Dalton Transactions

PERSPECTIVE

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Cite this: *Dalton Trans.*, 2016, **45**, 1823

Resolution of P-stereogenic P-heterocycles *via* the formation of diastereomeric molecular and coordination complexes (a review)

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Received 4th August 2015,
Accepted 29th October 2015

DOI: 10.1039/c5dt02999f

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TADDOL derivatives and the Ca^{2+}-salts of tartaric acid derivatives were found to be versatile and generally applicable resolving agents for the preparation of the enantiomers of P-stereogenic heterocyclic phosphine oxides and phosphinates *via* the formation of the corresponding diastereomeric molecular and coordination complexes. A few of the diastereomeric intermediates were characterized by single crystal X-ray crystallography to gain insights into the binding mode of the corresponding heterocyclic phosphine oxide ("guest") and the resolving agent ("host") and to study the underlying phenomenon of enantiomeric recognition.

1. Introduction

Optically active organophosphorus compounds are of great importance in organic syntheses.[1] An important application is the use of chiral P(III) derivatives (phosphorous, phosphonous and phosphinous esters/amides and especially phosphines) as P-ligands in transition metal complexes which are potential catalysts in enantioselective homogeneous catalytic transformations, such as hydrogenation or hydroformylation.[2–5] Among chiral organophosphorus compounds, the species bearing P-stereogenic center(s) are of special interest.[6–10]

P-stereogenic organophosphorus compounds cannot be found in the natural pool of chirality in an optically active form, thus resolution and asymmetric synthesis remain the primary sources for the preparation of such compounds.[9,11] Despite the wide variety of asymmetric syntheses,[12–21] the resolution of racemic P-compounds is a well-established method for the preparation of the corresponding optically active organophosphorus compounds.[9,11,21,22] In the following few paragraphs, selected examples are shown for the preparation of optically active P-stereogenic heterocycles *via* the for-

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Péter Bagi was born in Nyíregyháza (Hungary) in 1986. He graduated at the Budapest University of Technology and Economics in 2011 as a chemical engineer and earned his PhD in 2014. Currently, he is a postdoctoral fellow at the Budapest University of Technology and Economics and, besides educational activity, he has been working on the preparation and application of optically active P-stereogenic compounds. His research field includes optical resolution and the development of new catalysts.

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György Keglevich was born in 1957 in Budapest, and became a chemical engineer in 1981. He obtained PhD and DSc in 1990 and 1994, respectively, and was appointed to Professor in 1996. He has been the Head of Organic Chemistry and Technology Department, Budapest University of Technology and Economics since 1999. His research interests include organophosphorus and environmentally-friendly ("green") chemistry, catalytic and microwave-assisted reactions, and industrial organophosphorus syntheses. He has published 460 articles, and he serves as an editor for Curr. Org Chem., Curr Org Synth., Curr Green Chem., Lett. Org. Chem. *and* Lett. Drug Design Disc.

mation of diastereomers. The systematization of the optical resolution of the acyclic derivatives was not our aim, as this was covered by the review of Pietrusiewicz and Zablocka, as well as by the book of Grabulosa.[9,11]

One of the first examples for the preparation of optically active P-heterocycles *via* the formation of covalent diastereomers was described by Campbell and Way. They prepared diastereomeric amides by the reaction of an optically active dibenzophosphole oxide bearing a carboxyl functional group with 1-phenylethylamine.[23] Mathey *et al.* reported the synthesis of 1-phosphanorbornadiene-2-carboxaldehydes which were resolved *via* the corresponding diastereomeric acetals formed with (*S*,*S*)-1,2-diphenylethane-1,2-diol.[24]

Tang and his co-workers elaborated the resolution of *t*-butyl-hydroxy-benzodihydrooxaphosphole oxide by reacting the racemate with menthyl chloroformate. The separation of the covalent diastereomers followed by hydrolysis afforded the enantiomerically pure *t*-butyl-hydroxy-benzodihydrooxaphosphole oxide.[25,26] Pietrusiewicz *et al.* reported the oxidative resolution of phenylhexahydrocyclopenta[*b*]phosphole with menthyl bromoacetate. The corresponding enantiopure phenylhexahydrocyclopenta[*b*]phosphole oxide was obtained after purification and hydrolysis of the corresponding diastereomeric phosphonium salt.[11,27]

The resolution of P-stereogenic compounds may be elaborated *via* the formation of diastereomeric salts if the corresponding organophosphorus compound is a phosphonium salt or it contains an acidic or basic functional group. Ostrogovich and Kerek elaborated the resolution of 1-(4-diethylaminophenyl)-2-phospholene oxide by forming diastereomeric salts with camphorsulfonic acid.[28] Kobayashi *et al.* described the optically active borane complex of 1-phenylphospholane-2-carboxylic acid prepared *via* optical resolution by applying quinine.[29] For the preparation of optically active phosphonium salts, the silver salt of dibenzoyl-tartaric acid, camphorsulfonic acid or menthoxy-acetic acid finds wide-spread application. Using these resolving agents, the resolution of a few P-stereogenic phosphonium salts bearing a heterocyclic moiety is elaborated (Fig. 1).[30–35]

Organophosphorus compounds having neither acidic nor basic functional groups may be resolved *via* the formation of diastereomeric molecular complexes. *O*,*O*′-Dibenzoyl-(2*R*,3*R*)-tartaric acid was suitable for the preparation of optically active phosphine oxides,[36–43] among which a few P-heterocyclic and P-stereogenic examples can be found, such as 1-phenyl-2-phospholene oxide,[11] DuanPhos oxide[44] and a bis-benzophosphetane oxide (Fig. 2).[45]

Exploiting the coordination ability of phosphines to transition metals, the palladium complex of phenylethylamine or naphthylethylamine is a generally applicable resolving agent for P-stereogenic phosphines *via* the formation of the corresponding diastereomeric coordination complex. In this manner several mono- or bis-P-heterocyclic phosphines could be separated into their enantiomers (Fig. 3).[46–54]

Herein, our aim was to summarize the results obtained in the field of the resolution methods developed by our research group for the preparation of optically active five- and six-membered P-heterocyclic phosphine oxides, phosphinates and a few other derivatives (**1–8**) by applying TADDOL derivatives [(−)-**9** and (−)-**10**] or the Ca^{2+}-salts of tartaric acid derivatives [(−)-**11** and (−)-**12**] as the resolving agents (Fig. 4).

2. The optical resolution of P-heterocycles

2.1. Optical resolution of five- and six-membered P-heterocycles (1–8) with TADDOL derivatives [(−)-9 and (−)-10]

2.1.1. Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (1a–j) with TADDOL [(−)-9]. First, our aim was to elaborate the enantiomeric separation of 1-aryl- and 1-alkyl-3-

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Viktória Ujj was born in Vác (Hungary) in 1983. She graduated as a chemical engineer at the Budapest University of Technology and Economics in 2006, and obtained her PhD with her thesis on the resolution of P-chiral P-heterocycles in 2010. Then, she started working in the field of pharmaceutical research. Since 2012, she has been working as a senior research scientist at ComInnex Inc., focusing on the syntheses of heterocyclic organic compounds.

Mátyás Czugler

Mátyás Czugler was born in Tárnok (Hungary) in 1948, and graduated at the Technical University of Budapest as a chemical engineer in 1972. His research in crystallography involves mainly solid state description of organic supramolecular ensembles, often with biological importance. His DSc was defended in 2006. He led the Crystallography Department (Hungarian Academy) as academic research professor in the period of 2005–2013. In 2007, he was appointed as Adjunct Professor at TUB. His track record shows over 150 publications and experience in crystallizing and solving non-routine crystal structures.

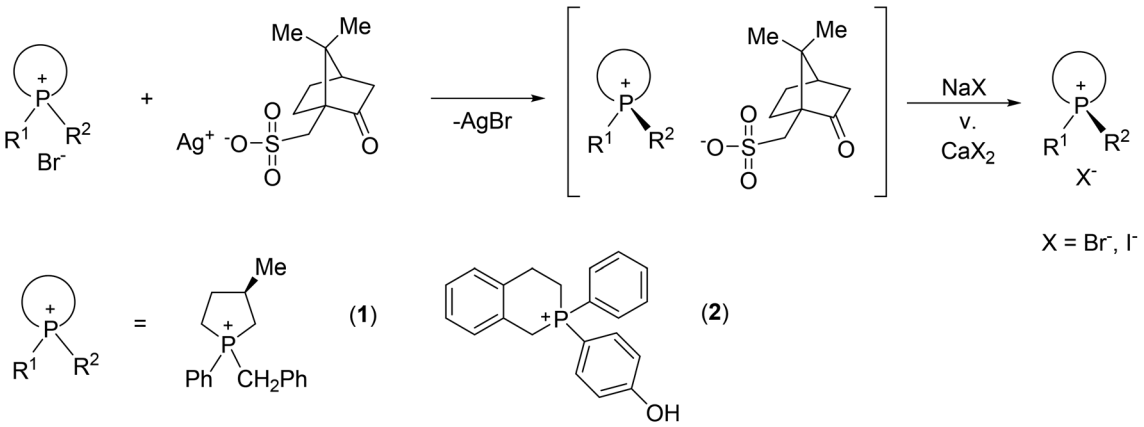


Fig. 1 Resolution of P-heterocyclic phosphonium salts using the silver salt of camphorsulfonic acid.

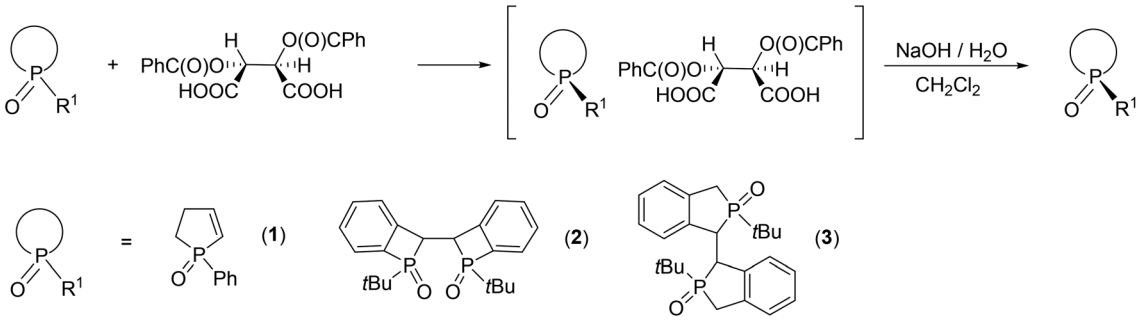


Fig. 2 Resolution of P-heterocyclic phosphine oxides using *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid.

methyl-3-phospholene 1-oxides (**1a–j**). As the cyclic phosphine oxides (**1a–j**) have neither acidic nor basic functional groups, we anticipated that the resolution methods based on the formation of diastereomeric molecular complexes were worth trying. In the initial screening study of the resolving agents, TADDOL [(−)-**9**] and spiro-TADDOL [(−)-**10**] seemed to be promising for the enantiomeric separation of racemic 3-phospholene oxides **1a–j**. Previously, TADDOL derivatives [(−)-**9** and (−)-**10**] were found to be excellent chiral host molecules in the resolution of racemates containing H-acceptor functional groups. To the best of our knowledge, this was the first case, when the TADDOL derivatives [(−)-**9** and (−)-**10**] were used as the resolving agents to prepare the enantiomers of P-stereogenic phosphine oxides.[55]

It was the first breakthrough, when TADDOL (−)-**9** was applied in the resolution of 1-aryl- and alkyl-3-methyl-3-phospholene 1-oxide (**1a–j**).[56] According to our resolution method (Scheme 1), the racemic phospholene oxide (**1a–j**) and half equivalent of TADDOL [(−)-**9**] were dissolved in ethyl acetate. Hexane was then added to the solution to promote the precipitation of the corresponding diastereomeric molecular associates. It was found that the maximum resolving capability could be obtained by using the "half equivalent method".[57–60] The diastereomeric complexes formed were further purified by two recrystallizations, and the 3-phospholene oxide (**1a–j**) enantiomers were then recovered from the corresponding diastereomers by flash column chromatography (Scheme 1). In all

Elemér Fogassy

Elemér Fogassy was born in 1934 in Budapest, and graduated at the Technical University of Budapest (Hungary) as a Chemical Engineer in 1957. He earned his PhD in 1974, and defended his DSc degree in 1986. He was working for pharmaceutical factories in the period of 1957–64, then he joined the Department of Organic Chemical Technology, TUB, and was appointed as Professor in 1987. From 2010, he is an Emeritus Professor. He is the author or co-author of 315 papers/patents in the subject of optical resolution. He received the Academic Patent Award and the Price for Pharmaceutical Research.

