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Resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide by diastereomeric complex formation using TADDOL derivatives and calcium salts of *O,O*'-dibenzoyl-(2*R*,3*R*)- or *O,O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid

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Abstract The 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide was prepared in optically active form by extending our resolution methods applying (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane ("TADDOL"), (−)-(2*R*,3*R*)-α,α,α',α'-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol ("spiro-TADDOL"), as well as the acidic and neutral Ca^{2+} salts of (−)-*O,O*'-dibenzoyl- and (−)-*O,O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid. In one case, the diastereomeric complex could be identified by single crystal X-ray analysis. The absolute P-configuration of the enantiomers of the phospholene oxide was also determined by CD spectoroscopy.

Keywords: Alkoxy-3-phospholene 1-oxide; P-chirality; Resolution methods; Optical isomers; X-ray crystallography; CD-spectroscopy; Absolute P-configuration

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1. Introduction

Chiral organophosphorus compounds, especially the ones having an asymmetric centre on phosphorous atom form an interesting group, as the transition metal complexes incorporating the corresponding P(III)-derivatives may be potential catalysts in a wide variety of homogenous catalytic reactions.[1-3]

Several reviews and book chapters have been published on the preparation of organophosphorus compounds in optically active form. These papers discuss different methods to obtain P-stereogenic compounds in enantiopure form, including the resolution of the corresponding racemic compounds via the formation of covalent diastereomers, diastereomeric salts, transition metal complexes and molecular complexes.[4-6] According to these methods described in the literature, *O*,*O*'-dibenzoyl-(2*R*,3*R*)-tartaric acid,[7-15] bromocamphorsulfonic acid,[16-18] camphorsulfonic acid,[18] mandelic acid,[19,20] 2,2'-dihydroxy-1,1'-binaphthalene[19,21] and α-methylbenzylamine[22] can be used to prepare secondary and or tertiary phosphine-oxides in optically active form via the formation of molecular complexes, but none of these methods have found widespread application. In the sphere of chiral P-heterocycles, *Pietrusiewicz* and his co-workers reported several special methods for the preparation of the enantiomers of 2- and 3-phospholene 1-oxides and their fused derivatives.[23-26]

In the last few years, our research group has developed efficient resolution methods for five- and six-membered P-heterocycles including 3-phospholene oxides, a phosphabicyclo[3.1.0]hexane oxide, a dihydro- and a tetrahydrophosphinine oxide via diastereomeric complex formation with TADDOL derivatives (**2** and **3**), and the Ca^{2+} salts of *O*,*O*'-dibenzoyl- and *O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid (**4**–**7**).[27-32]

In this paper, we describe the resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) using the methods developed in our research group (Fig. 1). The absolute configuration of the P-chiral center of the enantiomers of 3-phospholene oxide **1** was also identified.

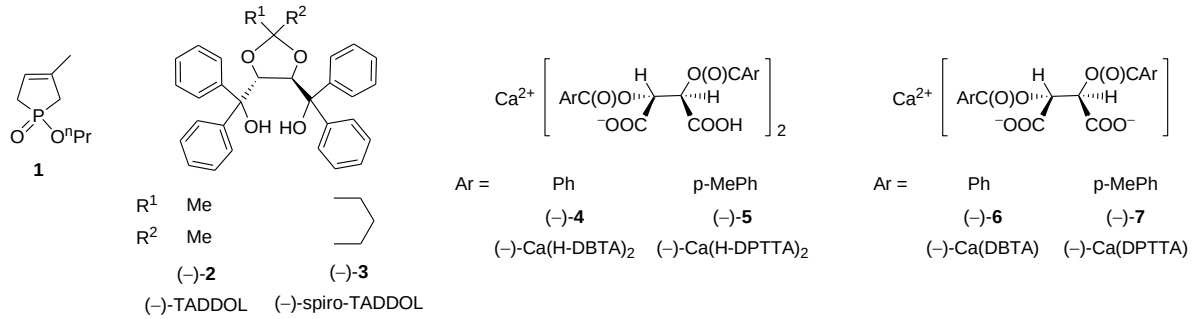


Figure 1. The 1-*n*-propoxy-3-methyl-3-phospholene oxide (**1**) and resolving agents [(−)-**2**-(−)-**7**] used in this study.

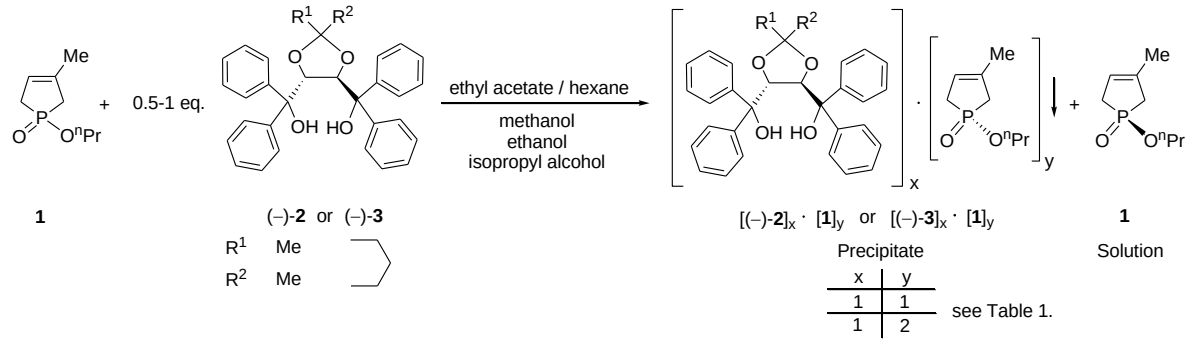
2. Results and discussion

*2.1. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL derivatives [(−)-**2** and (−)-**3**]*

Following the resolution method developed in our research group,[27,28] the resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) was attempted first with TADDOL derivatives [(−)-**2** and (−)-**3**] in a mixture of ethyl acetate and hexane. The mixture of racemic 3-phospholene 1-oxide (**1**) and TADDOL or spiro-TADDOL [(−)-**2** or (−)-**3**, respectively] was dissolved in hot ethyl acetate, and the corresponding diastereomeric complex precipitated after the addition of hexane to the mixture.

