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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

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ABSTRACT

A convenient and efficient resolution of 1-phenyl-**1a** and 1-naphthyl-3-methyl-3-phospholene 1-oxides **1b** is described. The separation is based on the finding that the calcium hydrogen *O,O′*-dibenzoyl-(2*R*,3*R*)-tartrate **2** or calcium hydrogen *O,O′*-di-*p*-toluyl-(2*R*,3*R*)-tartrate **3** forms diastereomeric coordination complexes with the enantiomers of phospholene 1-oxides **1a** and **1b**. The stereostructure of the supramolecular formation of Ca(**1a**)$_2$(H-DBTA)$_2$ and absolute configuration of the 3-phospholene oxide **1a** were elucidated by single crystal X-ray crystallography.

1. Introduction

Enantiomerically pure phosphine oxides are important chiral starting materials and intermediates in organic syntheses, since they are precursors of the corresponding phosphines. The chiral phosphines are widely used ligands in transition metal complexes that can be catalysts in a variety of highly efficient enantioselective homogeneous catalytic processes, such as hydrogenation and hydroformylation.[1,2] The primary source of chiral P-compounds is resolution and asymmetric synthesis. The methods described in the literature regarding the resolution of organophosphorus P(III) and P(V) compounds are based on the formation of separable covalent diastereomers, diastereomeric salts, diastereomeric transition metal complexes, molecular complexes, as well as chemical and enzymatic kinetic resolution.[2,3] Although these methods proved to be useful in some particular cases, they did not turn out to be general. Five-membered P-heterocycles, such as 1-substituted-3-phospholene 1-oxides, are of chemical importance since 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.[4–7] Pietrusiewicz et al. developed several methods for the resolution of 1-phenyl-2- or 1-phenyl-3-phospholene 1-oxides and their epoxide derivatives based on dipolar cycloaddition,[8] enantioselective desymmetrization,[9–11] and quaternization of the corresponding phosphines obtained by deoxygenation with a chiral reactant.[11] These methods, however, were not generalized, probably, because of their substrate specificity.

Recently, we have shown that 1-substituted-3-methyl-3-phospholene 1-oxides can be resolved by molecular complex formation with chiral hosts (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (TADDOL) or (−)-(2*R*,3*R*)-α,α,α′,α′-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol.[12–14] In the last 20 years, numerous TADDOL analogues have been described in the literature as host compounds for resolution via inclusion complex formation[15] or efficient ligands for enantioselective reactions.[16] Although these chiral hosts are excellent resolving agents for the resolution of a variety of phospholene oxides, they are quite expensive, and not available on a large scale, while the recovery of the substrate requires column chromatography.

To improve our resolution process for phospholene oxides **1a** and **1b**, we tried to use other TADDOL-like complex forming structures as a resolving agent. Since TADDOL is a tartaric acid derivative, we focused our attention on tartaric acid analogues. These compounds, such as tartaric acid (TA) and its *O,O′*-dibenzoyl-(DBTA) or *O,O′*-di-*p*-toluyl-(DPTTA) derivatives, are among the most frequently used chiral reagents in organic synthesis and resolution processes.[17–19] Although in most cases, the resolutions with TA or its derivatives were considered to be an acid-base protonation process, in a couple of cases it turned out to be based on complex formation.[20–22] Unfortunately, none of these TA derivatives can form complexes with phospholene oxides **1a** or **1b**. On the other hand, combination of the exceptional behavior of DBTA in chiral recognition processes and the coordination ability of metal ions, such as Ca^{2+}, Zn^{2+}, or Cu^{2+}, proved to be useful in numerous

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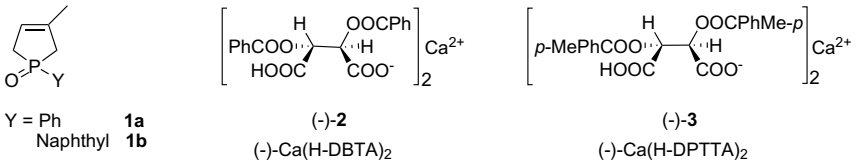
enantiomeric separations, such as in the resolution of α-hydroxy-esters[23,24] and α-alkoxy-carboxylic acids[24] and in the enantiomeric enrichment of alcohols and α-alkoxyalcohols.[25]

We adopted this approach, and a novel and convenient method for the resolution of 1-phenyl- and 1-naphthyl-3-methyl-3-phospholene 1-oxides **1a** and **1b** with (−)-Ca(H-DBTA)$_2$ **2** or (−)-Ca(H-DPTTA)$_2$ **3** via diastereomeric coordination complex formation is reported.[26] The use of coordinative metal complexes of DBTA as a resolving agent is known,[22–25] but the use of such complexes of DPTTA has not yet been described.