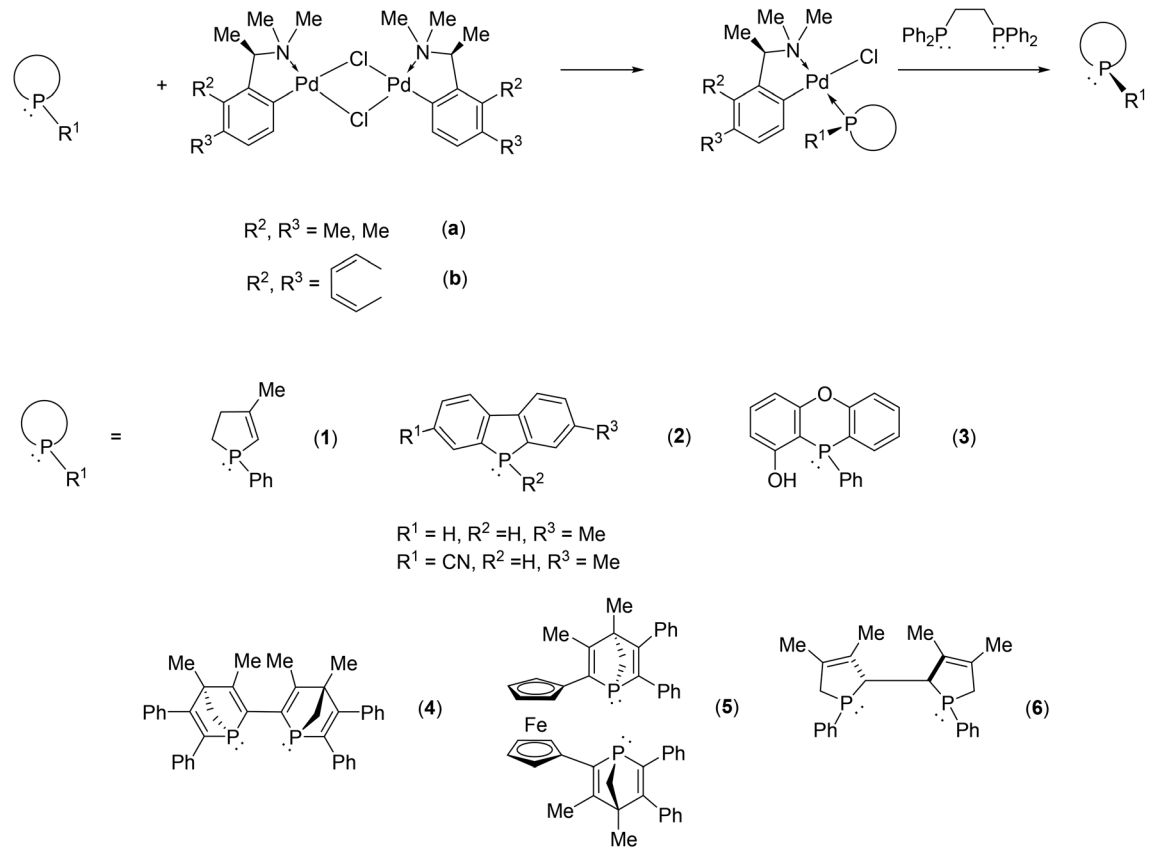


Fig. 3 Resolution of P-heterocyclic phosphines using the palladium complex of phenylethylamine or naphthylethylamine.

instances, the enantiomeric purity of the given enantiomeric mixtures was determined by HPLC or GC on chiral stationary phases. The selected results are summarized in Table 1.

Applying TADDOL [(−)-**9**] as the resolving agent for the enantiomeric separation of 3-phospholene oxides (**1**), the corresponding enantiomeric excess values fell in the range of 6–97%, whereas the resolving capability values (*S*) were 0.05–0.43 (Table 1).

It was observed that the ethyl derivative (**1e**) could be resolved with a lower efficiency (*S*) than the propyl derivative (**1f**) (compare Table 1, entries 5 and 6). It was also found that the enantiomers of 3-phospholene oxides bearing a branched substituent (**1g**, **1i** and **1j**) could be prepared with lower resolving capability (*S*) than the derivatives having the normal alkyl chain (**1e**, **1f** and **1h**) (compare Table 1, entries 7, 9 and 10 with 5, 6 and 8). On the one hand, these results reveal that an adequate length of the alkyl chain is necessary for the interactions being responsible for the enantiomeric recognition between the host [(−)-**9**] and the guest molecules (**1e–j**). On the other hand, the results also show that the increasing steric bulk of the alkyl chain may hinder or weaken the non-bonding interactions between the corresponding 3-phospholene oxide (**1e–j**) and the TADDOL [(−)-**9**] molecule that leads to less efficient enantiomeric separation.

In the case of phenyl-3-phospholene oxide (**1a**), it was observed that kinetic or thermodynamic effects did not affect significantly the resolving capability values obtained.[61] It was found that (*S*)-aryl-3-phospholene oxides (**1a–d**) could be prepared with TADDOL [(−)-**9**] (Table 1, entries 1–4). However, among the alkyl derivatives (**1e–j**), the TADDOL [(−)-**9**] resolving agent preferred diastereomeric complex formation with the (*R*)-enantiomers in all but one instance, and the only exception was the butyl-3-phospholene oxide (**1h**) (Table 1, entries 5–10). The ^{1}H NMR spectra of the corresponding diastereomers revealed that the ratio of the corresponding 3-phospholene oxide (**1a–g** and **1i**) and TADDOL [(−)-**9**] was 1 : 1 in most instances (Table 1, entries 1–7 and 9).

2.1.2. Resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (4a–d) with TADDOL [(−)-9]. Beside the resolution of five-membered cyclic phosphine oxides (**1a–j**), TADDOL [(−)-**9**] was also suitable for the resolution of the corresponding phosphinate analogues, namely alkoxy-3-phospholene oxides (**4a–d**). The resolution experiments were carried out as described in section 2.1.1 (Scheme 2). The selected results are summarized in Table 2.

The corresponding optically active alkoxy-3-phospholene oxides (**4a–d**) were prepared with an ee above 99% in three out of four instances (Table 2, entries 2–4). Similarly to the results obtained in the case of the alkyl derivatives (**1e–j**), it was observed that the length and the bulkiness of the alkoxy chain influenced the overall efficiency of the resolution (*S*). The enantiomeric excess and the resolving capability (*S*) values

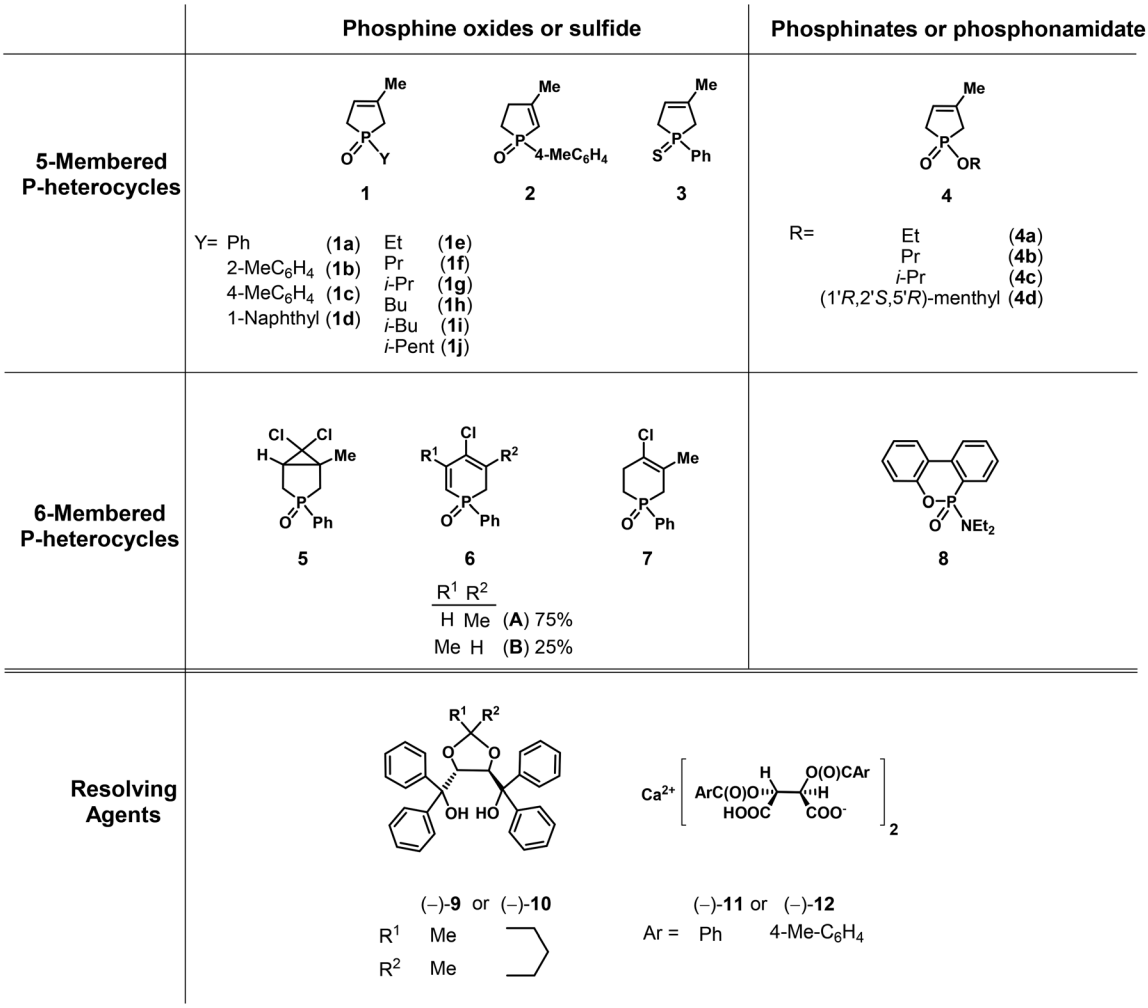
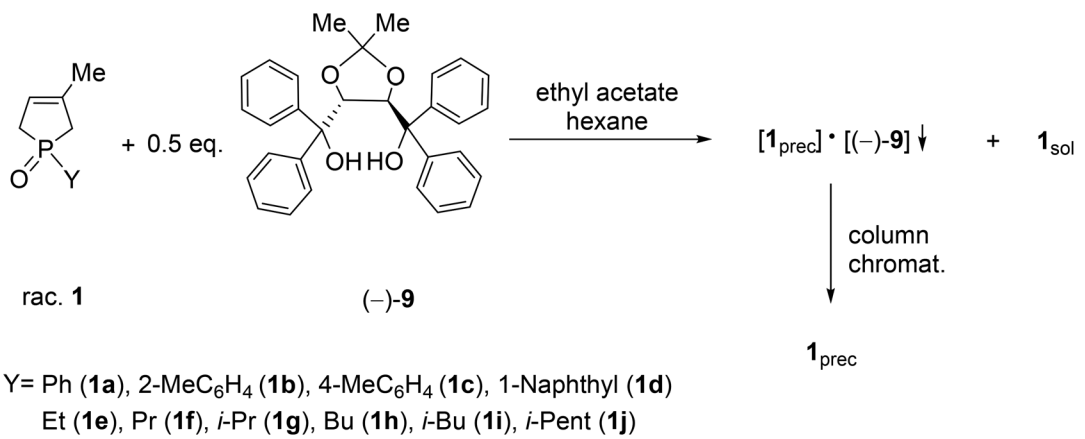


Fig. 4 The racemic compounds (**1–8**) and the resolving agents [(–)-**9** and (–)-**12**] included in this review.