Previously, it was found that the efficiency of the resolutions of the aryl-, alkyl- and alkoxy-substituted-3-phosphole oxides with TADDOL derivatives [(−)-**2** and (−)-**3**] may be influenced by changing the solvent.[33] Hence, the resolution of the 3-phospholene oxide (**1**) with TADDOL derivatives [(−)-**2** or (−)-**3**] was also attempted using methanol, ethanol and isopropyl alcohol as the solvent. In these instances, the mixture of the racemic 3-phospholene oxide (**1**) and TADDOL derivatives [(−)-**2** or (−)-**3**] was dissolved in hot alcohol, and crystalline diastereomeric complex appeared by cooling down the mixture to 26 °C (Scheme 1). In case of all resolution experiments, the half equivalent methodology[34] was followed, hence, considering the composition of the diastereomeric complexes, 0.5-1 equivalents of the resolving agents [(−)-**2** or (−)-**3**] were used. Results of the successful resolutions leading to crystalline diastereomers are summarized in Table 1.

In all cases, the diastereomers formed were crystallized for 3 hours, and then they were filtered off from the mother liquors. The diastereomeric complexes were purified further by two recrystallizations from the corresponding solvents. The 3-phospholene oxide (**1**) was recovered from the corresponding diastereomer by column chromatography using silica gel and 3% of methanol in dichloromethane as the eluent.



Scheme 1. General resolution procedure for racemic 3-phospholene oxide (**1**) using TADDOL derivatives [(−)-**2** and (−)-**3**].

The composition of the diastereomers was determined by ^{1}H NMR. It depended on the resolving agent [(−)-**2** or (−)-**3**] and the solvent used. Diastereomers were obtained mainly in a ratio of 1:1, but using spiro-TADDOL [(−)-**3**] in ethanol a 1:2 diastereomeric complex of **1**·[(−)-**3**]$_2$ was also formed (Table 1).

The diastereomeric complexes obtained were analysed by chiral GC after regenerating the 3-phospholene oxide (**1**) from the sample of the corresponding diastereomer by preparative TLC using silica gel and 3% of methanol in dichloromethane as eluent. After crystallization, the enantiomeric excess values were in the range of 40–77%. The enantiomeric purity increased significantly after two recrystallizations, when enantiomeric excess values of 87–99% had been achieved (Table 1).

It was found that the resolving agent [(−)-**2** or (−)-**3**] and the solvent used influence which of the 3-phospholene oxide (**1**) enantiomers was incorporated in the diastereomeric complex. The combination of the resolving agent [(−)-**2** or (−)-**3**] and the solvent had also an impact on the efficiency of the resolutions. Both TADDOL [(−)-**2**] and spiro-TADDOL [(−)-**3**] in a mixture of ethyl acetate and hexane were found to be efficient resolving agents for *n*-propoxy-phospholene oxide (**1**) (S = 0.38 and 0.40, respectively), however, the application of TADDOL [(−)-**2**] provided a higher enantiomeric excess (ee > 99%) (Table 1, entries 1 and 2). Generally, a decrease in resolving capability (S) was observed, when different alcohols were used as the solvent instead of a mixture of ethyl acetate and hexane. We were not successful when TADDOL [(−)-**2**] was used in alcohols, as no diastereomeric complexes were formed in these instances.

It is noteworthy that the use of spiro-TADDOL [(−)-**3**] in ethanol led to diastereomeric complex formation with (*S*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(*S*)-**1**], while the other enantiomer [(*R*)-**1**] was involved in all other instances (Table 1, entries 3 *vs.* 1-2 and 4).

Table 1. Resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL derivatives [(−)-**2** and (−)-**3**]

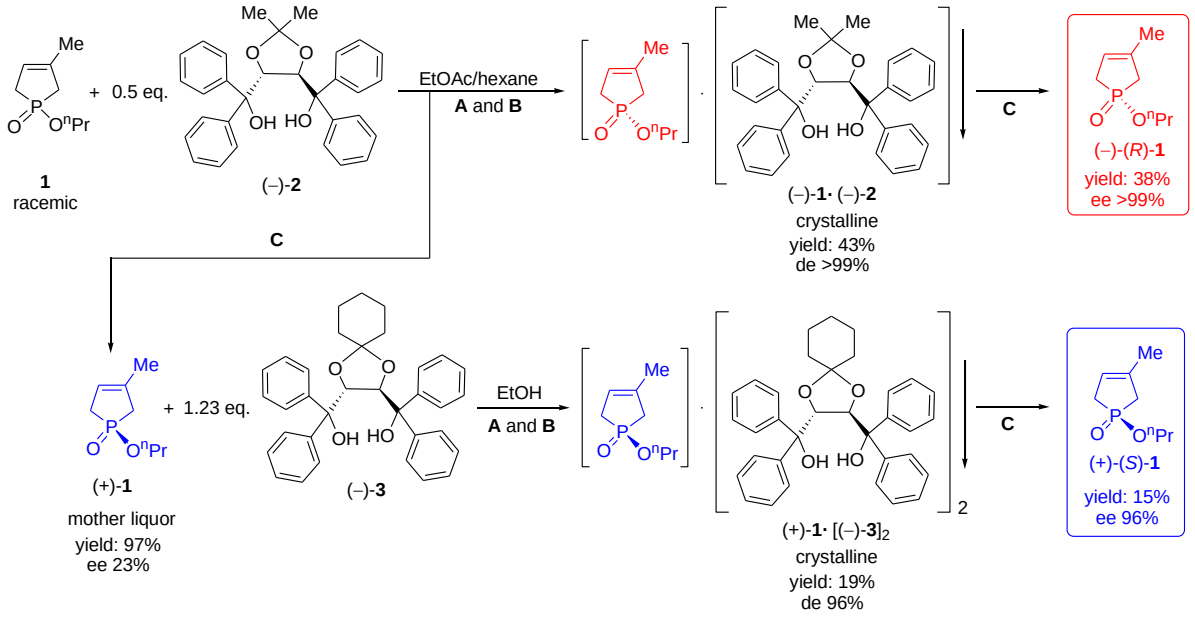
Entry	Resolving agent	Eq.	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	ee[d,f] (%)	S[e,f] (-)	Abs. Config.[g]
1	TADDOL	0.5	2×EtOAc/10×hexane	(**1**)(TADDOL)	(63) **38**	(77) **>99**	(0.48) **0.38**	(*R*)
2	spiro-TADDOL	0.5	2×EtOAc/10×hexane	(**1**)(spiro-TADDOL)	(72) **43**	(54) **93**	(0.39) **0.40**	(*R*)
3	spiro-TADDOL	1	6×EtOH	(**1**)(spiro-TADDOL)$_2$	(76) **15**	(40) **93**	(0.30) **0.14**	(*S*)
4	spiro-TADDOL	0.5	6×iPrOH	(**1**)(spiro-TADDOL)	(67) **10**	(55) **87**	(0.37) **0.08**	(*R*)