2. Results and discussion

Resolving agents Ca(H-DBTA)$_2$ (−)-**2** and Ca(H-DPTTA)$_2$ (−)-**3** can be prepared in advance and stored for a long period of time.[27]

To a solution of (−)-**2** in hot EtOH was added 4 equiv of 1-phenyl-**1a** or 1-naphthyl-phospholene oxide **1b** in ethyl acetate solution. After crystallization at room temperature, the precipitate was filtered off to give the corresponding complex Ca(**1a**)$_2$(H-DBTA)$_2$ or Ca(**1b**)$_2$(H-DBTA)$_2$. The coordinative complexes were further purified by digestion (i.e., simple stirring of the crystals in hot ethanol-water) in a 10:1 mixture of ethanol–water at 60 °C to afford Ca(**1a**)$_2$(H-DBTA)$_2$ or Ca(**1b**)$_2$(H-DBTA)$_2$ as colorless crystals. The complete dissolution of the crystals was not necessary, as the digestion was sufficient enough to obtain the diastereomerically pure complexes. The phospholene oxides **1a** or **1b** were recovered by the treatment of the chloroform solution of the complexes Ca(**1a**)$_2$(H-DBTA)$_2$ or Ca(**1b**)$_2$(H-DBTA)$_2$ with 10% aqueous ammonia. The enantiomeric purity of the products (+)-**1a** and (+)-**1b** was determined by chiral HPLC (Daicel Chem. Ind., Chiralpack AD). As is shown in Table 1, the diastereomeric excess of Ca(**1a**)$_2$(H-DBTA)$_2$ and Ca(**1b**)$_2$(H-DBTA)$_2$ was 53% and 60%, respectively, after the first precipitation (crystallization). After digestion, the diastereomeric purity of the complexes increased to 96% and 99%. Decomposition of the Ca(**1a**)$_2$(H-DBTA)$_2$ and Ca(**1b**)$_2$-(H-DBTA)$_2$ complexes led to the pure enantiomers of **1a** and **1b** of 96% and 99% ee and in 48% and 39% yield, respectively.[26]

The resolution of **1a** and **1b** was also achieved with resolving agent (−)-**3** according to the procedure described above, except that the complexes were crystallized from a 10:1 mixture of ethanol–water, and the precipitated complexes were filtered off after 24 h. Alteration of the solvent and the time of the crystallization were necessary in order to obtain the maximum resolvability. The resolution of **1a** and **1b** with (−)-**3** led to (−)-**1a** of 95% ee and to (+)-**1b** of 69% ee. As can be seen, the process for the resolution of **1b** with (−)-**3** proved to be less efficient than the resolution with (−)-**2**.

Based on the results, two things should be noted. (a) In all cases but one, the stoichiometry of the precipitated complexes was the same Ca(**1**)$_2$(TA$^{\#}$)$_2$ (where TA$^{\#}$ is H-DBTA or H-DPTTA), therefore the resolution was achieved by using 0.25 equiv of the resolving agents (−)-**2** or (−)-**3**. In the resolution of **1a** with (−)-**3**, the Ca(**1a**)(H-DPTTA)$_2$ complex was formed, so for the complex formation, 0.5 equiv of resolving agent (−)-**3** was used. Considering the different stoichiometry of Ca(**1a**)(H-DPTTA)$_2$, one may expect that the supramolecular structure of this complex is fundamentally different from the others. (b) Interestingly, the resolving agent (−)-**2** formed a complex with (+)-**1a**, while (−)-**3** preferred the complex formation with (−)-**1a**.