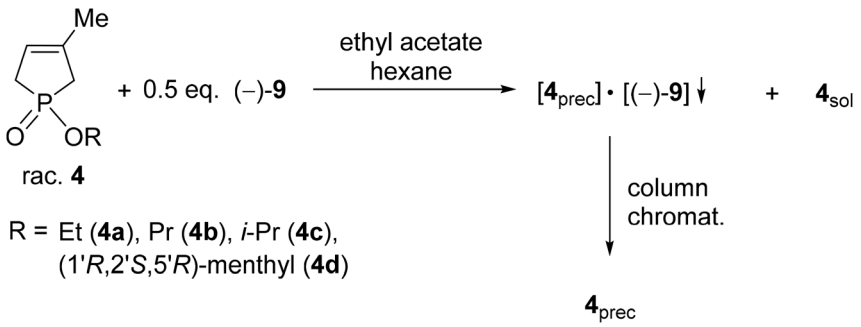
Scheme 1 General protocol for the resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with TADDOL [(–)-**9**].

were lower in the case of the ethoxy derivative (**4a**) than in that of the propoxy derivative (**4b**) (Table 2, entries 1 and 2). The (*R*)-i-propoxy-3-methyl-3-phospholene oxide [(*R*)-**4c**] was prepared with lower resolving capability than the propoxy derivative (**4b**) despite the fact that the corresponding enantiomeric excess values were identical (Table 2, entries 2 and 3).

Table 1 Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with 0.5 equiv. of TADDOL [(–)-**9**] in a mixture of ethyl acetate and hexane

Entry	Y	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	$S^{a,c}$ (–)	Abs. config.[d]	Ref.
1	Ph (**1a**)	(**1a**)·[(–)-**9**]	97	44	0.43	(*S*)	56, 61
2	2-MeC_6H_4 (**1b**)	(**1b**)·[(–)-**9**]	57	49	0.28	(*S*)	61
3	4-MeC_6H_4 (**1c**)	(**1c**)·[(–)-**9**]	69	42	0.29	(*S*)	61
4	1-Naphthyl (**1d**)	(**1d**)·[(–)-**9**]	70	42	0.29	(*S*)	61
5	Et (**1e**)	(**1e**)·[(–)-**9**]	24	36	0.09	(*R*)	61
6	Pr (**1f**)	(**1f**)·[(–)-**9**]	95	35	0.33	(*R*)	61
7	i-Pr (**1g**)	(**1g**)·[(–)-**9**]	6	81	0.05	(*R*)	62
8[e]	Bu (**1h**)	(**1h**)·[(–)-**9**]$_2$[g]	74	23	0.17	(*S*)	63
9	i-Bu (**1i**)	(**1i**)·[(–)-**9**]	35	14	0.05	(*R*)	64
10[f]	i-Pent (**1j**)	(**1j**)$_3$·[(–)-**9**]$_2$[g]	18	38	0.07	(*R*)	65

[a] Enantiomeric excess, yield and resolving capability obtained after recrystallizations. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] Determined by X-ray crystallography or CD spectroscopy. [e] 1 equiv. of TADDOL [(–)-**9**] was used. [f] 0.33 equiv. of TADDOL [(–)-**9**] was used. [g] The composition of the diastereomer was different from that of the predominant associate shown in Scheme 1.



Scheme 2 General procedure for the resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–d**) with TADDOL [(–)-**9**].

Table 2 Resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–d**) with 0.5 equiv. of TADDOL [(–)-**9**] in a mixture of ethyl acetate and hexane

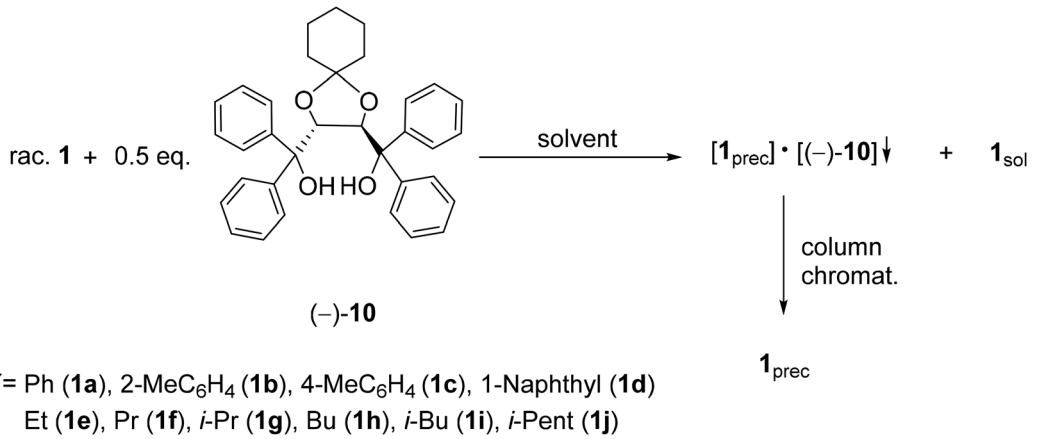
Entry	R	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	$S^{a,c}$ (–)	Abs. config.[d]	Ref.
1	Et (**4a**)	(**4a**)·[(–)-**9**]	44	25	0.11	(*S*)	61
2	Pr (**4b**)	(**4b**)·[(–)-**9**]	>99	38	0.38	(*R*)	67
3	i-Pr (**4c**)	(**4c**)·[(–)-**9**]	>99	5	0.05	(*R*)	61
4	Men (**4d**)	(**4d**)·[(–)-**9**]	>99	25	0.25	(–)[e]	68

[a] Enantiomeric excess, yield and resolving capability obtained after recrystallizations. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] Determined by X-ray crystallography or CD spectroscopy. [e] The sign of optical rotation. The absolute P-configuration was not determined.

Besides the phosphinates (**4a–c**) bearing only one asymmetric center, the 1 : 1 diastereomeric mixture of 1-[(1′*R*,2′*S*,5′*R*)-(–)-menthyloxy]-3-methyl-3-phospholene 1-oxide (**4d**) could also be separated using TADDOL [(–)-**9**], and the (–)-**4d** diastereomer was obtained with a diastereomeric purity above 99% (Table 2, entry 4). Interestingly, the separation of the two diastereomers of **4d** was not successful under achiral conditions (*e.g.* column chromatography or crystallization).

2.1.3. Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (1a–j) with spiro-TADDOL [(–)-10]. Inspired by the initial success achieved with TADDOL (–)-**9**, its analogue, spiro-TADDOL [(–)-**10**] was also used in our studies to prepare the enantiomers of 1-aryl- and 1-alkyl-3-phospholene oxides (**1a–j**). In these instances, the resolution experiments were carried out as described for TADDOL [(–)-**9**], and the mixture of ethyl acetate and hexane was the solvent used in each study (Scheme 3). The selected results are summarized in Table 3.

In all but one instance, spiro-TADDOL [(–)-**10**] was also found to be an applicable resolving agent for the preparation of optically active aryl- and alkyl-3-phospholene oxides (**1a–i**) with an ee of 25–99%, and resolving capability values of 0.10–0.55 (Table 3, entries 1–9). The i-pentyl-3-phospholene



Scheme 3 General route for the resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with spiro-TADDOL [(−)-**10**].

Table 3 Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with 0.5 equiv. of spiro-TADDOL [(−)-**10**] in a mixture of ethyl acetate and hexane

Entry	Y	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	$S^{a,c}$ (−)	Abs. config.[d]	Ref.
1	Ph (**1a**)	(**1a**)·[(−)-**10**]	>99	29	0.29	(*S*)	56, 61
2	2-MeC_6H_4 (**1b**)	(**1b**)·[(−)-**10**]	>99	41	0.41	(*S*)	61
3	4-MeC_6H_4 (**1c**)	(**1c**)·[(−)-**10**]	>99	30	0.30	(*S*)	61
4	1-Naphthyl (**1d**)	(**1d**)·[(−)-**10**]	>99	55	0.55	(*S*)	61
5	Et (**1e**)	(**1e**)·[(−)-**10**]	58	45	0.26	(*R*)	61
6[e]	Pr (**1f**)	(**1f**)·[(−)-**10**]$_2$ [f]	89	30	0.27	(*S*)	61
7	i-Pr (**1g**)	(**1g**)·[(−)-**10**]	64	60	0.39	(*R*)	62
8[e]	Bu (**1h**)	(**1h**)·[(−)-**10**]$_2$ [f]	95	52	0.49	(*S*)	63
9	i-Bu (**1i**)	(**1i**)·[(−)-**10**]	25	39	0.10	(*S*)	64
10	i-Pent (**1j**)	(**1j**)$_2$·[(−)-**10**]	Rac.	—	—	—	65

[a] Enantiomeric excess, yield and resolving capability obtained after recrystallizations. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] Determined by X-ray crystallography or CD spectroscopy. [e] 1 equiv. of spiro-TADDOL [(−)-**10**] was used. [f] The composition of the diastereomer was different from that of the predominant associate shown in Scheme 3.

oxide (**1j**) was the only five-membered P-heterocycle, where no enantiomeric discrimination could be observed (Table 3, entry 10).

The direct comparison of the results obtained with TADDOL [(−)-**9**] or spiro-TADDOL [(−)-**10**] in a mixture of ethyl acetate and hexane shows that in almost all instances the application of spiro-TADDOL [(−)-**10**] resulted in better enantiomeric separation of the corresponding 3-phospholene oxide (**1a–i**) leading to higher resolving capability values (compare Tables 1 and 3). Considering the resolving capability values, the phenyl- and propyl-3-phospholene oxides (**1a** and **1f**) were the exceptions, where the application of TADDOL [(−)-**9**] was more beneficial than that of spiro-TADDOL [(−)-**10**] (compare Table 1, entry 1 with Table 3, entry 1 and Table 1, entry 6 with Table 3, entry 6).

In all but three instances, the composition of the diastereomers was 1 : 1 [(**1**)·(−)-**10**] similarly to the results obtained with TADDOL [(−)-**9**] (compare Tables 1 and 3). In the case of the propyl-, butyl- and the i-pentyl-3-phospholene oxides (**1f**, **1h** and **1j**) the composition of the diastereomer was different, as the given complex contained the corresponding 3-phospholene oxide (**1f**, **1h** or **1j**) and spiro-TADDOL [(−)-**10**] in a ratio of 1 : 2 or 2 : 1 (Table 3, entries 6, 8 and 10).

According to our expectation, in most instances both TADDOL derivatives [(−)-**9** or (−)-**10**] preferred diastereomeric complex formation with the same enantiomer of the corresponding aryl- or alkyl-3-phospholene oxide (**1a–e**, **1g**, **1h** and **1j**). However, in the case of the propyl- and i-butyl derivatives (**1f** and **1i**), despite the same absolute configuration and chiral environment of the resolving agents [(−)-**9** and (−)-**10**], different 3-phospholene oxide enantiomers could be prepared with TADDOL [(−)-**9**] or spiro-TADDOL [(−)-**10**] (compare Tables 1 and 3).

In this series of experiments, it was also observed that the sterically demanding alkyl chains on the 3-phospholene moiety (**1i** or **1j**) decreased the overall efficiency of the resolution with TADDOL derivatives [(−)-**9** or (−)-**10**] (Table 3, entries 9 and 10).

2.1.4. Solvent dependent resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (1a–j) with spiro-TADDOL [(−)-10]. In the above instances (Tables 1–3), resolution experiments were carried out with TADDOL derivatives [(−)-**9** or (−)-**10**] in a mixture of ethyl acetate and hexane. Another aim of ours was to investigate if the nature of the solvents influenced enantiomeric separation of 1-aryl- and 1-alkyl-3-phospholene oxides (**1a–j**).