[a]Mixture of solvents for the crystallization and recrystallizations [mL of solvent/g of resolving agent].
[b]The ratio of **1** and (−)-**2** or (−)-**3** was determined by ^{1}H NMR.
[c]Based on the half of the racemate **1** that is regarded to be 100% for each antipode.
[d]Determined by chiral GC.
[e]Resolving capability, also known as the Fogassy parameter (S = Yield × ee).[35]
[f]Results obtained after the first crystallization are shown in parantheses, while results obtained after two recrystallizations are shown in boldface.
[g]The absolute configuration of **1** was determined by X-Ray analysis and CD spectroscopy.

The phenomena that TADDOL derivatives [(−)-**2** or (−)-**3**] may form diastereomeric complexes with both antipodes of the 3-phospholene oxides (**1**) in different solvents allowed us to develop a resolution procedure to obtain both enantiomers from racemic 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**).

Both enantiomers of the 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) were prepared by exploiting the different antipode preference of TADDOL [(−)-**2**] in ethyl acetate – hexane and that of the spiro-TADDOL [(−)-**3**] in ethanol. At first, the racemic *n*-propoxy-phospholene oxide (**1**) was resolved with 0.5 equivalent of TADDOL [(−)-**2**] in a mixture of ethyl acetate and hexane. The diastereomer [(−)-**1**]·[(−)-**2**] was purified by two recrystallizations, and (−)-(*R*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(−)-(*R*)-**1**] was recovered by column chromatography with an ee > 99% and in a yield of 38%. The combined mother liquors of the crystallization and recrystallization were purified by column chromatography to afford (+)-(*S*)-**1** with an ee of 23% and a yield of 97%. The crystallization of this enantiomeric mixture with 1.23 equivalent of spiro-TADDOL [(−)-**3**] in ethanol afforded the diastereomeric complex [(−)-**1**]·[(−)-**3**]$_2$, that was purified by two recrystallizations to obtain (+)-(*S*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(+)-(*S*)-**1**]

with an ee of 96% and in a yield of 15% after decomplexation by column chromatography (Scheme 2).



A: crystallization; **B**: recrystallizations; **C**: column chromatography

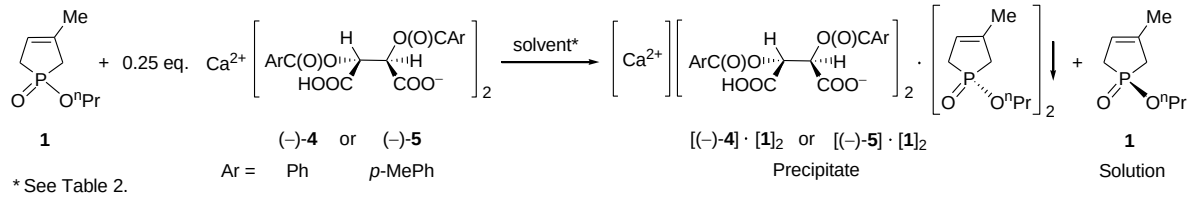
Scheme 2. The complete resolution process of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL and spiro-TADDOL [(−)-**2** and (−)-**3**].

*2.2. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with calcium hydrogen (−)-O,O'-dibenzoyl- or (−)-O,O'-di-p-toluoyl-(2R,3R)-tartrate [(−)-**4** or (−)-**5**]*

The resolution of the 3-phospholene oxide (**1**) was also attempted using the acidic Ca^{2+}-salts of the (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**4** or (−)-**5**]. The results are summarized in Table 2.

Similarly to our earlier studies, Ca(H-DBTA)$_2$ [(−)-**4**] was prepared as a stable reagent,[29,30] while Ca(H-DPTTA)$_2$ [(−)-**5**] was always prepared *in situ* by reacting (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid with CaO in a 10:1 mixture of ethanol and water. The racemic 3-phospholene oxide (**1**) in ethanol, ethyl acetate or acetonitrile was added to the hot ethanolic solution of 0.25 equivalents of Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**4** or (−)-**5**]. The crystalline diastereomers having the composition of Ca(**1**)$_2$(H-DBTA)$_2$ or Ca(**1**)$_2$(H-DPTTA)$_2$ were filtrated off after 24 hours of crystallization. These diastereomers [Ca(**1**)$_2$(H-DBTA)$_2$ or Ca(**1**)$_2$(H-DPTTA)$_2$] were purified by two digestions (*i.e.*, stirring the crystals in the corresponding solvent at 26 °C for 24 hours). The 3-phospholene oxide (**1**) was recovered by treating the dichloromethane solution of the corresponding complex Ca(**1**)$_2$(H-DBTA)$_2$ or

$Ca(\mathbf{1})_2(H\text{-}DPTTA)_2$ with 10% aqueous ammonia (Scheme 3). The enantiomeric excess of the 3-phospholene enantiomers (**1**) was determined by chiral GC.



Scheme 3. General resolution procedure for racemic 3-phospholene oxide (**1**) using $Ca(H\text{-}DBTA)_2$ or $Ca(H\text{-}DPTTA)_2$ [(−)-**4** or (−)-**5**].

Using $Ca(H\text{-}DBTA)_2$ [(−)-**4**] as resolving agent, the nature of the enantiomer of the 3-phospholene oxide (**1**) incorporated in the diastereomeric complex $Ca(\mathbf{1})_2(H\text{-}DBTA)_2$ depended on the solvent used. Resolution of racemic *n*-propoxy-3-phospholene oxide (**1**) with $Ca(H\text{-}DBTA)_2$ [(−)-**4**] in ethanol, or in a mixture of ethyl acetate and ethanol afforded (*S*)-*n*-propoxy-3-phospholene oxide [(*S*)-**1**], while the other enantiomer (*R*)-**1** could be obtained using a mixture of acetonitrile and ethanol as the solvent (Table 2, entries 1–3). Using $Ca(H\text{-}DPTTA)_2$ [(−)-**5**], the (*R*)-*n*-propoxy-3-phospholene oxide [(*R*)-**1**] could be prepared in all solvents used (Table 2, entries 4–6).