As a result of the opposite antipode preference of (−)-**2** and (−)-**3**, we could separate both enantiomers of **1a** of high enantiomeric purity (96% ee) with the natural (2*R*,3*R*)-TA derivatives. The whole resolution process of phospholene oxides **1a** is shown in Figure 1. After the resolution of the racemic 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** with 0.25 equiv of (−)-**2**, as described above, complex Ca((+)-**1a**)$_2$(H-DBTA)$_2$ of 96% ee and in 51% yield was obtained. To get the other antipode, (−)-**1a**, the mother liquor of the crystallization and the filtrate of the digestion were combined, and the organic phase so obtained was treated with aqueous ammonia to afford the (−)-**1a** of 36% ee and in 149% yield. To exploit the different antipode preference of resolving agents (−)-**2** and (−)-**3**, (−)-**1a** was further purified with 0.68 equiv [1 equiv for (−)-**1a**] of (−)-**3** from a mixture of ethanol and water. After crystallization and digestion of the crystals, complex Ca((−)-**1a**)(H-DPTTA)$_2$ of 96% ee was obtained in 52% yield. Decomposition of the complex Ca((−)-**1a**)(H-DPTTA)$_2$ gave (−)-**1a** in 96% ee and 42% yield.

The resolution of 1-naphthyl-3-methyl-3-phospholene 1-oxide **1b** with resolving agent (−)-**2** is shown in Figure 2. The preparation of (+)-**1b** was similar to that of (+)-**1a** as described above.

Table 1
Resolution of 1-phenyl-**1a** and 1-naphthyl-3-methyl-3-phospholene 1-oxides **1b** with resolving agents (−)-**2** and (−)-**3**

Subst.	Resolving agent	Coordination complex[a]	Solvents	Yield[d] (%)	ee[e] (%)	*S*[f]	Abs. config.
1a	0.25 equiv (*R*,*R*)-**2**	[Ca(**1a**)$_2$(H-DBTA)$_2$]	EtOAc/EtOH[b] EtOH/water[c]	48	96 (53)	0.46	(*R*)[g]
1b	0.25 equiv (*R*,*R*)-**2**	[Ca(**1b**)$_2$(H-DBTA)$_2$]	EtOAc/EtOH[b] EtOH/water[c]	39	99 (60)	0.39	
1a	0.5 equiv (*R*,*R*)-**3**	[Ca(**1a**)(H-DPTTA)$_2$]	EtOH/water[b,c]	55	95 (57)	0.52	(*S*)
1b	0.25 eq (*R*,*R*)-**3**	[Ca(**1b**)$_2$(H-DPTTA)$_2$]	EtOH/water[b,c]	29	69 (50)	0.20	

[a] The ratio of **1** and resolving agent **2** or **3** was determined by ^{1}H NMR.
[b] Mixture of solvents for crystallization.
[c] Mixture of solvents for recrystallization.
[d] Yield of the enantiomers of phospholene oxides **1a** and **1b** (obtained from the corresponding coordination complexes) is based on the half of the racemate **1a** and **1b** that is regarded to be 100% for each antipode.
[e] Enantiomeric excess of the phospholene oxides was determined by chiral HPLC (Daicel Chem. Ind., Chiralpack AD) after recrystallizations (and after crystallizations).
[f] Resolving capability, also known as the Fogassy parameter.
[g] Absolute configuration was determined by X-ray analysis.

