[h] [4]	52	96 (53)	0.50	*R*	177
1b	Ca[(**1b**)$_2$(H-DBTA)$_2$]	EtOAc-EtOH 1:1[g] [4] EtOH-Water 10:1[h] [4]	42	99 (60)	0.42		177
1c	Ca[(**1c**)$_2$(H-DBTA)$_2$]	MeCN-EtOH 2:3[g] [5] MeCN-EtOH 1:1[h] [4]	33	93 (68)	0.31	*R*	166
1d	Ca[(**1d**)$_2$(H-DBTA)$_2$]	MeCN-EtOH 2:3[g] [5] MeCN-EtOH 1:1[h] [4]	28	44 (31)	0.12	*S*	151
1f[i]	Ca[(**1f**)(H-DBTA)$_2$(H_2O)]	EtOH-Water 10:1[g] [3] EtOH-Water 10:1[h] [3]	18	96 (37)	0.17	*S*	152
1g	Ca[(**1g**)$_2$(H-DBTA)$_2$]	MeCN-EtOH 2:3[g] [5] MeCN-EtOH 1:1[h] [4]	29	91 (67)	0.26	*R*	164
1h	Ca[(**1h**)$_2$(H-DBTA)$_2$]	MeCN-EtOH 2:3[g] [5] MeCN-EtOH 1:1[h] [4]	36	92 (31)	0.33	*S*	171

[a]The ratio of **1** and resolving agent (–)-**2** was determined by ^{1}H NMR. Amount of the bound water in the complexes was measured by simultaneous TG/DTA method.
[b]Based on the half of the racemate **1** that is regarded to be 100% for each antipode.
[c]Determined by chiral HPLC or chiral GC after digestion (and after crystallization).
[d]Resolving capability, also known as the Fogassy parameter.[26]
[e]Determined by X-ray analysis and CD spectroscopy.[19,20]
[f]The melting was accompanied by decomposition of the diastereomeric complex.
[g]Mixture of solvents for crystallization [ml of solvent/g of resolving agent (–)-**2**].
[h]Mixture of solvents for digestion [ml of solvent/g of resolving agent (–)-**2**].
[i]Resolution was achieved with 0.5 equiv of (–)-2.

Resolution of 1-Phenyl-3-methyl-3-phospholene 1-oxide 1a with Magnesium hydrogen o,o′*-dibenzoyl-(2*R*,3*R*)-tartrate (−)-5 Representative Procedure B*

To 0.30 g (0.78 mmol) of (−)-DBTA·H_2O and 16 mg (0.39 mmol) of magnesium oxide in 1.0 ml of a 10:1 mixture of ethanol–water was added to 0.30 g (1.57 mmol) of rac-**1a** in 1.6 ml of ethyl acetate. After standing at room temperature for 24 h, the crystals were filtered off to give 0.17 g (39%) of Mg[((*R*)-**1a**)$_2$(H-DBTA)$_2$] with a de of 50%. The complex was taken up in 2.4 ml of a 3:5 mixture of ethanol–ethyl acetate, and the suspension was stirred at 60°C for 24 h. The crystals were filtered off to give 0.13 g (30%) of Mg[((*R*)-**1a**)$_2$(H-DBTA)$_2$] with a de of 60% as colorless crystals (mp. 169°C, dec.). The phospholene oxide (*R*)-**1a** was recovered by treatment of the chloroform solution (2 ml) of the complex with 2 ml of a 10% aqueous ammonia. The organic phase was washed with 0.5 ml of water, dried (Na_2SO_4), and concentrated to give 40 mg (0.21 mmol, 27%) of (*R*)-1-phenyl-3-methyl-3-phospholene 1-oxide (*R*)-**1a** with an ee of 60%.