The highest ee and resolving capability (S) values obtained with $Ca(H\text{-}DBTA)_2$ or $Ca(H\text{-}DPTTA)_2$ [(−)-**4** or (−)-**5**] were 59% and 0.20, respectively, after purification by two digestions (Table 2, entries 3 and 4). The application of $Ca(H\text{-}DPTTA)_2$ [(−)-**5**] led to higher resolving capability values than that of $Ca(H\text{-}DBTA)_2$ [(−)-**4**] (Compare Table 2, entries 1–3 and 4–6).

Table 2. Resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with 0.25 equivalent of Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**4** or (−)-**5**]

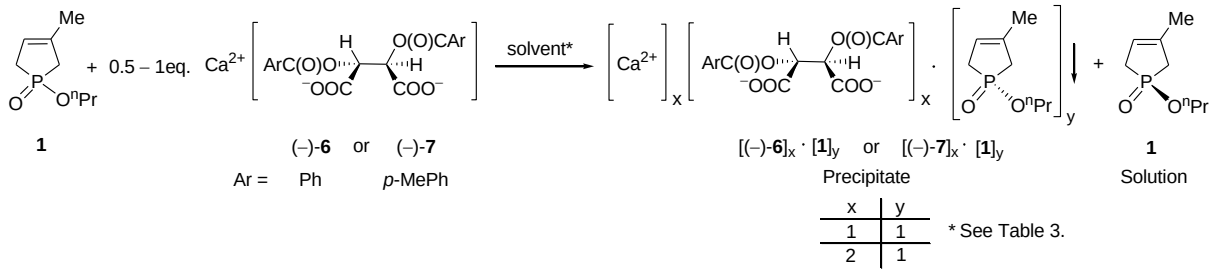
Entry	Resolving agent	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	ee[d,f] (%)	S[e,f] (-)	Abs. Config.[g]
1	Ca(H-DBTA)$_2$	3×EtOAc/3×EtOH	Ca(**1**)$_2$(H-DBTA)$_2$	(80) **34**	(17) **17**	(0.14) **0.06**	(*S*)
2	Ca(H-DBTA)$_2$	6×EtOH	Ca(**1**)$_2$(H-DBTA)$_2$	(60) **7**	(18) **22**	(0.11) **0.02**	(*S*)
3	Ca(H-DBTA)$_2$	3×MeCN/3×EtOH	Ca(**1**)$_2$(H-DBTA)$_2$	(73) **18**	(11) **59**	(0.08) **0.11**	(*R*)
4	Ca(H-DPTTA)$_2$	3×EtOAc/3×EtOH/10%H_2O	Ca(**1**)$_2$(H-DPTTA)$_2$	(65) **36**	(41) **55**	(0.26) **0.20**	(*R*)
5	Ca(H-DPTTA)$_2$	6×EtOH/10%H_2O	Ca(**1**)$_2$(H-DPTTA)$_2$	(66) **35**	(44) **47**	(0.29) **0.17**	(*R*)
6	Ca(H-DPTTA)$_2$	3×MeCN/3×EtOH/10%H_2O	Ca(**1**)$_2$(H-DPTTA)$_2$	(69) **30**	(46) **56**	(0.31) **0.17**	(*R*)

See Table 1 for footnotes.

*2.3. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with calcium (−)-O,O'-dibenzoyl- and (−)-O,O'-di-p-toluoyl-(2R,3R)-tartrate [(−)-**6** and (−)-**7**]*

The resolution of *n*-propoxy-3-phospholene oxide (**1**) was also attempted with the neutral Ca^{2+} salts of (−)-*O*,*O*'-dibenzoyl- and (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**6** and (−)-**7**], respectively, as these resolving agents were also found suitable for the resolution of some 3-phospholene oxides previously.[30] Successful experiments resulting in crystalline diastereomers are summarized in Table 3.

Ca(DBTA) and Ca(DPTTA) [(−)-**6** and (−)-**7**], respectively were prepared *in situ* by the reaction of CaO and (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid having 1:1 ratio in a mixture of ethanol and water. To this solution was added the racemic 3-phospholene oxide (**1**) in ethanol, ethyl acetate or acetonitrile. The crystalline diastereomers formed were filtrated off after 24 hours. The diastereomers were purified by digestions (Scheme 4). In a few cases, only one purification was applied, as in certain cases the corresponding diastereomeric complex dissolved completely during the second digestion (Table 3, entries 1-3).



Scheme 4. General resolution procedure for racemic 3-phospholene oxides (**1**) using CaDBTA or CaDPTTA [(−)-**6** or (−)-**7**].

In all but one instances, the ratio of the 3-phospholene oxide (**1**) and CaDBTA or CaDPTTA [(−)-**6** or (−)-**7**], determined by ^{1}H NMR, was 1:1 (Table 3, entries 1-4 and 6), the exception was a diastereomer with a stoichiometry of 1:2 (Table 3, entry 5). With CaDBTA [(−)-**6**] as the resolving agent, both enantiomers of *n*-propoxy-3-phospholene oxide (**1**) could be prepared using different solvent mixtures, while the resolutions with CaDPTTA [(−)-**7**] afforded exclusively the (*R*)-*n*-propoxy-3-phospholene oxide [(*R*)-**1**] (Table 3).

Using CaDBTA and CaDPTTA [(−)-**6** and (−)-**7**], the resolving capability (S) was in the range of 0.01-0.10 after purification, what is lower than the values obtained with the corresponding acidic Ca^{2+} salts [(−)-**4** and (−)-**5**] (Compare Tables 2 and 3). As the enantiomeric excess values were in the same range with the acidic and the neutral Ca^{2+} salts of the (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**4** – (−)-**7**], respectively (17–59% and 16-62%, respectively), the difference in resolving capability (S) may be explained by the lower yields (2–17%) obtained with CaDBTA [(−)-**6**] and CaDPTTA [(−)-**7**].