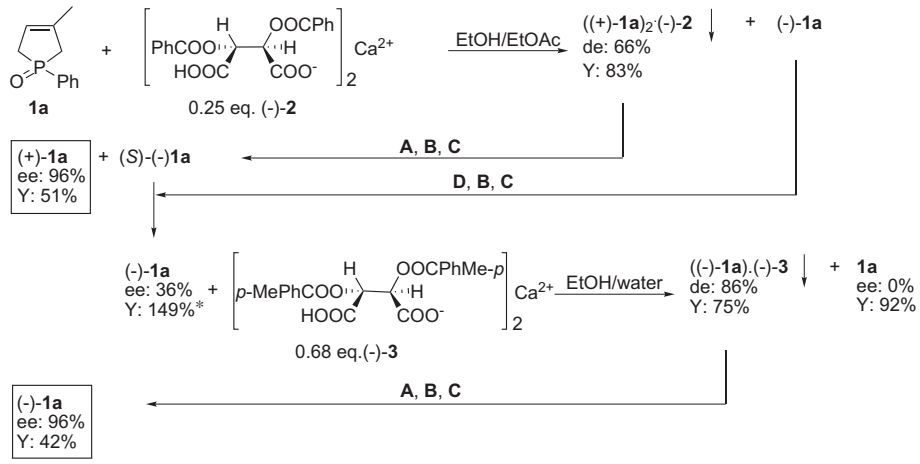


Figure 1. The complete resolution process of 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** with (−)-**2** and (−)-**3**. * The yield in the mother liquor may be >100%, as it represents both antipodes (for explanation, see footnote 'd' of Table 1).

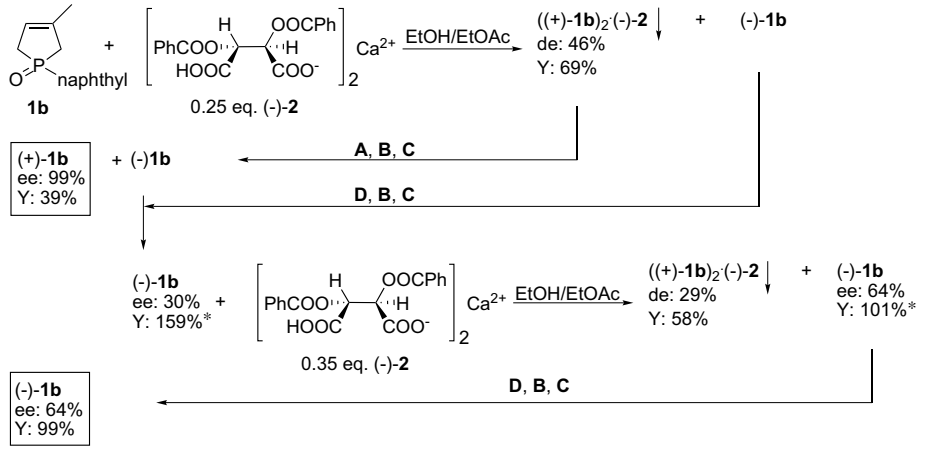


Figure 2. The complete resolution process of 1-naphthyl-3-methyl-3-phospholene 1-oxide **1b** with (−)-**2**. * The yield in the mother liquor may be >100%, which represents both antipodes (for explanation, see footnote 'd' of Table 1).

To obtain species (−)-**1b**, the mother liquors of the crystallization and the filtrate of the digestion of the crystals were combined, and the enantiomeric mixture was treated with aqueous ammonia to give (−)-**1b** of 30% ee and in 159% yield. The crystallization of the enantiomeric mixture with 0.35 equiv [0.5 equiv for (−)-**1b**] of (−)-**2** resulted in the corresponding Ca((+)-**1b**)$_2$(H-DBTA)$_2$ complex in low diastereomeric excess. In this case, (−)-**1b** was enriched in the mother liqueur, so we could prepare the (−)-**1b** antipode of 64% ee and in 99% yield.

To clarify the mode of binding and the absolute configuration of (+)-**1a**, the supramolecular formation Ca(**1a**)$_2$(H-DBTA)$_2$ was subjected to single crystal X-ray analysis. It can be seen that by using Ca(**1a**)$_2$(H-DBTA)$_2$, two phospholene oxide molecules **1a** and two units of H-DBTA are coordinated to the central calcium ion in the complex, as shown in Figures 3 and 4. Firstly, it is relevant to note that the crystal structure shows an infinite *catena* polymeric structure, whose asymmetric unit (the unit cell in this case) is its monomeric entity. The stoichiometry of the complex follows the 'hemisalt' arrangement (i.e., 2:2:1 for **1a**:H-DBTA:Ca). The basis of this system is, at first glance, a pseudo-centrosymmetric arrangement of all molecular and ionic components regarding the Ca^{2+} ion site