RESULTS AND DISCUSSION

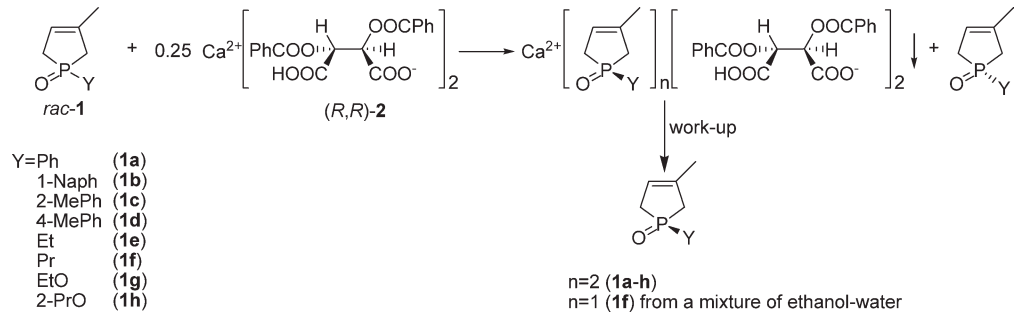
Resolution of 3-Phospholene 1-oxides Using (−)-Ca(H-DBTA)$_2$

As an extension, our simple method utilizing (−)-Ca(H-DBTA)$_2$ [(−)-**2**] or (−)-Ca(H-DPTTA)$_2$ [(−)-**3**], which

TABLE 2. The resolution of *rac*-3-phospholene 1-oxides 1 using resolving agent (–)-3

Subst.	Coordination complex[a]	Yield[b] (%)	Ee[c] (%)	S[d]	Abs. config.[e]	Mp[f] (°C) Dec.
1a[g]	Ca[(**1a**)(H-DPTTA)$_2$(H_2O)]	55	93 (54)	0.51	*S*	164
1b	Ca[(**1b**)$_2$(H-DPTTA)$_2$(H_2O)]	29	69 (50)	0.20		183
1c	Ca[(**1c**)$_2$(H-DPTTA)$_2$]	13	45 (28)	0.06	*R*	
1d	Ca[(**1d**)$_2$(H-DPTTA)$_2$]	15	32 (20)	0.05	*S*	
1e	Ca[(**1e**)$_2$(H-DPTTA)$_2$(H_2O)$_2$]	34	73 (45)	0.25	*S*	169
1f	Ca[(**1f**)$_2$(H-DPTTA)$_2$]	42	41 (33)	0.17	*S*	
1g	Ca[(**1g**)$_2$(H-DPTTA)$_2$]	44	75 (55)	0.33	*R*	191
1h	Ca[(**1h**)$_2$(H-DPTTA)$_2$]		Racemate			

[a]The ratio of **1** and resolving agent (–)-**3** was determined by ^{1}H NMR. Amount of the bound water in the complexes was measured by simultaneous TG/DTA method.
[b]Based on the half of the racemate **1** that is regarded to be 100% for each antipode.
[c]Determined by chiral HPLC or chiral GC after digestion (and after crystallization).
[d]Resolving capability, also known as the Fogassy parameter.[26]
[e]Determined by X-ray analysis and CD spectroscopy.[19,20]
[f]The melting was accompanied by decomposition of the diastereomeric complex.
[g]Resolution was achieved with 0.5 equiv of (–)-**3**.



Scheme 2. The general resolution process of *rac*-3-phospholene 1-oxides **1** using resolving agent (−)-**2**.

was successfully used for the resolution of 3-phospholene 1-oxides **1a** and **1b**[1] was further developed for the resolution of 1-aryl-, 1-alkyl-, and 1-alkoxy-3-phospholene 1-oxides **1c-h** (Scheme 2).

According to our original procedure, to the solution of (−)-Ca(H-DBTA)$_2$ [(−)-**2**] in hot ethanol was added a solution of 1-substituted phospholene oxide **1** in ethyl acetate. After crystallization at room temperature, the precipitate was filtered off to give diastereomeric complex Ca[(**1**)$_2$(H-DBTA)$_2$] that was further purified by digestion in a 10:1 mixture of ethanol and water at 60°C. The phospholene oxides **1** were recovered by the treatment of the chloroform solution of the complexes Ca[(**1**)$_2$(H-DBTA)$_2$] with a 10% aqueous ammonia. The enantiomeric excess (ee) of products was determined by chiral HPLC (for **1c** and **1d**), or by chiral GC (for **1e-h**). The resolution process by our original method using agent (−)-**2** in the case of 1-(2-methylphenyl)- and 1-(4-methylphenyl)-3-phospholene 1-oxides **1c** and **1d** was completely inefficient, as the products were racemic after the first precipitation. The resolution by our original method of alkyl- and alkoxy-phospholene oxides **1e-h** led to poor results. After the digestion and decomposition, phospholene oxides **1e-h** were obtained with an ee of 49, 61, 75, 32%, respectively.