Considering the enantiomeric excess and the resolving capability (S), the application of TADDOL derivatives [(−)-**2** or (−)-**3**] seems more advantageous, as compared to the acidic and neutral salts of DBTA and DPTTA [(−)-**4** – (−)-**7**]. However, the application of the Ca(H-DBTA)$_2$ [(−)-**4**] and Ca(H-DPTTA)$_2$ [(−)-**5**] may seem more favourable when the price difference between (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid and the TADDOL derivatives [(−)-**2** and (−)-**3**] is considered. Moreover, the decomposition of the diastereomeric complexes of the Ca(H-DBTA)$_2$ and Ca(H-DPTTA)$_2$ [(−)-**4** and (−)-**5**] is simpler, than that of the TADDOL derivatives [(−)-**2** and (−)-**3**] (extraction *versus* column chromatography).

Table 3. Resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with Ca(DBTA) or Ca(DPTTA) [(−)-**6** or (−)-**7**]

Entry	Resolving agent	Eq.	Solvents[a]	Diastereomer complex[b]	Yield[c,f] (%)	ee[d,f] (%)	S[e,f] (-)	Abs. Config.[g]
1	CaDBTA	0.5	3×EtOAc/3×EtOH/10%H_2O	Ca(**1**)(DBTA)	(31) **5***	(17) **17***	(0.05) **0.01***	(*S*)
2	CaDBTA	0.5	6×EtOH/10%H_2O	Ca(**1**)(DBTA)	(32) **2***	(15) **16***	(0.05) **0.01***	(*S*)
3	CaDBTA	0.5	3×MeCN/3×EtOH/10%H_2O	Ca(**1**)(DBTA)	(33) **3***	(39) **62***	(0.13) **0.02***	(*R*)
4	CaDPTTA	0.5	3×EtOAc/3×EtOH/10%H_2O	Ca(**1**)(DPTTA)	(73) **14**	(59) **59**	(0.43) **0.08**	(*R*)
5	CaDPTTA	1	6×EtOH/10%H_2O	Ca_2(**1**)$(DPTTA)_2$	(43) **17**	(57) **61**	(0.25) **0.10**	(*R*)
6	CaDPTTA	0.5	3×MeCN/3×EtOH/10%H_2O	Ca(**1**)(DPTTA)	(33) **11**	(59) **59**	(0.20) **0.07**	(*R*)

See Table 1 for footnotes.
* Diastereomeric complex was purified with one recrystallization.

*2.4. Single crystal X-ray analysis of diastereomeric complex [Ca(**1**)$_2$(H-DPTTA)$_2$]*

Results from the crystal structure determination (Fig. 2) apart from revealing the respective molecular structures as well as absolute configurations also give an insight into some aspects of molecular recognition. Disorder phenomenon is especially obvious for the Ca^{2+} - salt system [Ca(**1**)$_2$(H-DPTTA)$_2$] (*c.f.* Fig. 3). The disordered propoxy-chain indicates alternating conformations of this component of the guest molecule. This fact indicates that the phospholene rings do keep some intrinsic pseudo-rotatory ability. It also gives an indication as to the origin of the relative low scattering power from such crystals.

The diastereomeric salt associate including phospholene oxide **1** (Fig. 2) also shows a similar binding type, as described in an analogous crystal structure.[29]

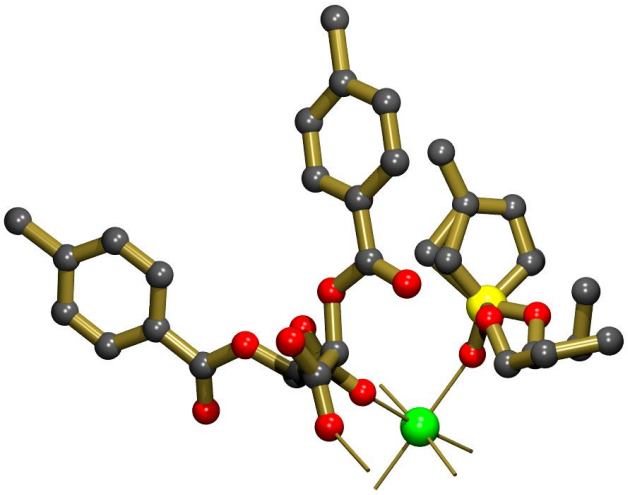


Figure 2. Perspective view of the crystallographic asymmetric unit of the Ca^{2+}:**1**:H-DPTTA 1:2:2 system. For the sake of clarity all H atoms were omitted from the drawing, thin lines indicate the coordinative bonds from and to the Ca^{2+} cation. Disorder atomic sites are visible at the propoxy side chain, as well as some alternating atomic sites for some puckered ring C-atoms.

Ca^{2+} ions acting as the primary binding tool fuse these associated molecules into an endless catena- structure in the solid state. The coordination sphere around the metal ion is like as it was in the acidic Ca^{2+} salt of dibenzoyl-tartaric acid,[29] albeit phospholene guests differ both in size and ramification. The coordination sphere is octahedral in both cases, and the shortest distances, *i.e.* strongest interactions, occur between similar moieties of the host and guest. From inspecting packing features, it is also visible that the voids, filled by the target phospholene-oxide molecules are well-suited for enabling variable positions for the alkoxy-tails from the chiral P-centre (Fig. 3). Apolar *p*-toluoyl moieties of the H-DPTTA host are directed outwards in the crystals such that only feeble contacts are possible from this environment to the non-O atoms of the phospholene oxide derivative (**1**). All these features are largely similar to the dibenzoyl - tartaric acid host system[29] underlining the basic recognition motifs in the crystalline state being affected by the metal coordination, supported and assisted by the tartaric acid framework. Thus one could perhaps rightly assume that the Ca-tartaric acid hemi-salts alike behaviour attests a synthon-like feature.