First, the resolution of phenyl-3-phospholene oxide (**1a**) with spiro-TADDOL [(−)-**10**] was carried out in ethyl acetate and hexane as described above, but 2 equivalents of a given solvent (*i.e.* acetone, DMSO, DMF, acetonitrile, acetic acid, water, ethanol, methyl ethyl ketone or methyl isobutyl ketone) were also added to the reaction mixture. It was found that additives with a dielectric constant between 5 and 40 improved the resolution efficiency. Whereas, the resolving capability values decreased significantly, when solvents having a dielectric constant above 40 (*e.g.* DMSO or water) were added to the reaction mixture.[69]

This correlation observed between the dielectric constant of the solvent and the efficiency of the resolution led us to the conclusion that the application of H-acceptor or H-donor solvents could be beneficial for the optical resolution of 1-aryl- and 1-alkyl-3-phospholene oxides (**1a–j**) with TADDOL derivatives [(−)-**9** or (−)-**10**], as the solvents may influence the coordination sphere of the TADDOL derivatives [(−)-**9** or (−)-**10**] which subsequently affect the enantiomeric recognition and resolving capability. This assumption was also supported by the fact that in a few instances acetone was incorporated into the molecular complex, when crystals were grown using acetone.[56]

Motivated by these results, the resolution of a few 3-phospholene oxides (**1a–f**) was carried out with spiro-TADDOL [(−)-**10**] in acetone or in a mixture of acetone and hexane. In other experiments (**1g–j**), alcohols were used as solvents (Scheme 3). The selected results are summarized in Table 4.

In 7 out of 11 cases (Table 4, entries 1, 2, 5, 6, 7, 10 and 11), the application of the above mentioned H-acceptor or H-donor solvents was beneficial as the resolving capability values were higher or showed parity with the results obtained in a mixture of ethyl acetate and hexane (compare Tables 3 and 4). One of the most remarkable examples was the phenyl-3-phospholene oxide (**1a**), where the resolving capability values changed from 0.29 to 0.81 with the solvent change (compare Table 3, entry 1 and Table 4, entry 1). Moreover, the i-pentyl-3-phospholene oxide (**1j**) could be prepared with spiro-TADDOL [(−)-**10**] in i-propanol with an ee above 99%, whereas no enantiomeric separation was observed in a mixture of ethyl acetate and hexane (compare Table 3, entry 10 and Table 4, entry 11). Another intriguing observation was that in the case of the ethyl-, i-propyl-, butyl- and i-butyl derivatives (**1e** and **1g–i**) the solvent influenced which 3-phospholene oxide enantiomer was incorporated into the corresponding diastereomeric associate. In this manner, both antipodes of the corresponding 3-phospholene oxide (**1e** and **1g–i**) could be prepared with the same resolving agent that was spiro-TADDOL [(−)-**10**] simply by changing the solvent (compare Table 3, entries 5, 7, 8, and 9 with Table 4, entries 5, 7, 8, 9 and 10). The underlying phenomena of this solvent dependent enantioselection may be that the solubility of the corresponding diastereomeric complexes is different in various solvents, or the corresponding solvents incorporated into the diastereomeric associates change the mode of binding of the host [(−)-**10**] and guest molecules (**1e** and **1g–i**).

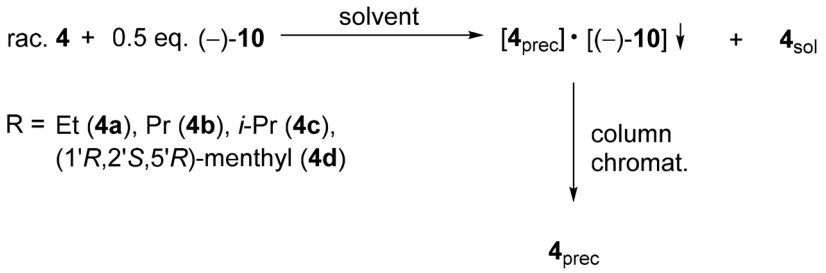
In a few cases (**1e–j**), a change in the solvent influenced the composition of the diastereomers, and diastereomeric complexes having a composition of (**1**)·[(−)-**10**]$_2$ were formed in all, but one instance contrary to the previously prevalent diastereomeric composition of (**1**)·[(−)-**10**] (compare Table 3, entries 5–10 and Table 4, entries 5–11).

2.1.5. Resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (4a–d) with spiro-TADDOL [(−)-10]. Besides the aryl- and alkyl-3-phospholene oxides (**1a–j**), their phosphinate analogues (**4a–d**) were also the subject of our systematic resolution studies with spiro-TADDOL [(−)-**10**]. Similarly to the cases described in sections 2.1.3 and 2.1.4, the resolution experi-

Table 4 Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with 0.5 equiv. of spiro-TADDOL [(−)-**10**] in various solvents

Entry	Y	Solvent	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	$S^{a,c}$ (−)	Abs. config.[d]	Ref.
1	Ph (**1a**)	Acetone	(**1a**)·[(−)-**10**]	97	83	0.81	(*S*)	69
2	2-MeC_6H_4 (**1b**)	Acetone	(**1b**)·[(−)-**10**]	88	48	0.42	(*S*)	69
3	4-MeC_6H_4 (**1c**)	Acetone–hexane	(**1c**)·[(−)-**10**]	97	18	0.18	(*S*)	70
4	1-Naphthyl (**1d**)	Acetone	(**1d**)·[(−)-**10**]	71	32	0.23	(*S*)	69
5[e]	Et (**1e**)	Acetone	(**1e**)·[(−)-**10**]$_2$[g]	55	41	0.23	(*S*)	70
6[e,f]	Pr (**1f**)	Acetone	(**1f**)·[(−)-**10**]$_2$[g]	91	66	0.60	(*S*)	70
7	i-Pr (**1g**)	EtOH	(**1g**)·[(−)-**10**]$_2$[g]	95	50	0.47	(*S*)	62
8[f]	Bu (**1h**)	EtOH	(**1h**)·[(−)-**10**]$_2$[g]	70	17	0.12	(*R*)	63
9[f]	Bu (**1h**)	i-PrOH	(**1h**)·[(−)-**10**]$_2$[g]	78	43	0.33	(*S*)	63
10[f]	i-Bu (**1i**)	EtOH	(**1i**)·[(−)-**10**]$_2$[g]	96	26	0.25	(*R*)	64
11[f]	i-Pent (**1j**)	i-PrOH	(**1j**)·[(−)-**10**]$_2$[g]	>99	16	0.16	(*R*)	65

[a] Enantiomeric excess, yield and resolving capability obtained after recrystallizations. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] Determined by X-ray crystallography or CD spectroscopy. [e] 1 mol of acetone was incorporated into the diastereomer. [f] 1 equiv. of spiro-TADDOL [(−)-**10**] was used. [g] The composition of the diastereomer was different from that of the predominant associate shown in Scheme 3.



Scheme 4 General method for the resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–d**) with spiro-TADDOL [(–)-**10**].

Table 5 Resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–d**) with 0.5 equiv. of spiro-TADDOL [(–)-**10**] in various solvents

Entry	R	Solvent	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	$S^{a,c}$ (–)	Abs. config.[d]	Ref.
1	Et (**4a**)	EtOAc–hexane	(**4a**)·[(–)-**10**]	95	50	0.48	(*R*)	61
2	Et (**4a**)	acetone	(**4a**)·[(–)-**10**]$_2$[g]	58	38	0.22	(*R*)	70
3	Pr (**4b**)	EtOAc–hexane	(**4b**)·[(–)-**10**]	93	43	0.40	(*R*)	67
4[e]	Pr (**4b**)	EtOH	(**4b**)·[(–)-**10**]$_2$[g]	93	15	0.14	(*S*)	67
5	i-Pr (**4c**)	EtOAc–hexane	(**4c**)·[(–)-**10**]	>99	37	0.37	(*R*)	61
6	i-Pr (**4c**)	acetone–hexane	(**4c**)·[(–)-**10**]	>99	56	0.56	(*R*)	69
7	Men (**4d**)	EtOAc–hexane	(**4d**)·[(–)-**10**]	90	45	0.41	(–)[f]	68

[a] Enantiomeric excess, yield and resolving capability obtained after recrystallizations. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] Determined by X-ray crystallography or CD spectroscopy. [e] 1 equiv. of spiro-TADDOL [(–)-**10**] was used. [f] The sign of optical rotation. The absolute P-configuration was not determined. [g] The composition of the diastereomer was different from that of the predominant associate shown in Scheme 4.

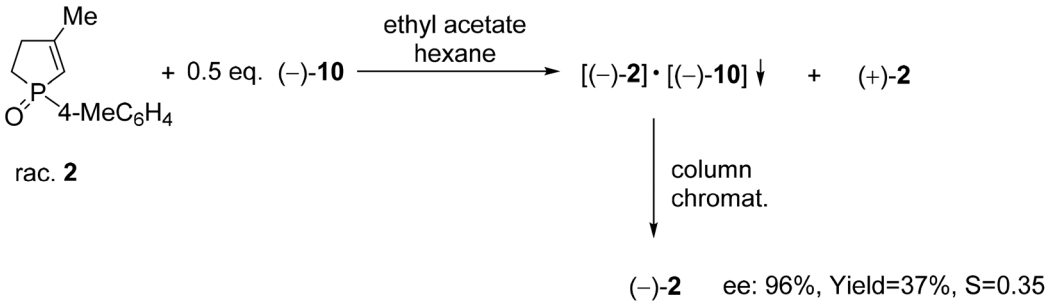
ments were carried out in a few solvents or solvent mixtures according to the procedure described in section 2.1.3 (Scheme 4). The selected results are summarized in Table 5.

In the case of the alkoxy-3-phospholene oxides (**4a–d**), the enantiomeric excess values were in the range of 58–99%, whereas the corresponding resolving capability values were 0.14–0.56 (Table 5). The direct comparison of the result obtained with either spiro-TADDOL [(–)-**10**] or TADDOL [(–)-**9**] in a mixture of ethyl acetate and hexane revealed that the application of spiro-TADDOL [(–)-**10**] was more advantageous considering the resolving capability values (compare Table 2, entries 1–4 and Table 5, entries 1, 3, 5 and 7). Moreover, the TADDOL derivatives [(–)-**9** or (–)-**10**] formed diastereomeric molecular complexes with the same antipodes of the corresponding alkoxy-3-phospholene oxides (**4b–d**) in all but one instance. The exception was the ethoxy derivative (**4a**), in which case different antipodes of **4a** could be prepared with TADDOL [(–)-**9** or spiro-TADDOL [(–)-**10**] (compare Table 2, entry 1 and Table 5, entry 1) similarly to the case described for the two alkyl-3-phospholene oxides (**1f** and **1i**).

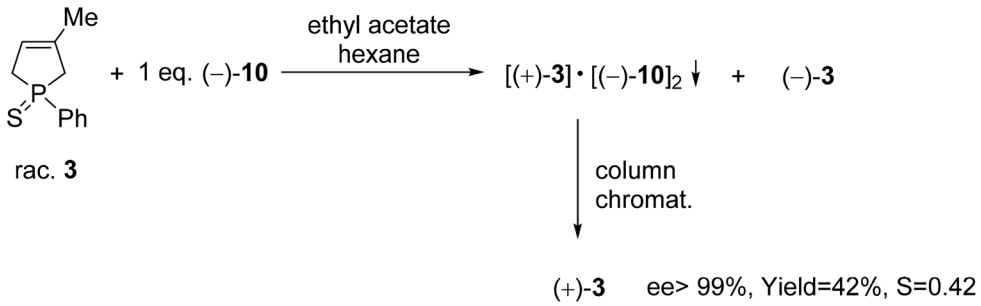
In two out of three cases, the solvents other than the mixture of ethyl acetate and hexane lowered the overall efficiency (S) of the resolution of the alkoxy-3-phospholene oxides (**4a** and **4b**) (compare Table 5, entry 1 with 2 and entry 3 with 4). Moreover, in the case of the propoxy derivative (**4b**), the solvent influenced the enantiopreference of spiro-TADDOL [(–)-**10**], and both antipodes of **4b** could be prepared with the same resolving agent in different solvents (Table 5, entries 3 and 4).