As it can be seen, the original process elaborated for the resolution of **1a** and **1b** with (−)-**2** could not be adapted efficiently for the resolution of **1c-h**. Refining the conditions of the resolution, such as choosing more appropriate solvents, varying the amount of solvents, and the amount of resolving agent, we could significantly increase the efficiency of the resolutions. Results of the optimized resolutions of **1a-h** using (−)-**2** are shown in Table 1.

In all cases but one, the stoichiometry of the precipitated complexes was the same corresponding to structure Ca[(**1**)$_2$(H-DBTA)$_2$], therefore, the resolutions were achieved by the use of 0.25 equivalent of the resolving agent (−)-**2**. In the course of the resolution of **1f** using (−)-**2**, the Ca[((*S*)-**1f**)(H-DBTA)$_2$(H$_2$O)]complex was formed in aqueous ethanol, so 0.5 equiv. of (−)-**2** was used.

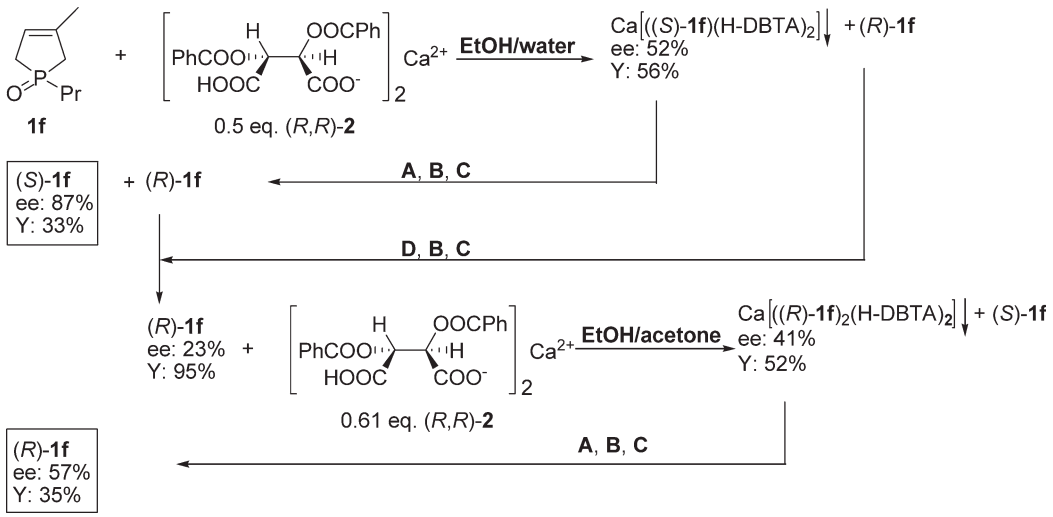
It was found that changing ethyl acetate–ethanol to acetonitrile–ethanol in the resolution of aryl- and alkoxy-substituted derivatives **1c-d**, **g-h,** the ee in most cases, increased above 90%. When acetonitrile–ethanol was used, the de of Ca[((*R*)-**1c**)$_2$(H-DBTA)$_2$], Ca[((*S*)-**1d**)$_2$(H-DBTA)$_2$], Ca[((*R*)-**1g**)$_2$(H-DBTA)$_2$], and Ca[((*S*)-**1h**)$_2$(H-DBTA)$_2$]was increased to 93, 44, 91, and 92%, respectively, after the first digestion, and the complexes were obtained in 33, 28, 29, and 36% yield, respectively.

From practical point of view, the refined resolution process using (−)-**2** seemed to be quite general and more advantageous as compared to that accomplished with TADDOL derivatives. Although, applying TADDOL derivatives for the resolution of phospholene oxides **1**, pure enantiomers could be obtained, but it is a disadvantage that the resolving agent is considerably more expensive and decomposition of the diastereomeric complexes requires column chromatography. At the same time, our new procedure applies a low-cost resolving agent, and the method can be carried out easily on a bigger scale, moreover, the decomposition of diastereomeric complexes is very simple. On the other hand, the calcium salt of *o*,*o*′-dibenzoyl-(*2R*,*3R*)-tartaric acid (−)-**2** shows good compatibility with phospholene oxides **1**.