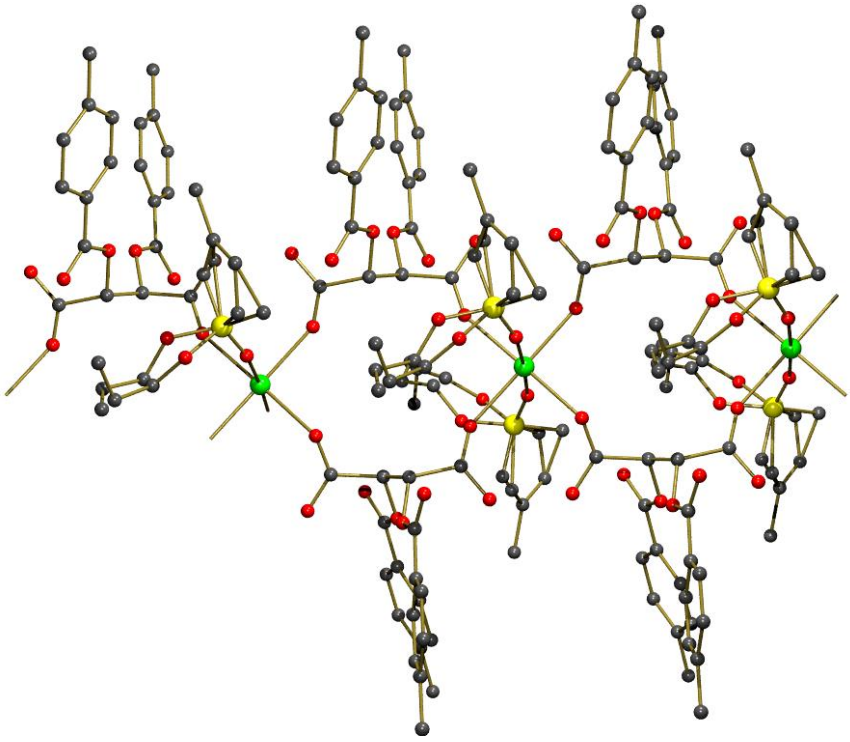


Figure 3. Packing motif from the crystal structure of the Ca^{2+}:**1**:H-DPTTA 1:2:2 system. For the sake of clarity all H atoms are omitted from the drawing.

*2.5. CD spectra of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**)*

The UV absorption and CD spectra of the 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) were recorded (Table 4) and analyzed. To facilitate the assignment of the absolute configuration of the title compound (**1**), DFT (density functional theory) quantum chemical calculations were performed using the PBE0 functional and the 6-311++G** basis set..

Table 4. Observed UV and CD spectral bands of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**)

	UV spectra		CD spectra	
	λ [nm]	ε [$dm^3mol^{-1}cm^{-1}$]	λ [nm]	Δε [$dm^3mol^{-1}cm^{-1}$]
1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**)	191	6100		
	219 (sh)	400	222	1,9
			243	–0,5

In the calculations a simplified model compound, 1-methoxy-3-methyl-3-phospholene 1-oxide (Fig. 4.) was considered as a model for 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**). This simplification results in significant savings in computation time, but it is not expected to influence the assignment of the absolute configuration, as the UV-visible and CD

spectra of the compounds are almost independent of the alkyl-groups connected to the oxygen atom. This is justified by the good agreement of the spectra measured in this study and the spectra of alkoxy-substituted-phospholene-derivatives considered in our previous papers.[28]

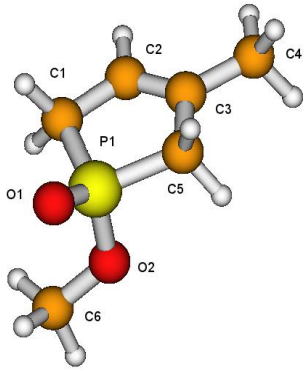


Figure 4. DFT-optimized geometry for the most stable conformer of 1-methoxy-3-methyl-3-phospholene 1-oxide. Characteristic bond lengths (in Å) and angles (in degree) are as follows: P1-O1 1.495, P1-C1 1.827, C1-C2 1.502, C2-C3 1.339, C3-C4 1.491, C3-C5 1.509, C5-P1 1.817, P1-O2 1.622, C1-P1-C5 97, O1-P1-O2 114, O1-P1-O2-C6 52, O1-P1-C1-C2 138.

First, a systematic conformation analysis was carried out for the model molecule. Three conformers were found differing in the position of the methoxy-group. Two of them are practically isoenergetic, and the third one lies at about 4 kJ/mol above the first two ones. The geometries for all of the three conformers were optimized, and excitation energies, as well as oscillator and rotator strengths were computed.

The optimized geometry of the most stable conformer is displayed in Fig. 4, while the calculated and measured spectra are presented in Fig. 5. The agreement of the measured and computed absorption spectra of the compounds is good and justifies the selection of the theoretical model employed. The sign of the dominant features in the experimental and theoretical CD spectra are identical, which means that the absolute configuration of the synthesized compounds is identical to that of the enantiomer considered in the calculations.

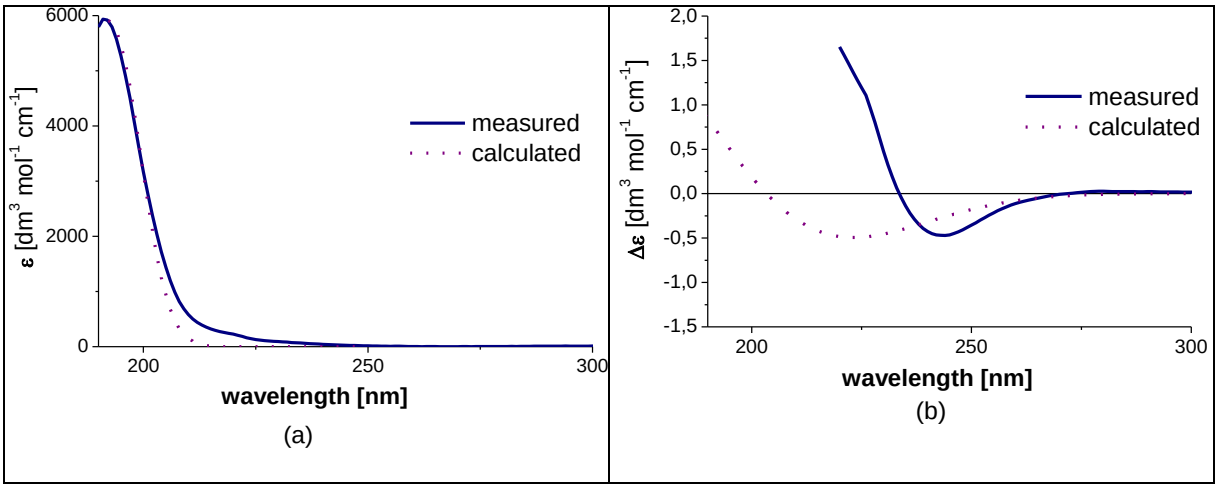


Figure 5. The calculated (dashed line) UV absorption (a) and CD (b) spectra of (*R*)-1-methoxy-3-methyl-3-phospholene 1-oxide together with the measured (solid line) spectra of (−)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(−)-**1**].