2.1.6. Resolution of a 3-methyl-2-phospholene oxide (2), a 3-methyl-3-phospholene sulfide (3), six-membered P-heterocyclic phosphine oxides (5–7) and a six-membered phosphonamidate (8) with TADDOL derivatives [(–)-9 and (–)-10]. After thorough investigation of the resolution of 1-aryl-, 1-alkyl- and 1-alkoxy-3-phospholene oxides (**1** and **4**) with TADDOL and spiro-TADDOL [(–)-**9** and (–)-**10**], we were interested in investigating if these resolution methods were of more general value, so the enantiomeric separation of other five- and six-membered P-heterocyclic phosphine oxides, a phosphine sulfide and a phosphonic ester-amide (**2**, **3** and **5–8**) was also studied. The resolution of the corresponding racemic compound (**2**, **3** and **5–8**) was carried out according to the method described in section 2.1.1. The results are summarized in Schemes 5–10.

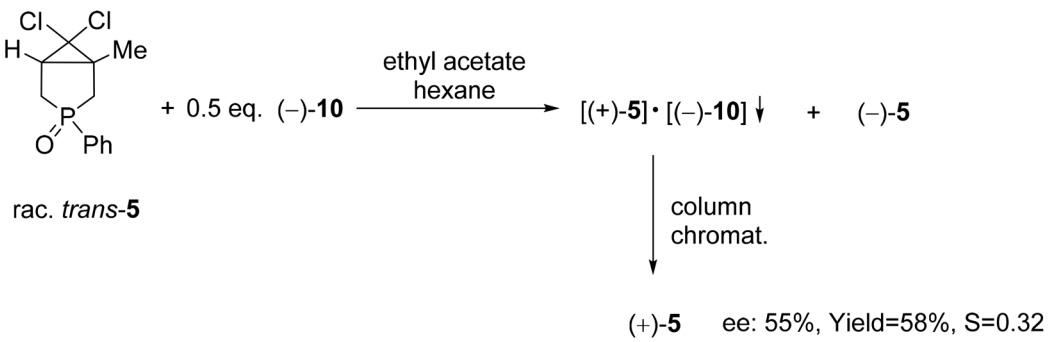
The resolution procedure applying spiro-TADDOL [(–)-**10**] as the resolving agent was also suitable for the enantiomeric separation of 1-(4-methylphenyl)-3-methyl-2-phospholene 1-oxide (**2**). The (–)-**2** enantiomer was obtained with an ee of 96% and a resolving capability of 0.35 which is in good agreement with the results obtained in the case of the corresponding 3-phospholene oxide analogue (**1c**) (compare Scheme 5 and Table 3, entry 3). This result suggests that the position of the double-bond in the phospholene moiety does not affect significantly the overall efficiency of resolution with spiro-TADDOL [(–)-**10**].[70]



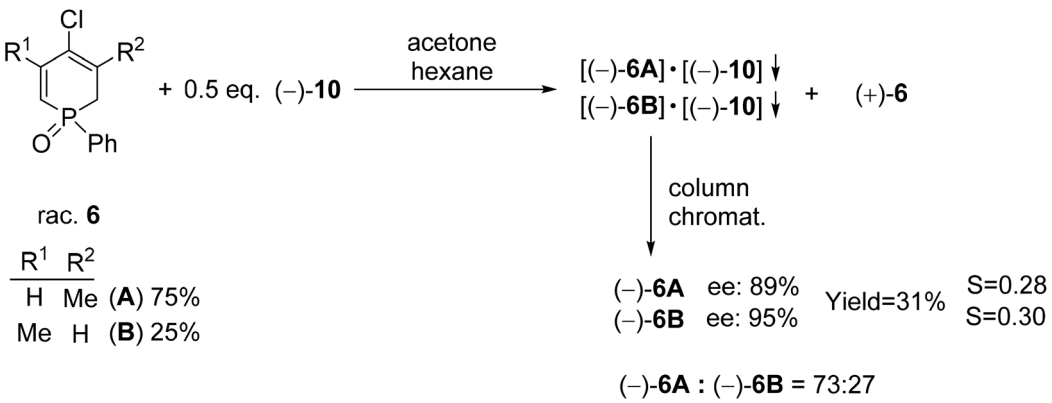
Scheme 5 The resolution of 1-(4-methylphenyl)-3-methyl-2-phospholene 1-oxide (**2**) with spiro-TADDOL [(–)-**10**].



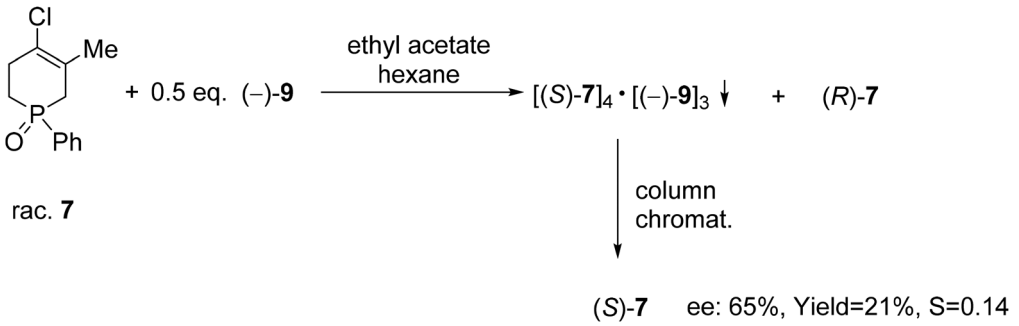
Scheme 6 The resolution of 1-phenyl-3-methyl-3-phospholene sulfide (**3**) with spiro-TADDOL [(–)-**10**].



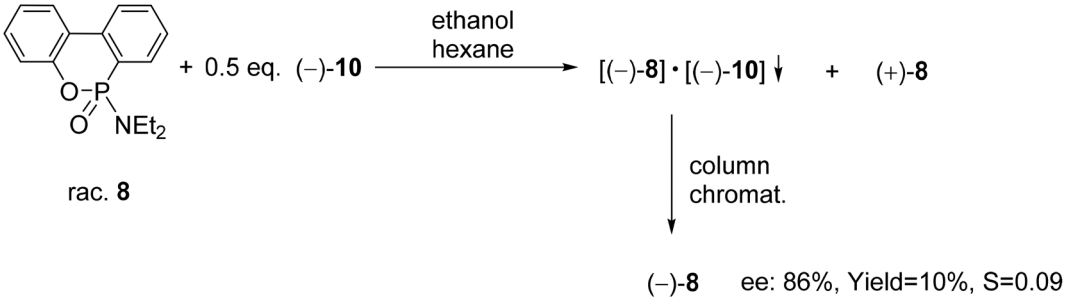
Scheme 7 The resolution of 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**5**) with spiro-TADDOL [(–)-**10**].



Scheme 8 The resolution of 4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxide (**6**) with spiro-TADDOL [(–)-**10**].



Scheme 9 The resolution of 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**7**) with TADDOL [(–)-**9**].



Scheme 10 The resolution of 6-diethylamino-dibenzo[*c*,*e*][5,6]oxaphosphorine 6-oxide (**8**) with spiro-TADDOL [(–)-**10**].

The (+)-1-phenyl-3-methyl-3-phospholene sulfide [(+)-**3**] was also prepared by resolution with spiro-TADDOL [(–)-**10**], the ee was above 99% in this case (Scheme 6). The crude product of the phospholene sulfide (**3**) was used as the starting material in this resolution experiment. Interestingly, less efficient enantioseparation of phosphine sulfide **3** was achieved, when purified phenyl-3-phospholene sulfide (**3**) was used as the racemic starting material.[61]

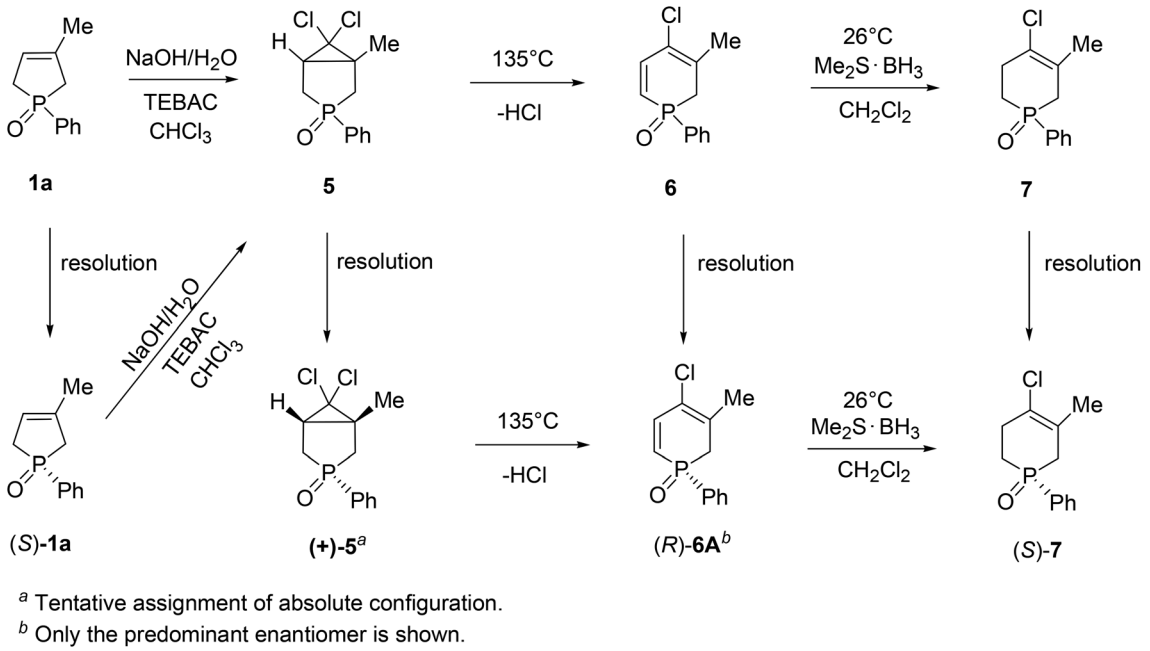
The wide applicability of TADDOL derivatives [(–)-**9** and (–)-**10**] for the preparation of optically active five-membered phosphine oxides (**1** and **2**), a sulfide (**3**) and phosphinates (**4**) motivated us to extend this method to six-membered derivatives as well, such as phosphine oxides (**5–7**) and a phosphonic ester-amide (**8**). Among the six-membered P-heterocyclic phosphine oxides, the (+)-6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide [(+)-**5**] bearing the dichlorocyclopropane ring and the P═O function in the position *trans* disposition could be prepared with an ee of 55% using spiro-TADDOL [(–)-**10**] as the resolving agent (Scheme 7).[71]

Racemic 4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxide (**6**) comprised a 3 : 1 mixture of two double-bond isomers (**6A** and **6B**) that could not be separated. Therefore, the mixture of dihydrophosphinine oxides **6A** and **6B** was resolved using spiro-TADDOL [(–)-**10**] in a mixture of acetone–hexane. The ratio of the double-bond isomers (**6A** and **6B**) did not change significantly during the resolution procedure. However, the enantiomeric excess of **6A** and **6B** was slightly different (89% and 95%, respectively) (Scheme 8).[72]

TADDOL [(–)-**9**] was also suitable for the partial resolution of 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**7**), whereupon (*S*)-**7** was obtained with an ee of 65% (Scheme 9).[71] Recently, X-ray crystallographic and CD spectroscopic studies have allowed us to assign (*S*) absolute configuration to the (–)-4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide enantiomer [(–)-**7**].[73]

A six-membered phosphonic ester-amide, the 6-diethylamino-dibenzo[*c*,*e*][5,6]oxaphosphorine 6-oxide (**8**) was partially resolved with spiro-TADDOL [(–)-**10**], and as a result, (–)-**8** was obtained with an ee of 86% (Scheme 10).[70]

Besides the systematic resolution experiments of the six-membered heterocyclic phosphine oxides (**5–7**) with TADDOL derivatives (–)-**9** or (–)-**10**, we investigated the stereochemical outcome of the 3-methyl-1-phenyl-3-phospholene 1-oxide (**1a**) → 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]-hexane 3-oxide (**5**) → 4-chloro-1-phenyl-1,2-dihydrophosphinine 1-oxide (**6**) → 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**7**) reaction sequence described earlier by our research group.[74,75] It was proven that the dichlorocarbene addition on the double-bond of phenyl-3-phospholene oxide (**1a**) involved racemization on the P-stereogenic center. However, the thermolytic ring opening of 3-phosphabicyclo[3.1.0]hexane oxide (**5**), and the selective reduction of the α,β-double bond of the 4-chloro-3-methyl-1-



[a] Tentative assignment of absolute configuration.
[b] Only the predominant enantiomer is shown.