A Detailed Study on the Resolution of 1-Propyl-3-methyl-3-phospholene 1-oxide Using (−)-Ca(H-DBTA)$_2$

In the course of the crystallization of **1f** with (−)-**2** in the mixture of ethanol and ethyl acetate, the *R* enantiomer of **1f** was enriched in the complex Ca[(**1f**)$_2$(H-DBTA)$_2$] with an ee of 7%, but, surprisingly, after the digestion in aqueous ethanol, the other, (*S*) enantiomer was enriched in the complex Ca[(**1f**)(H-DBTA)$_2$] with an ee of 61%, and the ratio of the ligands was also changed. The nature of solvents used, effected the enantiocomplementarity. Hence, the configuration of the incorporated phospholene oxide **1f** in the diastereomeric complexes depends on the solvents applied for crystallization. Therefore, resolution of **1f** using (−)-**2** was achieved in different mixtures of solvents. The best result (78% ee) for the preparation of (*S*)-**1f** was obtained, when the solvent was aqueous ethanol. The resolution machinery is affected by the presence of water, and it must be regarded as a kind of reactant. For the preparation of (*R*)-**1f** with an ee of 39%, a 1:1 mixture of acetone and ethanol should be used.

As a result of the opposite antipode preference of (−)-**2** in respect of different mixture of solvents used (as shown above), we could separate both enantiomers of **1f** using natural TA derived resolving agent (−)-**2**. The resolution process of phospholene oxide **1f** is shown in Scheme 3. After the crystallization and the first digestion in a 10:1 mixture of ethanol and water, complex Ca[((*S*)-**1f**)(H-



Scheme 3. The resolution process for 1-propyl-3-methyl-3-phospholene 1-oxide **1f** using resolving agent (−)-**2**. (**A**: digestion; **B**: NH_3/H_2O; **C**: extraction, evaporation; **D**: evaporation).

$DBTA)_2(H_2O)$] (mp: 152°C, dec.) with a de of 87% and in a 33% yield was obtained. To get the other antipode of **1f**, the mother liquor of the crystallization and the filtrate of the digestion were combined and the mixture so obtained was treated with aqueous ammonia to afford the (*R*)-**1f** with an ee of 23% and in a 95% yield. The enantiomeric mixture was further purified using 0.61 equiv. of (−)-**2** (0.5 equiv. for (*R*)-**1f**) in a mixture of ethanol and acetone. After crystallization and digestion, complex Ca[((*R*)-**1f**)$_2$(H-DBTA)$_2$] (mp: 166°C, dec.) with a de of 57% was obtained in a yield of 38%.

Resolution of 3-Phospholene 1-oxides Using (−)-Ca(H-DPTTA)$_2$

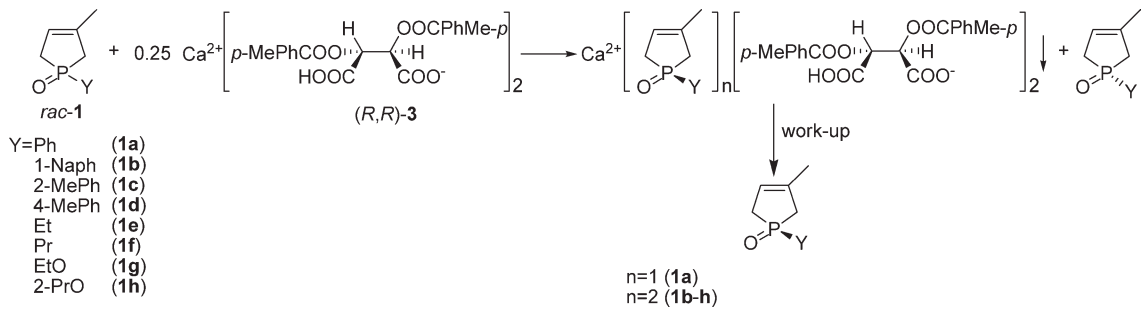
The resolution of phospholene oxides **1c-g** was also achieved with resolving agent (−)-**3** as shown in Scheme 4 and Table 2. The crystallization and digestion of complexes were accomplished in a 10:1 mixture of ethanol and water. In general, the resolution of phospholene oxides **1** using (−)-**3** proved to be less efficient as compared to the resolutions accomplished with (−)-**2**. However, for the resolution of ethyl- and ethoxy-substituted derivatives **1e** and **1g**, respectively, resolving agent (−)-**3** was found to be more appropriate considering the resolving capabilities.