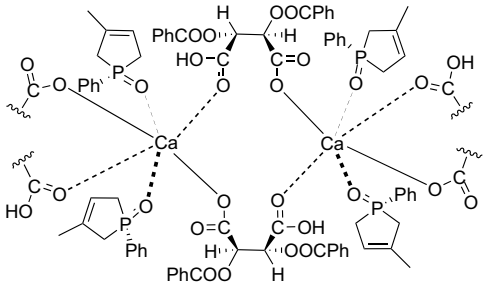


Figure 3. Schematic representation of the polymeric structure of the Ca^{2+}·**1a**·H-DBTA 1:2:2.

as the pseudo-center. The arrangement of the ligands resembles those of two independent and near perpendicular pseudo-twofold axes relating the two (+)-**1a** phospholene-oxides and the two tartaric acids independently. Intersection of these two pseudo axes then leads to the creation of a pseudo-symmetry center. Ca^{2+} ions are instrumental in the creation of the macroscopic crystal in such

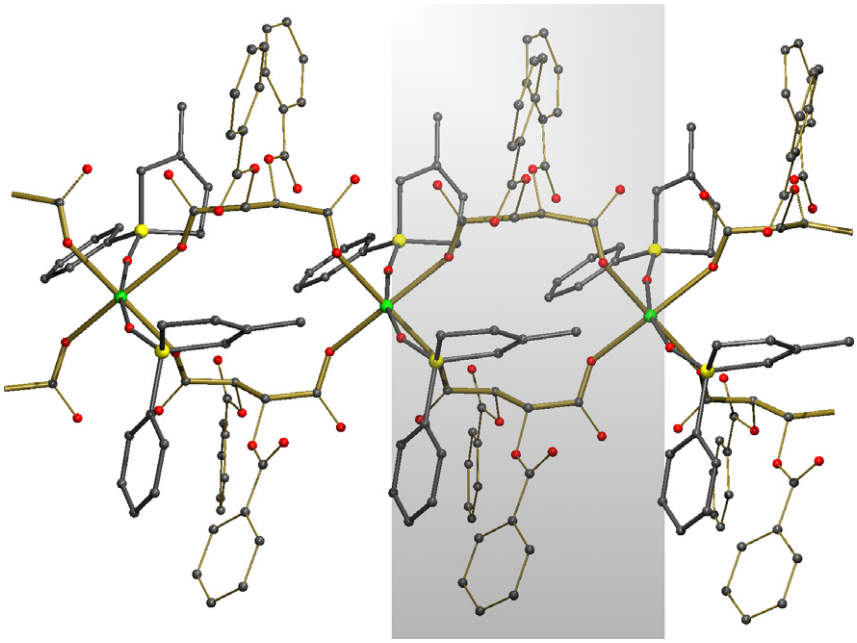


Figure 4. Perspective view of the ordered model of the *catena*-polymeric Ca^{2+} salt of **1a**·H-DBTA 1:2:2 system, with the essential covalent—coordinative network trace shown in thick bronze color slabs, while rest of the tartaric acid bonds are thin. The bonds of **1a** molecules are a thicker gray colored to accentuate the polymeric recognition environment. Gray rectangle approximates the unit cell content amounting to the monomeric entity of this *catena* polymer.

a way that these metal ions establish an infinite one-dimensional (1D) chain with the (100) base vector (i.e. polymeric along the crystallographic *a*-axis), thus setting the periodicity of the crystal in that direction. The binding of the two symmetry independent, identical ligands **1a** is clearly affected by coordination to the Ca^{2+} ion as the primary recognition instrument. Other support, required for effective 3D-enantio-differentiation, comes from the relative strong meta—C9–H···O4 contact from a carboxylate/carboxylic O atom and steric restraints posed by the benzyl groups of the neighboring H-DBTA ions.

The structure separates ionic and apolar regions rather clearly such that the DBTA phenyl groups protrude outwards (see Fig. 5) and establish a multitude of weak stacking and C–H···π interactions, effective in sustaining the crystal lattice in the *b* and *c* directions. The Ca^{2+} ion is 6-coordinated by the ligand O atom sites and forms an acceptably regular octahedron. The presence of two independent, partly occupied atomic sites in the scattering model appears to complement this coordination sphere, albeit their presence can only be rationalized in a much bigger structural entity (formally about every fourth molecule out of eight independent monomeric units links themselves into an endless *catena* polymer, if an ordered model would be feasible). Idealized octahedral coordination distances around the Ca^{2+} ion are shown in Table 2.