Scheme 11 Preparation of optically active six-membered P-heterocyclic phosphine oxides (**5–7**).

phenyl-1,2-dihydrophosphinine 1-oxide (**6A**) could be accomplished without the loss of optical activity.

Knowing the stereochemical outcome of the **6A** → **7** transformation, and considering the absolute configuration of the phenyl-1,2,3,6-tetrahydrophosphinine oxide (**7**) enabled us to make an indirect assignment of (*R*) absolute configuration to the P atom of (−)-4-chloro-3-methyl-1-phenyl-1,2-dihydrophosphinine 1-oxide (**6A**) enantiomer.[71] In Scheme 11, the possible ways of preparing optically active six-membered P-heterocyclic phosphine oxides (**5–7**) are summarized.

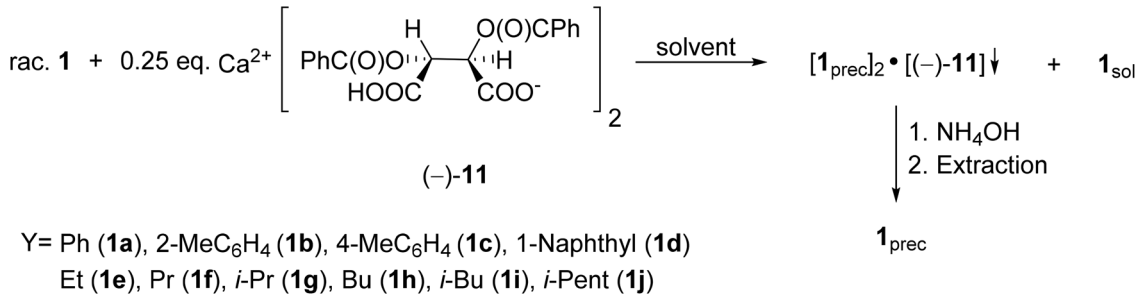
2.2. Optical resolution of five- and six-membered P-heterocycles with the calcium salts of tartaric acid derivatives

2.2.1. Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (1a–j) with calcium hydrogen *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartrate [(−)-11]. TADDOL derivatives [(−)-**9** or (−)-**10**] were applied successfully as resolving agents for a wide variety of P-heterocyclic compounds (**1–8**) as described in section 2.1. However, these chiral hosts [(−)-**9** or (−)-**10**] are rather expensive, they are not available on a large scale, and the recovery of the corresponding enantiomers (**1–8**) required column chromatography.

To overcome these disadvantages deriving from the application of TADDOL derivatives (−)-**9** or (−)-**10**, we attempted the application of cheap and readily available tartaric acid and its derivatives. Unfortunately, none of the tartaric acid derivatives tried out could form a diastereomeric molecular complex with 3-phospholene oxides (**1** or **4**). Then, we focused on the acidic calcium salts of *O*,*O*′-dibenzoyl- and *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acids [Ca(H-DBTA)$_2$ (−)-**11** and Ca(H-DPTTA)$_2$ (−)-**12**, respectively]. These resolving agents combine the advantage of the chiral recognition ability of the tartaric acid scaffold and the coordination ability of the calcium ion which is beneficial for the enantiomeric separation of α-alkoxyalcohols, α-alkoxycarboxylic acids, as well as α- and β-hydroxycarboxylic acid esters.[76–78]

The first proof of this concept was the successful resolution of 1-phenyl- and 1-(1-naphthyl)-3-methyl-3-phospholene oxides (**1a** and **1d**) with Ca(H-DBTA)$_2$ (−)-**11** or Ca(H-DPTTA)$_2$ (−)-**12**.[79] Then, these resolution methods were extended to other 1-aryl- and 1-alkyl-3-phospholene oxides (**1b**, **1c** and **1e–j**). According to our general procedure, the solutions of the given 3-phospholene oxides (**1a–j**) were added to the solution of the resolving agent (−)-**11**. The crystalline diastereomeric coordination complexes obtained were purified by digestion in the suitable solvent. Then the phospholene oxides (**1a–j**) were recovered by the treatment of the dichloromethane solution of the diastereomeric complexes with aqueous ammonia (Scheme 12). The best results obtained after optimization are summarized in Table 6.

Upon applying Ca(H-DBTA)$_2$ [(−)-**11**] as the resolving agent, the corresponding enantiomeric excess values of the aryl- and alkyl-3-phospholene oxides (**1a–j**) fell in the range of 13–99%, whereas the resolving capability values (*S*) were 0.02–0.50 (Table 6). In 5 out of 10 cases, the 3-phospholene oxides (**1a**, **1b**, **1d**, **1f** and **1j**) could be prepared with an ee above 90% (Table 6, entries 1, 2, 4, 6 and 11). It is noteworthy that the resolving capability values (*S*) obtained in the instance of the aryl-3-phospholene oxides (**1a–d**) (*S* = 0.12–0.50) were significantly higher than in the case of the corresponding alkyl derivatives (**1e–j**) (*S* = 0.02–0.17) (compare Table 6, entries 1–4



Scheme 12 General route for the resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with Ca(H-DBTA)$_2$ [(−)-**11**].

Table 6 Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with 0.25 equiv. of Ca(H-DBTA)$_2$ [(−)-**11**]

Entry	Y	Solvent	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	S[a,c] (−)	Abs. config.	Ref.
1	Ph (**1a**)	EtOAc–EtOH[d] EtOH–water[e]	(**1a**)$_2$·(−)-**11**[g]	96	52	0.50	(*R*)	80
2	2-MeC$_6$H$_4$ (**1b**)	MeCN–EtOH[d,e]	(**1b**)$_2$·(−)-**11**	93	33	0.31	(*R*)	80
3	4-MeC$_6$H$_4$ (**1c**)	MeCN–EtOH[d,e]	(**1c**)$_2$·(−)-**11**	44	28	0.12	(*S*)	80
4	1-Naphthyl (**1d**)	EtOAc–EtOH[d] EtOH–water[e]	(**1d**)$_2$·(−)-**11**	99	42	0.42	(*R*)	80
5	Et (**1e**)	EtOAc–EtOH[d,e]	(**1e**)$_2$·(−)-**11**	49	25	0.12	(*R*)	80
6[f]	Pr (**1f**)	EtOH–water[d,e]	(**1f**)·(−)-**11**[g,h]	96	18	0.17	(*S*)	80
7	i-Pr (**1g**)	EtOH[d,e]	(**1g**)$_2$·(−)-**11**	43	8	0.03	(*R*)	62
8	Bu (**1h**)	MeCN–EtOH[d,e]	(**1h**)$_2$·(−)-**11**	76	21	0.16	(*S*)	63
9	Bu (**1h**)	EtOAc–EtOH[d,e]	(**1h**)$_2$·(−)-**11**	13	14	0.02	(*R*)	63
10	i-Bu (**1i**)	EtOAc–EtOH[d,e]	(**1i**)$_2$·(−)-**11**	29	7	0.02	(*R*)	64
11	i-Pent (**1j**)	MeCN–EtOH[d,e]	(**1j**)$_2$·(−)-**11**	99	17	0.17	(*S*)	65

[a] Enantiomeric excess, yield and resolving capability obtained after digestions. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] Solvent used for crystallization. [e] Solvent used for digestions. [f] 0.5 equiv. of Ca(H-DBTA)$_2$ [(−)-**11**] was used. [g] Water was incorporated into the diastereomer. [h] The composition of the diastereomer was different from that of the predominant associate shown in Scheme 12.

and 5–11). The underlying reason for this difference may be that the strength and the nature of the non-bonding interactions between the resolving agent [(−)-**11**] and the given 3-phospholene oxide are presumably different in the case of the aryl- and alkyl derivatives (**1a–d** or **1e–j**).

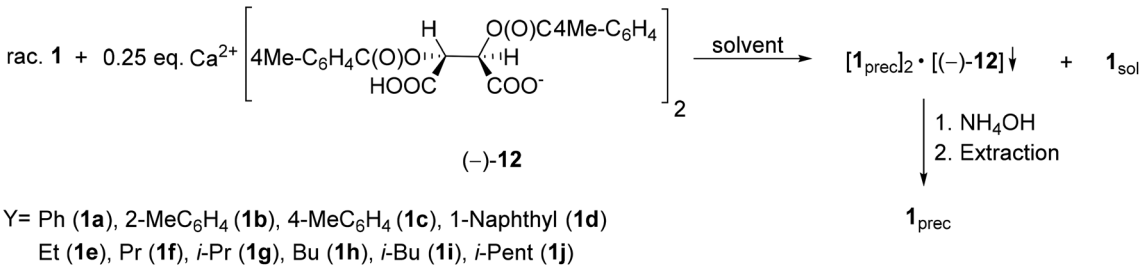
Generally, the enantiomeric excess values obtained with the acidic Ca^{2+}-salt of the *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid [(−)-**11**] were comparable with the ee values obtained with TADDOL derivatives [(−)-**9** or (−)-**10**]. However, Ca(H-DBTA)$_2$ [(−)-**11**] underperformed TADDOL and spiro-TADDOL [(−)-**9** and (−)-**10**] in terms of the resolving capability values (S) (compare Table 6 with Tables 1, 3 and 4).

In this series of resolution experiments, the solvent did not influence in which an antipode of the 3-phospholene oxide (**1a–g**, **1i** and **1j**) was incorporated into the diastereomer. The only exception was the 1-butyl-3-phospholene oxide (**1h**) (Table 6, entries 8 and 9). However, the significance of this solvent dependent enantioselection was not as pronounced, as in the case of spiro-TADDOL [(−)-**10**] (Tables 3 and 4).

The ^{1}H NMR studies revealed that the predominant composition of the diastereomers may be described by the formula Ca(**1**)$_2$(H-DBTA)$_2$ (Table 6). The only exception was the propyl-3-phospholene oxide (**1f**), where one 3-phospholene oxide molecule was incorporated into the diastereomer (Table 6, entry 6).

2.2.2. Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (1a–j) with calcium hydrogen *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartrate [(−)-12]. Beside the acidic calcium salt of *O*,*O*′-dibenzoyl-(2*R*,3*R*)-tartaric acid [(−)-**11**], the corresponding *O*,*O*′-di-*p*-toluoyl derivative [(−)-**12**] was also applied to prepare optically active 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) according to the procedure described in section 2.2.1 (Scheme 13). The selected results are summarized in Table 7.

Regarding the aryl-3-phospholene oxides (**1a–d**), lower resolving capability values (S) could be obtained with Ca(H-DPTTA)$_2$ [(−)-**12**] than with Ca(H-DBTA)$_2$ [(−)-**11**] (compare Table 6, entries 2–4 and Table 7, entries 2–4). The only exception was the 1-phenyl-3-phospholene oxide (**1a**), in which case the results showed parity (compare Table 6, entry 1 and Table 7, entry 1). Interestingly, this tendency reversed for the series of the alkyl-3-phospholene oxides (**1e–j**), where, in 5 out of 6 instances, the application of Ca(H-DPTTA)$_2$ [(−)-**12**] was more advantageous (compare Table 6, entries 5 and 7–11 with Table 7, entries 5 and 7–10). Both Ca(H-DBTA)$_2$ and Ca(H-DPTTA)$_2$ [(−)-**11** and (−)-**12**] were equally applicable for



Scheme 13 General protocol for the resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with Ca(H-DPTTA)$_2$ [(–)-**12**].