Resolution of 3-Phospholene 1-oxides Using (−)-Ca(DBTA)

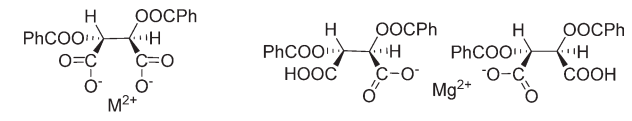
So far, in all experiments the ratio of CaO and DBTA or DPTTA was 1:2, and an acidic calcium salt was prepared. To get a neutral calcium salt (Scheme 5), 1:1 ratio of CaO and DBTA was used for the resolution of **1a** and **1c**. The resolution of **1a** and **1c** proved to be efficient as Ca[((*R*)-**1a**)(DBTA)] and Ca[((*R*)-**1c**)(DBTA)] were obtained with a de of 90 and 71% in a yield of 18 and 22%, respectively, after crystallization and digestion from a mixture of ethyl acetate and aqueous ethanol. In the case of **1b**,**d**,**e-h** the resolution process was less efficient, as the de of Ca[$^{(1)}$(DBTA)]was lower than 50% and it was obtained in a low yield.

Resolution of 3-Phospholene 1-oxides Using (−)-Mg(H-DBTA)$_2$ and (−)-Mg(DBTA)

Theoretically, any metal ion can be used as the central ion of the coordination compounds.[7] To expand the range of such coordination resolutions, the central metal ion was replaced. When ZnO, $Cu(OAc)_2$, $Co(OAc)_2$ were used in place of CaO, none of them could form complexes with phospholene oxides **1**, but using MgO, colorless crystals were obtained, and an enantiomeric discrimination was observed. The resolution of **1a** and **1f** was accomplished according to the representative procedure B using a 1:2



Scheme 4. The general resolution process of *rac*-3-phospholene 1-oxides **1** using resolving agent (−)-**3**.



Scheme 5. The resolving agents (−)-**4**, (−)-**5**, and (−)-**6**.

ratio of MgO and DBTA, that is (−)-Mg(H-DBTA)$_2$ [(−)-**5**] (Scheme 5). The best result was obtained for the resolution of **1a** in a mixture of aqueous ethanol and ethyl acetate to afford Mg[((*R*)-**1a**)$_2$(H-DBTA)$_2$] with a de of 60% and in a 30% yield after digestion. In the case of the resolution of **1f**, from a mixture of aqueous ethanol and diethyl ether, complex Mg[((*R*)-**1f**)$_2$(H-DBTA)$_2$] was obtained with a de of 64% and in a 35% yield. The presence of water in the mixtures also had a significant importance to promote crystallization of the diastereomeric complexes. In the case of **1b-e**,**g-h** the resolution process was less efficient, as the de of Mg[(**1**)(H-DBTA)] was lower than 50% and it was obtained in a low yield.

The resolution of **1** was also attempted by using a 1:1 ratio of MgO and DBTA that is (−)-Mg(DBTA) [(−)-**6**], but this resolving agent could not form complexes with phospholene oxides **1**.

Thermoanalytical Investigations of the Coordination Complexes

The simultaneous thermogravimetry and differential thermoanalysis (TG/DTA) of the coordination complexes have also provided valuable data on their composition, melting behavior, and stability. The melting points of the diastereomeric complexes are shown in Table 1 and 2. In all cases, the diastereomeric coordination complexes of the samples were found to be thermally stable up to their melting, which occurred as sharp endothermic DTA-peaks in the temperature range of 150–195°C. The complexes melted with decomposition showing immediate weight loss, and in most cases immediately after the appearance of the endothermic peak of melting, an overlapping exothermic peak could be seen as a result of decarboxylation[27] of the calcium hydrogen dibenzoyl- or di-*p*-toluyltartrates. The initial evolution of CO_2 has been proven by in situ evolved gas analysis measurements (TG/DTA-EGA-MS).

Most of the samples released water in one or two steps before melting and decomposition. We assumed that the water leaving at lower than 90°C was a weakly bound lattice solvent of crystallization. On the other hand, the bound water lost above 100°C was able to establish stronger hydrogen bonds with the DBTA or DPTTA or more probably they were coordinated to the central calcium ion in the complexes. This latter significant interaction (coordination) could influence the resolution mechanism, the enantiomeric discrimination, and hence the preferred configuration of the P-ligand and finally the stoichiometry of the P-heterocycle in the diastereomeric coordination complexes. On the basis of simultaneous TG and DTA examinations, five diastereomeric coordination complexes contained strongly bound water that is probably coordinated water. Complexes are shown in Table 1 and 2.