3. Conclusions

Resolution procedures were developed for 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) using TADDOL derivatives [(−)-**2** and (−)-**3**], as well as acidic and neutral Ca^{2+} salts of (−)-*O*,*O*'-dibenzoyl- or (−)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**4** – (−)-**7**]. It was found that the solvent used had a significant effect on the efficiency of the resolutions. Both antipodes of 1-*n*-propoxy-3-phospholene 1-oxide (**1**) were prepared with an ee > 96% by exploiting the different antipode preference of the TADDOL derivatives [(−)-**2** and (−)-**3**].

The absolute configuration of the enantiomers of 3-phospholene oxide **1** was determined by CD spectroscopy, using TD-DFT quantum chemical calculations for the analysis of the spectra, as well as X-ray crystallography. The X-ray crystallographic measurement also revealed the interactions between resolving agent $Ca(H\text{-}DPTTA)_2$ [(−)-**5**] and the 3-phospholene oxide **1**.

4. Experimental

4.1. General

The ^{31}P and ^{1}H NMR spectra were taken on a Bruker AV-300 or DRX-500 spectrometer operating at 121.5 and 300 or 202.4 and 500 MHz, respectively.

The enantiomeric excess (ee) values of the 3-phospholene oxide **1** were determined by chiral GC on Agilent 4890D instrument equipped with a Supelco BETA DEX™ 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: 10 psi, at 1:100 split ratio). Retention times of **1** by chiral GC

(program: 2 min at 140 °C, 5 °C/min to 190 °C, then kept at 190 °C): 13.95 min for (*S*)-**1** and 14.14 min for (*R*)-**1**.

Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

The 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**),[36] (−)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane [(−)-**2**], the (–)-(2*R*,3*R*)-α,α,α',α'-tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol [(−)-**3**][37] and the calcium hydrogen (−)-*O*,*O*'-dibezoyl-(2*R*,3*R*)-tartrate [(−)-**4**][29] were synthesized as described earlier. The (−)-*O*,*O*'-dibezoyl- and the (–)-*O*,*O*'-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid was purchased from Aldrich Chemical Co.

*4.2. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL [(−)-**2**] (Representative Procedure A)*

1.7 g (9.6 mmol) of racemic 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) and 2.2 g (4.8 mmol) of TADDOL [(−)-**2**] was dissolved in 4.4 mL of hot ethyl acetate, and then 22 mL of hexane was added. Colourless crystalline diastereomeric complex (*R*)-**1**·TADDOL appeared immediately. After standing at 26 °C for 3 h, the crystals were separated by filtration to give 1.9 g (63%) of (*R*)-**1**·TADDOL with a de of 77%. The diastereomeric complex (*R*)-**1**·TADDOL was purified further by two recrystallizations from a mixture of 4.4 mL of ethyl acetate and 22 mL of hexane to afford 1.3 g (43%) of the complex (*R*)-**1**·TADDOL with a de above 99%. The (*R*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] was recovered from the diastereomer by column chromatography (silica gel, dichloromethane:methanol 97:3) to give 0.32 g (38%) of phospholene oxide (*R*)-**1** with an ee above 99%. $[\alpha]_D^{25} = -14.6$ (c 2.2, $CHCl_3$) (Table 2, entry 1).

*4.3. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with sprio-TADDOL [(−)-**3**]*

1-*n*-propoxy-3-phospholene oxide (**1**) was resolved with spiro-TADDOL [(−)-**3**] according to the *Representative Procedure A*. When the resolutions were carried out in methanol, ethanol or isopropyl alcohol, the racemic 3-phospholene oxide (**1**) and the spiro-TADDOL [(−)-**3**] were dissolved in hot alcohol, and the corresponding diastereomeric complexes precipitated by cooling down the mixture to 26 °C. The conditions and the results are shown in Table 1.

*4.4. Resolution of 1- n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with calcium hydrogen O,O'-dibenzoyl-(2R,3R)-tartrate [(−)-**4**] (Representative Procedure B)*

To 0.19 g (0.24 mmol) of Ca(H-DBTA)$_2$·(H$_2$O)$_2$ [(−)-**4**·(H$_2$O)$_2$] in 0.56 mL of hot ethanol was added 0.17 g (0.95 mmol) of racemic 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) in 0.56 mL of acetonitrile. After the addition, the solution was allowed to cool down to 26 °C, whereupon colourless crystals appeared. After standing at 26 °C for 24 h, the crystals were filtered off to give 0.19 g (73%) of Ca[((*R*)-**1**)$_2$(H-DBTA)$_2$] with a de of 11%. The diastereomeric complex was purified further by two digestions, by stirring the suspension of the diastereomeric complex at 26 °C in a mixture of 0.56 mL of ethanol, 0.56 mL of acetonitrile for 24 h to afford 0.062 g (24%) of Ca[((*R*)-**1**)$_2$(H-DBTA)$_2$] with a de of 59%. The phospholene oxide (*R*)-**1** was recovered from the diastereomeric complex by treatment of the 2 mL dichloromethane solution of the Ca[((*R*)-**1**)$_2$(H-DBTA)$_2$] with 2 mL of a 10% aqueous ammonia. The organic layer was washed with 0.5 mL of water, dried (Na$_2$SO$_4$), and concentrated to give 0.015 g (18%) of (*R*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(*R*)-**1**)] with an ee of 59%. Resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with Ca(H-DBTA)$_2$ [(−)-**4**] was also performed in a mixture of ethanol and ethyl acetate, or in ethanol. The conditions and the results are shown in Table 2, entries 1-3.