Table 7 Resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**) with 0.25 equiv. of Ca(H-DPTTA)$_2$ [(–)-**12**]

Entry	Y	Solvent	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	S[a,c] (–)	Abs. config.	Ref.
1[d]	Ph (**1a**)	EtOH–water	(**1a**)·(–)-**12**[e,f]	93	55	0.51	(*S*)	80
2	2-MeC$_6$H$_4$ (**1b**)	EtOH–water	(**1b**)$_2$·(–)-**12**	45	13	0.06	(*R*)	80
3	4-MeC$_6$H$_4$ (**1c**)	EtOH–water	(**1c**)$_2$·(–)-**12**	32	15	0.05	(*S*)	80
4	1-Naphthyl (**1d**)	EtOH–water	(**1d**)$_2$·(–)-**12**[e]	69	29	0.20	(*R*)	80
5	Et (**1e**)	EtOH–water	(**1e**)$_2$·(–)-**12**[e]	73	34	0.25	(*S*)	80
6	Pr (**1f**)	EtOH–water	(**1f**)$_2$·(–)-**12**	41	42	0.17	(*S*)	80
7	i-Pr (**1g**)	EtOAc–EtOH–water	(**1g**)$_2$·(–)-**12**	92	10	0.09	(*S*)	62
8	Bu (**1h**)	EtOH–water	(**1h**)$_2$·(–)-**12**	77	27	0.21	(*S*)	63
9	i-Bu (**1i**)	EtOAc–EtOH–water	(**1i**)$_2$·(–)-**12**	73	23	0.17	(*R*)	64
10	i-Pent (**1j**)	EtOH–water	(**1j**)$_4$·[(–)-**12**]$_5$[f]	95	32	0.30	(*S*)	81

[a] Enantiomeric excess, yield and resolving capability obtained after digestions. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66] [d] 0.5 equiv. of Ca(H-DPTTA)$_2$ [(–)-**12**] was used. [e] Water was incorporated into the diastereomer. [f] The composition of the diastereomer was different from that of the predominant associate shown in Scheme 13.

the enantiomeric separation of 1-propyl-3-phospholene oxide (**1f**) in terms of resolving capability (S), but a higher enantiomeric excess could be obtained with Ca(H-DBTA)$_2$ [(–)-**11**] (compare Table 6, entry 6 and Table 7, entry 6). In this series of experiments, the formation of diastereomers with a composition of Ca(**1**)$_2$(H-DPTTA)$_2$ was observed in most of the cases (Table 7) similarly to the instances described for the use of Ca(H-DBTA)$_2$ [(–)-**11**] (Table 6).

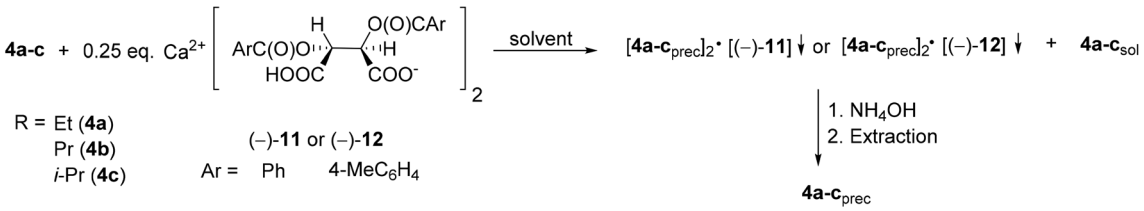
The impact of the similar chiral environment of the *O*,*O*′-dibenzoyl- or *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid was that the resolving agents (–)-**11** and (–)-**12** preferred diastereomeric complex formation with the same enantiomers of a given 3-phospholene oxide (**1b–d**, **1f** and **1h–1j**) in the majority of the instances (compare Table 6, entries 2–4, 6 and 8–11 with Table 7, entries 2–4, 6 and 8–10). However, in the case of the phenyl-, ethyl or i-propyl-derivatives (**1a**, **1e** and **1g**) different antipodes could be prepared with Ca(H-DBTA)$_2$ and Ca(H-DPTTA)$_2$ [(–)-**11** or (–)-**12**] (compare Table 6, entries 1, 5 and 7 with Table 7, entries 1, 5 and 7). It is worth mentioning that no solvent dependent enantiopreference could be observed, when Ca(H-DPTTA)$_2$ [(–)-**12**] was used as the resolving agent.

2.2.3. Resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (4a–c) with calcium hydrogen *O*,*O*′-dibenzoyl- and di-*p*-toluoyl-(2*R*,3*R*)-tartrate [(–)-11 and (–)-12]. After the resolution of 1-aryl- and 1-alkyl-3-methyl-3-phospholene 1-oxides (**1a–j**), we extended our resolution methods by applying Ca(H-DBTA)$_2$ (–)-**11** or Ca(H-DPTTA)$_2$ (–)-**12** for the enantiomeric separation of the corresponding phosphinate analogues, 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–c**). The resolutions were carried out as described in section 2.2.1 (Scheme 14). The selected best results are summarised in Table 8.

When Ca(H-DBTA)$_2$ [(–)-**11**] was the resolving agent, the alkoxy-3-phospholene oxides (**4a–c**) were prepared with an ee of 17–92%, whereas the corresponding resolving capability values fell in the range of 0.06–0.33 (Table 8, entries 1–4). By applying Ca(H-DPTTA)$_2$ [(–)-**12**], the (*R*)-enantiomer of ethoxy- and propoxy-3-phospholene oxide could be prepared with an ee of 75% and 55%, respectively, and with a resolving capability value of 0.33 and 0.20, respectively (Table 8, entries 5 and 6). It is noteworthy that Ca(H-DPTTA)$_2$ [(–)-**12**] could not differentiate between the two antipodes of i-propoxy-3-phospholene oxide (**4c**) (Table 8, entry 7).

The results in Table 8 indicate that the longer alkoxy chain may influence the non-bonding interactions with the resolving agent in a negative manner (compare Table 8, entry 1 with 2 and 3 and entry 5 with 6).

The 1-propoxy-3-phospholene oxide (**4b**) was the only alkoxy derivative whose (*R*)- and (*S*)-enantiomers could be prepared



Scheme 14 General method for the resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–c**) with Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**11** or (−)-**12**].

Table 8 Resolution of 1-alkoxy-3-methyl-3-phospholene 1-oxides (**4a–c**) with 0.25 equiv. of Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**11** or (−)-**12**]

Entry	R	Resolving agent	Solvent	Diastereomeric complex	ee[a] (%)	Yield[a,b] (%)	$S^{a,c}$ (−)	Abs. config.	Ref.
1	Et (**4a**)	(−)-**11**	MeCN–EtOH	(**4a**)$_2$·(−)-**11**	91	29	0.26	(*R*)	80
2	Pr (**4b**)	(−)-**11**	MeCN–EtOH	(**4b**)$_2$·(−)-**11**	59	18	0.11	(*R*)	67
3	Pr (**4b**)	(−)-**11**	EtOAc–EtOH	(**4b**)$_2$·(−)-**11**	17	34	0.06	(*S*)	67
4	i-Pr (**4c**)	(−)-**11**	MeCN–EtOH	(**4c**)$_2$·(−)-**11**	92	36	0.33	(*S*)	80
5	Et (**4a**)	(−)-**12**	EtOH–water	(**4a**)$_2$·(−)-**12**	75	44	0.33	(*R*)	80
6	Pr (**4b**)	(−)-**12**	EtOAc–EtOH–water	(**4b**)$_2$·(−)-**12**	55	36	0.20	(*R*)	67
7	i-Pr (**4c**)	(−)-**12**	EtOH–water	(**4c**)$_2$·(−)-**12**	Rac.	—	—	—	80

[a] Enantiomeric excess, yield and resolving capability obtained after digestions. [b] Based on the half of the racemate that is regarded to be 100% for each antipode. [c] Resolving capability, also known as the Fogassy parameter [S = (Yield/100) × (ee/100)].[66]

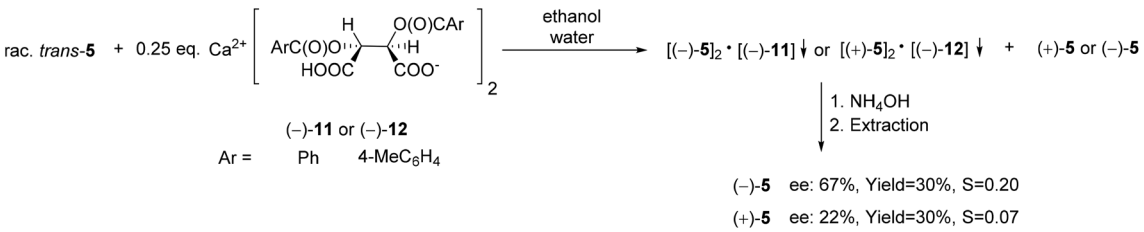
with the same resolving agent, Ca(H-DBTA)$_2$ [(−)-**11**] using different solvents (ee for (*R*)-**4b**: 59% and ee for (*S*)-**4b**: 17%) (Table 8, entries 2 and 3).

The diastereomers formed on resolution contained the corresponding 1-alkoxy-3-phospholene oxides (**4a–c**) and Ca(H-DBTA)$_2$ [(−)-**11**] or Ca(H-DPTTA)$_2$ [(−)-**12**] in a ratio of 2 : 1 similarly to the cases described for the resolution of most of the aryl- and alkyl-3-phospholene oxides (compare Table 8 with Tables 6 and 7).

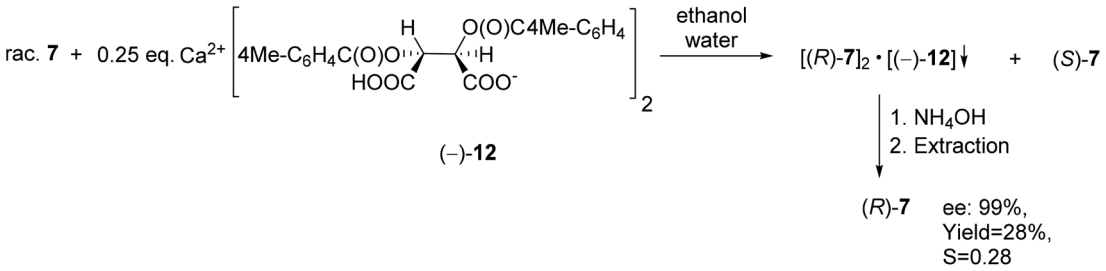
2.2.4. Resolution of six-membered P-heterocyclic phosphine oxides and a phosphonic ester-amide (5, 7 and 8) with calcium hydrogen *O*,*O*′-dibenzoyl- and di-*p*-toluoyl-(2*R*,3*R*)-tartrate [(−)-11 and (−)-12]. The success with the acidic calcium salts of *O*,*O*′-dibenzoyl- or *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(−)-**11** or (−)-**12**] in the optical resolution of five-membered phosphine oxides and phosphinates (**1a–j** and **4a–c**) encouraged us to try the enantiomeric separation of six-membered phosphine oxides and a phosphonic ester-amide. The 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**5**), 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**7**) and 6-diethylamino-dibenzo[*c*,*e*][5,6]oxaphosphorine 6-oxide (**8**) served as model compounds, and the resolutions were carried out as described in section 2.2.1. The results are summarized in Schemes 15–17.