Between the DBTA molecules, there are also H-bridges formed by the anions and the resolved phospholene-oxides **1a**. Although

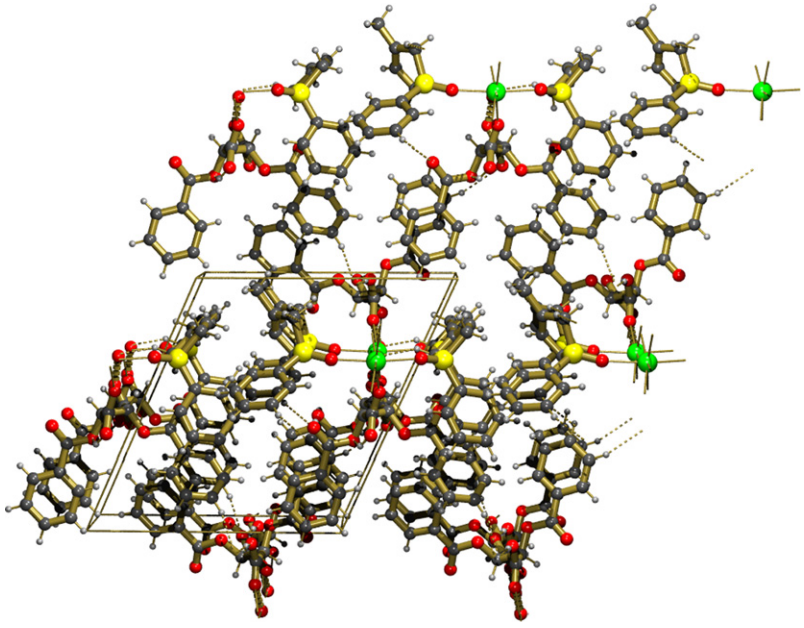


Figure 5. Packing view in the crystal of the Ca-salt of **1a**·H-DBTA·1:2:2 with the coordination around the Ca^{2+}-ion and the separate grouping of apolar–polar regions visible.

Table 2
Octahedral coordination distances around the Ca^{2+} ion

O_L	$d_{Ca\cdots O}$ (Å)	O_L	$d_{Ca\cdots O}$ (Å)
Ca1–O2	2.331(4)	Ca1–O3	2.318(4)
Ca1–O11	2.341(4)	Ca1–O12	2.311(4)
Ca1–O19	2.280(5)	Ca1–O20	2.240(6)

Table 3
Possible H-bond contacts in the Ca(**1a**)$_2$(H-DBTA)$_2$ complex, only meaningful s.u.s' are given

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
O10–H14···O17	0.84	2.15	2.656(6)	118
O1–H1···O4	0.84	1.64	2.473(5)	174
C48–H40···$O5_a$	0.99	2.43	3.116(9)	126
C58–H52···O20	0.95	2.56	2.970(10)	106
C21–H16···O11	1.00	2.58	2.939(6)	101
C9–H5···$O13_b$	0.95	2.57	3.476(11)	159
C34–H24···$O4_c$	0.95	2.38	3.305(9)	164
C37–H27···O15	0.99	2.47	3.460(8)	174
C57–H52···$O20_a$	0.95	2.51	3.423(10)	162

Symmetry position code a = 1 + *x*, *y*, *z*; b = *x* − 1, *y*, 1 + *z*; c = *x*, 1 + *y*, *z* − 1.

a totally satisfactory analysis of the H-bridges scheme is hampered by the uncertainty in non-trivial H-atom positions of the X-ray model, an approximate view of these interactions can still be visualized. Analysis of potential hydrogen bonds and schemes is summed up in Table 3. It is obvious that apart from the expected strong O–H···O type interactions,[28,29] there are numerous weaker C–H···O interactions present.[30,31]

3. Conclusion

A resolution procedure was developed which is the first example of the enantiomeric separation of chiral P-compounds **1a**,**b** via coordination complex formation. From a practical point of view, the use of the calcium hydrogen *O*,*O*′-dibenzoyl tartrate (−)-**2** or calcium hydrogen *O*,*O*′-di-*p*-toluyl tartrate (−)-**3** seemed to be the most advantageous choice because of the easy large scale preparation, the low price, and low toxicity of the resolving agents; the good compatibility of the calcium salt with different ligands; and in most cases, the good crystallization abilities of the coordinative complexes. Crystallization and subsequent single crystal X-ray determination led to a catena-polymeric structure clearly indicating the role of the phospholene ligands and their recognition mode in the Ca(**1a**)$_2$(H-DBTA)$_2$ crystal.