*4.5. Resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with calcium hydrogen O,O'-di-p-toluoyl-(2R,3R)-tartrate [(−)-**5**] (Representative Procedure C)*

To 0.21 g (0.52 mmol) of DPTTA·H$_2$O in a mixture of 0.63 mL of ethanol and 0.06 mL of water was added 0.014 g (0.26 mmol) of CaO, and the mixture was heated at the boiling point until it became clear. 0.18 g (1.0 mmol) of racemic 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) in 0.63 mL of ethyl acetate was then added to the solution of the *in situ* formed resolving agent Ca(H-DPTTA)$_2$ [(−)-**5**]. After the addition, the solution was allowed to cool down to 26 °C, whereupon colourless crystals appeared. After standing at 26 °C for 24 h, the crystals were filtered off to give 0.19 g (65%) of Ca[((*R*)-**1**)$_2$(H-DPTTA)$_2$] with a de of 41%. The diastereomeric complex was purified further by two digestions, by stirring the suspension of the diastereomeric complex at 26 °C for 24 h in a mixture of 0.63 mL of ethanol, 0.63 mL of ethyl acetate and 0.06 mL of water to afford 0.13 g (42%) Ca[((*R*)-**1**)$_2$(H-DPTTA)$_2$] with a de of 55%. The phospholene oxide (*R*)-**1** was recovered by treatment of the 2 mL dichloromethane solution of the complex with 2 mL of 10% aqueous ammonia. The organic phase was washed with 0.5 mL of water, dried (Na$_2$SO$_4$), and concentrated to give 0.032 g (36%) of (*R*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] with an ee of 55%. The

resolution of 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with Ca(H-DPTTA)$_2$ [(−)-**5**] was accomplished in a mixture of ethanol and water, or in a mixture of ethanol, water and acetonitrile. The conditions and the results are shown in Table 2, entries 4-6.

*4.6. The resolution of 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with calcium O,O'-di-benzoyl-(2R,3R)-tartrate and calcium O,O'-di-p-toluoyl-(2R,3R)-tartrate [(−)-**6** and (−)-**7**]*

1-*n*-propoxy-3-phospholene oxide (**1**) was resolved with Ca(DBTA) and Ca(DPTTA) [(−)-**6** and (−)-**7**] according to *Representative Procedure C*. When Ca(DBTA) and Ca(DPTTA) [(−)-**6** and (−)-**7**] were used as resolving agents, the ratio of CaO and DBTA or DPTTA was 1:1. The conditions and the results are shown in Table 3.

*4.7. The complete resolution process for 1-n-propoxy-3-methyl-3-phospholene 1-oxide (**1**) with TADDOL derivatives [(−)-**2** and (−)-**3**]*

The resolution of 1.7g (9.6 mmol) of racemic 1-*n*-propoxy-3-methyl-3-phospholene 1-oxide (**1**) was performed with 2.2 g (4.8 mmol) of TADDOL [(−)-**2**] in a mixture of 4.4 mL of ethyl acetate and 22 mL of hexane as described in *Representative Procedure A*. 0.32 g (38%) of (*R*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(*R*)-**1**] was obtained in an ee above 99% after two recrystallizations and decomposition of the diastereomeric complex with column chromatography (silica gel, dichloromethane:methanol 97:3). The mother liquors of the crystallization and recrystallizations were combined and purified by column chromatography (silica gel, dicholomethane:methanol 97:3) to give 0.81 g (97%) of (*S*)-**1** in an ee of 23%. To this enantiomeric mixture, 2.9 g (5.7 mmol) of spiro-TADDOL [(−)-**3**] was added, and the resolution was elaborated in 17 mL of ethanol according to *Representative Procedure A*. The diastereomeric complex (*S*)-**1**·(spiro-TADDOL)$_2$ was purified by two recrystallizations from 17 mL of ethanol, and 0.13 g (15%) of (*S*)-1-*n*-propoxy-3-methyl-3-phospholene 1-oxide [(*S*)-**1**] was obtained in an ee of 96% after the decomposition of the diastereomeric complex by column chromatography (silica gel, dichloromethane:methanol 97:3).

4.8. X-ray measurements

X-ray quality crystals of the diastereomeric complex Ca^{2+}:**1**:H-DPTTA 1:2:2 were grown from a saturated methanol solution of 3.1 mg (0,018 mmol) of (*R*)-**1** and 3.6 mg (0.0045 mmol) of Ca(H-DPTTA)$_2$ prepared *in situ* as described in Representative Procedure C.

A selected single crystal colourless, prism, (0.35 × 0.55 × 0.55 mm) of Ca(**1**)$_2$(H-DPTTA)$_2$ was mounted on a Rigaku R-AXIS RAPID diffractometer (graphite

monochromator Cu-*K*α radiation, λ = 1.54178 Å). Data collection was performed at ambient temperatures (T = 295(2) K). Crystal data for Ca(**1**)$_2$(H-DPTTA)$_2$:$C_{54}H_{64}CaO_{20}P_2$, monoclinic, space group *C*2, *a* = 30.6520(6)Å, *b* = 7.6583(1)Å, *c* = 13.7082(3)Å, b = 109.356(1), *V* = 3036.0(1) Å^3, *T* = 295(2) K, *Z* = 2, D_x = 1.268 Mg/m^3, μ = 1.991 mm^{-1}. Initial structure model was obtained by SHELXS-97,[38] completed by successive difference Fourier syntheses and refined to convergence by SHELXL-97,[38] R^1 = 0.0456 and wR^2 = 0.1117 for 3330 [I>2σ(I)] and R^1 = 0.0604 and wR^2 = 0.1369 for all (3869) intensity data. Refined absolute structure parameter x = 0.011(16).[39]

Crystallographic data for Ca(**1**)$_2$(H-DBTA)$_2$ have been deposited at the Cambridge Crystallographic Data centre under deposition number CCDC 965084. Copies of these data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 00 44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.9. CD measurements

The UV absorption and CD spectra were measured in acetonitrile solution. The UV spectra were recorded on an Agilent 8453 diode array spectrometer, the CD spectra were obtained with a Jasco J-810 spectropolarimeter.

4.10. Theoretical calculations

The quantum chemical calculations were carried out at the density functional theory (DFT) level using the PBE0[40] functional and the 6-311++G** basis set. For the calculation of the absorption and CD spectra the time-dependent DFT method[41,42] was invoked. Rotator strengths were calculated in the velocity gauge. The calculations were performed using the polarized continuum model[43] with acetonitrile as the solvent since the experimental spectra were measured in the latter. The theoretical calculations were performed by the Gaussian 09 package.[44]

The theoretical UV absorption (CD) curves for each conformer were obtained as superpositions of Gaussian functions placed at the wavelengths of the computed transitions with heights proportional to the corresponding calculated oscillator (rotator) strengths. The spectra of the conformers were Boltzmann-weighted. The averaged spectra were normalized so that the height of the biggest peak be identical to that of the experimental spectra, furthermore, the spectra were shifted to longer wavelengths so that the position of the most intense band of the absorption spectra be identical.

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