Both Ca(H-DBTA)$_2$ [(−)-**11**] and Ca(H-DPTTA)$_2$ [(−)-**12**] were applicable for the partial enantiomeric separation of phenyl-phosphabicyclo[3.1.0]hexane oxide (**5**). Interestingly, resolving agents (−)-**11** or (−)-**12** formed diastereomeric coordination complexes with the different enantiomers of phosphabicyclo[3.1.0]hexane oxide **5**. In this manner, (−)-**5** and (+)-**5** could be prepared with an ee of 67% and 22%, respectively (Scheme 15).[71]

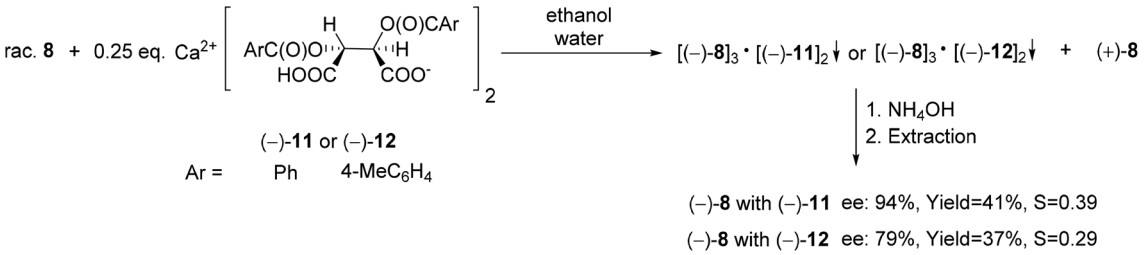
Using Ca(H-DPTTA)$_2$ [(−)-**12**] as the resolving agent, enantiopure (*R*)-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide



Scheme 15 The resolution of 6,6-dichloro-1-methyl-3-phenyl-3-phosphabicyclo[3.1.0]hexane 3-oxide (**5**) with Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(−)-**11** or (−)-**12**].



Scheme 16 The resolution of 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine 1-oxide (**7**) with Ca(H-DPTTA)$_2$ [(–)-**12**].



Scheme 17 The resolution of 6-diethylamino-dibenzo[*c*,*e*][5,6]oxaphosphorine 6-oxide (**8**) with Ca(H-DBTA)$_2$ or Ca(H-DPTTA)$_2$ [(–)-**11** or (–)-**12**].

[(*R*)-**7**] could be prepared (Scheme 16). It is noted that no crystalline diastereomers were formed, when Ca(H-DBTA)$_2$ [(–)-**11**] was used.[79]

The acidic calcium salts *O*,*O*′-dibenzoyl- or *O*,*O*′-di-*p*-toluoyl-(2*R*,3*R*)-tartaric acid [(–)-**11** or (–)-**12**] were also suitable resolving agents for the preparation of the (–)-6-diethylamino-dibenzo[*c*,*e*][5,6]oxaphosphorine 6-oxide [(–)-**8**]. Among all of the resolving agents [(–)-**9**–(–)-**12**] used for the enantioseparation of dibenzooxaphosphorine oxide **8**, the highest ee and resolving capability values were obtained with Ca(H-DBTA)$_2$ [(–)-**11**] (Scheme 17).[70]

2.3. X-Ray analysis of the diastereomeric complexes

The crystallization process plays an important role in these investigations not only by forming well defined solid precipitates, but also through the manipulation possibilities through solubility and insolubility properties, as well as affecting *e.g.* the dielectric properties by a designed engineering approach (fine tuning by crystal engineering). Thus, crystal structure determinations[56–64,67,73,79] of these complex associate molecular systems may be of use in responding to queries regarding the structural background of the physical processes taking place during the experiments.

Crystallographic data shed light not only on the solvent[56,64] or co-solvent by identifying not only the presence of these species but also their role in the structure of the respective crystals. An interesting example was provided by the crystal structure of the quaternary (*R*)-i-butyl-3-phospholene oxide [(*R*)-**1i**]–spiro-TADDOL [(–)-**10**]–isopropanol 1 : 2 : 1 molecular assembly.[64] In this case, a molecule of the applied solvent was also included in the crystal. The competitive binding of the solvent to the two host molecules and also to the (*R*)-i-butyl-3-phospholene oxide [(*R*)-**1i**] resolution target could be traced back to the slightly stronger binding of the solvent than that of the respective (*R*)-i-butyl-3-phospholene oxide guest [(*R*)-**1i**].

In another neutral complex case, the key feature of the resolution process was the formation of the 2 : 1 associate of spiro-TADDOL [(–)-**10**] with the (*S*)-(–)-1-isopropyl-3-methyl-3-phospholene oxide [(*S*)-**1g**] guest.[65] Apart from the well-defined

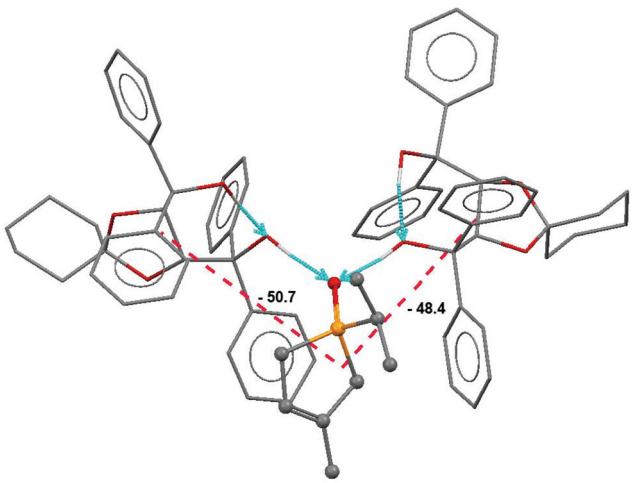
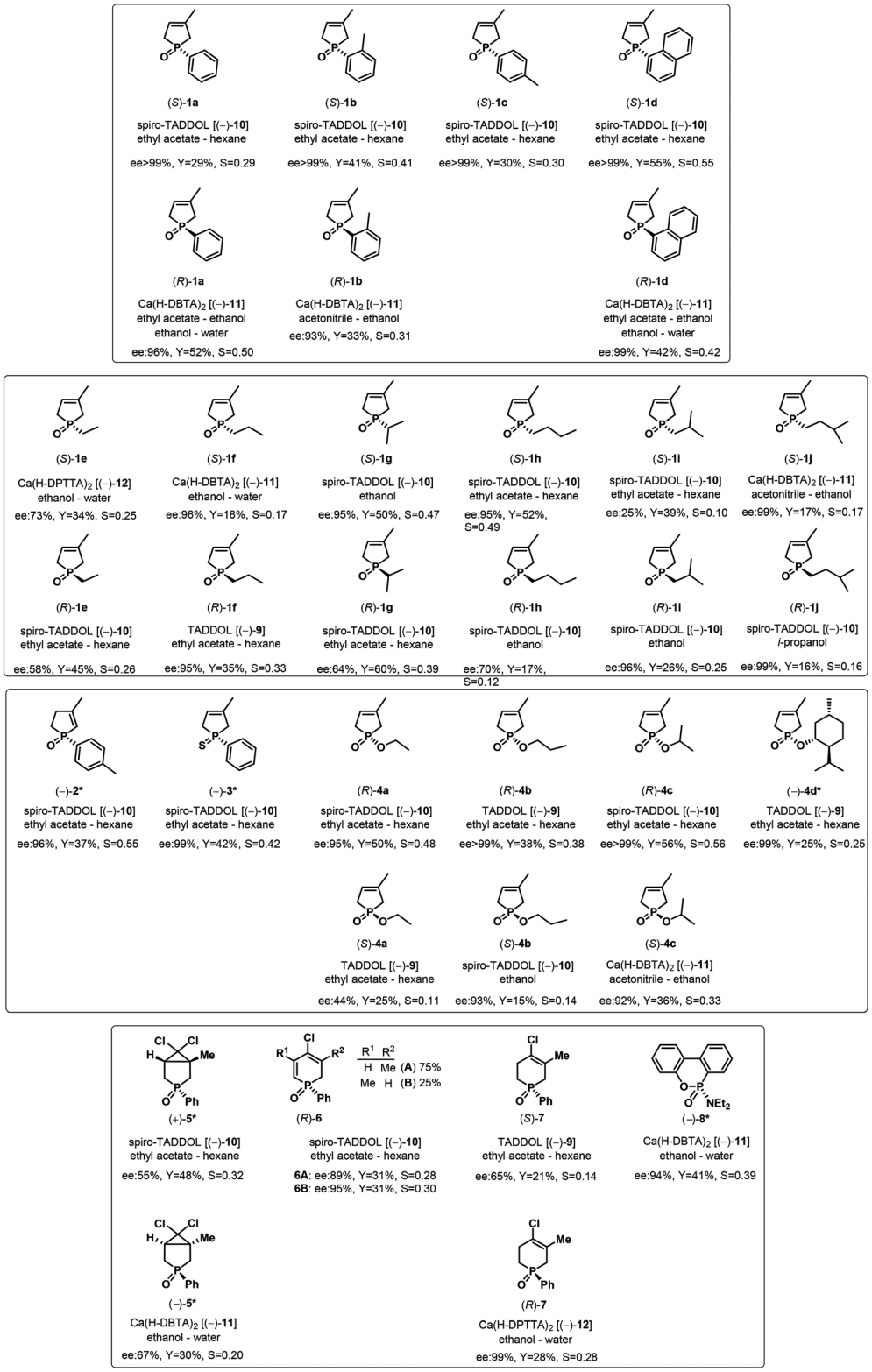


Fig. 5 The two largest attractive interactions (in kJ mol^{-1}) indicated also by red broken lines between the respective molecular centres in the crystal of the (*S*)-(–)-1-isopropyl-3-methyl-3-phospholene oxide guest [(*S*)-**1g**] with two independent spiro-TADDOL [(–)-**10**] hosts. Arrows indicate the donor–acceptor directions of the H-bond vectors.



* Tentative assignment of the absolute P-configuration.

Fig. 6 The best results for the resolution of five- and six-membered P-heterocyclic phosphine oxides, phosphinates, a phosphine sulfide and a phosphonic ester-amide (**1–8**).

classical H-bridges, a large number of short C–H···O contacts were also present. Further support for the quantification of binding forces was obtained from force field calculations and from a semi-empirical computational analysis. These provided nearly same and cohesive binding energies in the range of −135 to −125 kJ mol^{-1}.[62] Thus, the major binding effects were successfully recognized in the structure discussed (Fig. 5).

This identifies the major cohesive forces in the solid state that possibly also operate under the conditions of resolution.

The crystal structures of the acidic Ca-tartrate salt complexes[67,73,79] disclosed a more alike pattern both in the composition, and in the way of binding the target phospholene oxides (**1**). The common feature in these crystals is that two acidic tartrate anions and two phospholene oxides contributed to a square-pyramid coordination sphere around the Ca^{2+} cation and the formation of a catena-type endless chain using crystallographic translations. The acidic proton forms a H-bridge with the anion, so that the coordination from the carboxylic/carboxylate groups provide a partial negative charge distributed evenly. A further feature of the coordination sphere is that either a perfect or an approximate twofold symmetry or pseudo-symmetry rules their global shape.

As it turned out clearly from this series of crystal structure determinations,[56–64,67,73,79] the obvious and common binding of the P-oxides is realized through the P═O oxygen atom. As it is described, the binding is primarily established through H-bonding in the neutral type assemblies incorporating TADDOL derivatives [(−)-**9** and (−)-**10**]. The acidic Ca salt matrices involved the binding of the P═O function into the sixfold coordination sphere of the metal ion. These observations may be explained by the enhanced negative charge on the P═O oxygen atom.

3. Conclusions

In this paper, our versatile resolution methods applying TADDOL derivatives [(−)-**9** and (−)-**10**] or the Ca^{2+}-salts of tartaric acid derivatives [(−)-**11** and (−)-**12**] are summarized, and the methods are widely applicable for the preparation of five- and six-membered P-heterocyclic phosphine oxides, phosphinates, a phosphine sulfide and a phosphonic ester-amide (**1–8**) in an optically active form (Fig. 6). The corresponding enantiomers (**1–8**) were obtained with an ee above 95% in the majority of the instances. The P-heterocycles (**1–8**) discussed are unknown in the literature in an optically active form. The absolute configuration of the P-stereogenic centers was also determined in most of the instances. In a few cases, diastereomeric molecular or coordination complexes were characterized by X-ray crystallography and the characteristic non-bonding interactions between the host and the molecules were identified. The optically active P-heterocyclic phosphine oxides are precursors of the corresponding P(III)-compounds which could be applied as ligands in platinum complexes (**14**).[62,81–85]

Acknowledgements

The authors are grateful to the Hungarian Research Fund for financial support (Grant No. K83118, K104769 and PD116096).

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