Acknowledgments

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26. Resolution of 1-phenyl-3-methyl-3-phospholene 1-oxide **1a** with the calcium hydrogen *O*,*O*′-dibenzoyl tartrate (−)-**2**—A representative procedure. To 17 g (21.5 mmol) of (−)-**2** in 40 mL of ethanol was added 16.5 g (86.1 mmol) of racemic **1a** in 40 mL of ethyl acetate. After the addition, colorless crystals appeared immediately. After standing at room temperature for 4 h, the crystals were filtered off to give 21.4 g (85%) of Ca(**1a**)$_2$(H-DBTA)$_2$ of 53% ee (determined by HPLC, Daicel Chem. Ind., Chiralpack AD). The complex was taken up in 44 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 13.2 g (52%) of Ca(**1a**)$_2$(H-DBTA)$_2$ of 96% ee as colorless crystals (mp: 177–178 °C). The phospholene oxide (+)-**1a** was recovered by the treatment of the chloroform solution (40 mL) of the complex with 40 mL of 10% aqueous solution of ammonia in water. The organic phase was washed with 10 mL of water, dried, and concentrated to give 4.0 g (48%) of (+)-1-phenyl-3-methyl-3-phospholene 1-oxide (+)-**1a** of 96% ee; $[\alpha]_D^{25} = +35.5$ (*c* 1, $CHCl_3$).
27. A representative procedure for the synthesis of resolving agent (−)-**2**. To 38 g (100 mmol) of DBTA·H_2O in 200 mL of a 9:1 mixture of ethanol and water was added 2.8 g (50 mmol) of CaO, and the mixture was kept at reflux until it became clear. After cooling, the solvent was evaporated and the residue dried in vacuum to give 38 g (96%) of Ca(H-DBTA)$_2$ as colorless crystals. On the basis of thermal examination (TG and DTA), resolving agents **2** and **3** contained 4.6% and 4.3% (ca. 2 equiv) of water, respectively.
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31. Crystal data for Ca(**1a**)$_2$(H-DBTA)$_2$: $C_{58.75}H_{52}CaO_{18}P_2$, FW 1148.03; Rigaku *R*-axis RAPID diffractometer, *T* (K) = 93(2), Mo Kα, λ = 0.71073, triclinic, *P*1 (No. 1), *a* = 7.690(2) [Å], *b* = 13.451(4) [Å], *c* = 15.190(5) [Å], α = 65.35(1)[°], β = 75.94(1) [°], γ = 85.62(1) [°], *V* [Å^3] 1384.7(7), *Z* = 1, total/unique data: 33,350/12,427, $R_{(int)}$ = 0.062, observed data [$I > 2.0\sigma(I)$] 8070, parameter number: 732, R_1, wR_2, *S* values: 0.0876, 0.2374, 0.99, Flack x = 0.03(5). Around the convergence of the refinement procedure, the presence of two symmetry-independent, but also apparently pseudo-symmetry related, partly occupied atomic sites was conceived from difference electron density maps. These were first tentatively assigned as partially occupied O atoms of putative water sites. Somewhat unusual U-values indicated that these densities may stem from lower atomic number elements, possibly C atoms. This notion is also supported that these sites are only about 1.4–1.6 Å far from two neighboring carboxyl O atoms each. As such 'binding' O atoms also have normal displacement values supporting fully populated atomic sites for these, the possibility of water involvement is less probable. Although the final scattering model incorporates two such partial C sites, no further tracing and improvement seemed neither possible nor feasible. So these conclusions point to the suggestion that the crystal studied in the XRD experiment was either contaminated with a minute amount of some ester or underwent esterification while crystallization took place, thus forming a solid solution. Such a totally incommensurate solid solution would also explain the unanticipated and relative extensive disorder leading to a somewhat poor scattering model. 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 693853. 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].