CONCLUSION

A simple and economical procedure was developed for the resolution of a variety of 3-methyl-3-phospholene 1-oxides, such as 1-aryl-, 1-alkyl-, and 1-alkoxy-derivatives **1a-h** via coordination complex formation using (−)-Ca(H-DBTA)$_2$ [(−)-**2**] and (−)-Ca(H-DPTTA)$_2$ [(−)-**3**]. The appropriate choice of the resolving agent and the optimum conditions suitable for the efficient resolution of the given phospholene oxide were explored for each particular case. From among the eight 3-phospholene 1-oxides (**1a-h**) studied, six species (**1a-c**,**f-h**) could be resolved with ee of >90%. As a result of the opposite antipode preference of (−)-**2** in respect of different mixture of solvents used, we could separate both enantiomers of **1f** using the natural tartaric acid derived resolving agent (−)-**2**. The new method involving crystallization with (−)-**2** or (−)-**3** and digestion of the corresponding diastereomeric complexes may be of more general value and may be suitable for the resolution of other tertiary phosphine oxides as well. As a further extension and generalization, the resolution of **1** with (−)-Ca(DBTA) [(−)-**4**] or (−)-Mg(H-DBTA)$_2$ [(−)-**5**] was also accomplished. A detailed study with these resolving agents is in progress. Simultaneous TG/DTA investigations on samples of diastereomeric coordination complexes provided information on their composition, melting behavior and stability.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Tibor Novák for the fruitful discussions.

LITERATURE CITED

1. Ujj V, Schindler J, Novák T, Czugler M, Fogassy E, Keglevich G. Coordinative resolution of 1-phenyl- and 1-naphthyl-3-methyl-3-phospholene 1-oxides with calcium hydrogen *o,o′*-dibenzoyl-(2*R*,3*R*)-tartrate or calcium hydrogen *o,o′*-di-*p*-toluyl-(2*R*,3*R*)-tartrate. Tetrahedron: Asymmetry 2008;19:1973–1977.
2. Noyori R. Asymmetric catalysis in organic synthesis. New York: John Wiley & Sons; 1994. p400.
3. Imamoto T. Optically active phosphorus compounds. In: Engel R, editor. Handbook of organophosphorus chemistry. New York: Marcel Dekker; 1992. p 1–53.
4. Murakami H. From racemates to single enantiomers—chiral synthetic drugs over the recent 20 years. In: Sakai K, Hirayama N, Tamura R, editors. Novel optical resolution technologies. Vol.269. Heidelberg: Springer Berlin; 2007. p 273–299.
5. Fogassy E, Nógrádi M, Kozma D, Egri G, Pálovics E, Kiss V. Optical resolution methods. Org Biomol Chem 2006;4:3011–3030.
6. Faigl F, Fogassy E, Nógrádi M, Pálovics E, Schindler J. Strategies in optical resolution: a practical guide. Tetrahedron: Asymmetry 2008; 19:519–536.
7. Faigl F, Kozma D. Optical resolution via complex formation with *o,o′*-dibenzoyl-tarataric acid. In: Toda F, editor. Enantiomer separation: fundamentals and practical methods. Dordrecht: Kluwer Academic Press; 2004. p 73–101.
8. Jacques J, Collet A, Wilen SH. Enantiomers, racemates, and resolutions. New York: Wiley; 1981. p 217.
9. Ács M, Fogassy E, Kassai C, Kozma D, Nógrádi M. CRC Handbook of optical resolutions via diastereoisomeric salt formation. Kozma D, editor. Boca Raton: CRC Press; 2002. p 683.

10. Synoradzki L, Bernas U, Ruskowski P. Tartaric acid and its *o*-acyl derivatives. II. Application of tartaric acid and of *o*-acyl tartaric acids and anhydrides. Resolution of racemates. Org Prep Proced Int 2008;40:165–200.
11. Kumli KF, McEwen WE, Vander Werf CA. Resolution of a non-heterocyclic quaternary phosphonium iodide. J Am Chem Soc 1959;81:248–249.
12. Pietrusiewicz KM, Zablocka M. Preparation of scalemic *P*-chiral phosphines and their derivatives. Chem Rev 1994;94:1375–1411.
13. Kassai C, Juvancz Z, Bálint J, Fogassy E, Kozma D. Optical resolution of racemic alcohols via diastereoisomeric supramolecular compound formation with *o,o′*-dibenzoyl-(2*R*,3*R*)-tartaric acid. Tetrahedron 2000; 56:8355–8359.
14. Takaya H, Mashima K, Koyano K, Yagi M, Kumobayashi H, Taketomi T, Akutagawa S, Noyori R. Practical synthesis of (*R*) -or (*S*)-2,2′′-bis(diarylphosphino)-1,1′-binaphtyls (BINAPs). J Org Chem 1986;51:629–635.
15. Mravik A, Böcskei Z, Katona Z, Markovits I, Pokol G, Menyhárd DK, Fogassy E. A new optical resolution method: coordinative resolution of mandelic acid esters. The crystal structure of calcium hydrogen (2*R*,3*R*)-*o,o′*-dibenzoyltartrate-(2*R*)-methyl mandelate. J Cem Soc Chem Commun 1996:1983–1984.
16. Mravik A, Böcskei Z, Katona Z, Markovits I, Fogassy E. Coordination-mediated optical resolution of carboxylic acids with *o,o′*-dibenzoyltartaric acid. Angew Chem Int Ed En 1997;36(13-14):1534–1536.
17. Mravik A, Böcskei Z, Simon K, Elekes F, Izsáki Z. Chiral recognition of alcohols in the crystal lattice of simple metal complexes of *o,o′*-dibenzoyltartaric acid: enantiocomplementarity and simultaneous resolution. Chem Eur J 1998;4:1621–1627.
18. Seebach D, Beck A, Heckel A. TADDOLs, Their derivatives, and TADDOL analogues: versatile chiral auxiliaries. Angew Chem Int Ed 2001;40:92–138.
19. Novák T, Schindler J, Ujj V, Czugler M, Fogassy E, Keglevich G. Resolution of 3-methyl-3-phospholene 1-oxides by molecular complex formation with TADDOL derivatives. Tetrahedron: Asymmetry 2006;17:2599–2602.
20. Novák T, Ujj V, Schindler J, Czugler M, Kubinyi M, Mayer ZA, Fogassy E, Keglevich G. Resolution of 1-substituted-3-methyl-3-phospholene 1-oxides by molecular complex formation with TADDOL derivatives. Tetrahedron: Asymmetry 2007;18:2965–2972.
21. Novák T, Schindler J, Ujj V, Czugler M, Fogassy E, Keglevich G. Chiral P-heterocycles: efficient method for the resolution of 3-methyl-3-phospholene 1-oxides. Phosphorus, Sulfur, Silicon 2008;183: 543–546.
22. Keglevich G, Petneházy I, Miklós P, Almásy A, Tóth G, Tőke L, Quin LD. Ring expansion in the addition of dichlorocarbene to 2,5-dihydro-1H-phosphole 1-oxides. J Org Chem 1987;52:3983–3986.
23. Keglevich G, Brlik J, Janke F, Tőke L. Convenient synthesis of 1-alkoxy-1,2-dihydrophosphinine 1-oxides by ring enlargement. Heteroatom Chem 1990;1:419–424.
24. Keglevich G, Tőke L, Lovász C, Újszászy K, Szalontai G. Synthesis of the P-sulfide derivatives of 3-phosphabicyclo[3.1.0]hexanes and 1,2-dihydrophosphinines. Heteroatom Chem 1994;5:395–401.
25. Keglevich G, Szelke H, Bálint A, Imre T, Ludányi K, Nagy Z, Hanusz M, Simon K, Harmat V, Tőke L. Fragmentation-related phosphinylations using 2-aryl-2-phosphabicyclo[2.2.2]oct-5-ene- and -octa-5,7-diene 2-oxides. Heteroatom Chem 2003;14:443–451.
26. Sheldon RA. Chirotechnology. Marcel Dekker: New York, 1993.
27. Nassimbeni LR, Su H. Inclusion compounds of alkaline-earth metal *o,o′*-dibenzoyl tartrates: structure and thermal stability. J Chem Soc Dalton Trans 2000:349–352.