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Lipase-mediated stereoselective transformations of chiral organophosphorus *P*-boranes revisited: revision of the absolute configuration of alkoxy(hydroxymethyl)phenylphosphine *P*-boranes

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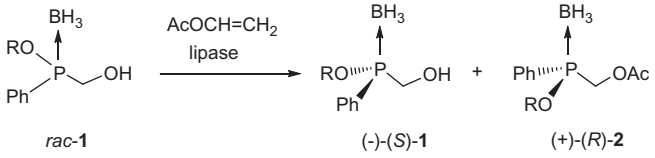
ABSTRACT

The lipase-promoted kinetic resolution of a series of alkoxy(hydroxymethyl)phenylphosphine *P*-boranes proceeded with moderate stereoselectivity to give both the unreacted substrates and their *O*-acetyl derivatives. The absolute configurations of the products, which were earlier ascribed on the basis of the stereoselective reduction of the corresponding phosphine oxides with borane and comparison with the literature data concerning bicyclic phosphine oxides, were disputed by theoretical calculation. Some additional studies were carried out, including theoretical calculations and more accurate chemical correlation, which proved that the borane reduction of acyclic phosphine oxides proceeded with inversion of configuration at the phosphorus center and, therefore, the former assignment of the absolute configurations was incorrect. On this basis, the stereochemistry of the enzymatic reaction was ultimately determined. A mechanism of the borane reduction of acyclic phosphine oxides explaining inversion of configuration at phosphorus is proposed.

1. Introduction

Chiral, non-racemic organophosphorus compounds containing a stereogenic phosphorus atom play an important role in various areas of current research, such as asymmetric organic synthesis, biochemistry and catalysis. For example, trivalent phosphorus compounds, especially tertiary phosphines, are used as chiral ligands in transition metal catalysts. Recently, there has been growing interest in the synthesis and transformation of borane complexes of trivalent phosphorus compounds.[1,2] In contrast to phosphines and other derivatives of trivalent phosphorus, which are prone to oxidation and are usually difficult to handle, they are stable compounds and can be easily converted into the corresponding P^{III} compounds without racemization. Following this tendency and taking into account the fact that many hydrolytic enzymes proved to be capable of recognizing and stereoselectively binding heteroatom stereogenic centers, among them those located on the phosphorus,[3] we[4] and others[5,6] applied biocatalytic methods in the synthesis of optically active borane complexes of chiral P^{III} compounds. Our investigations concerned the kinetic resolution of racemic *P*-stereogenic alkoxy(hydroxymethyl)phenylphosphine *P*-boranes **1** via their enzymatic acetylation (Eq. 1).

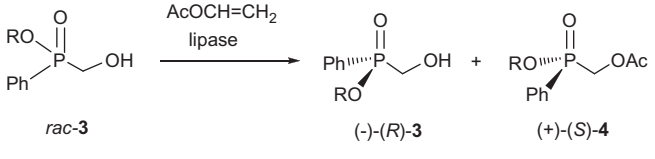


rac-**1** (-)-(*S*)-**1** (+)-(*R*)-**2**

a, R=Me **b**, R=Et **c**, R=*i*-Pr

(1)

The results showed that the *P*-boranes, in contrast to the analogous *P*-stereogenic alkoxy(hydroxymethyl)phenylphosphine oxides **3** described previously (Eq. 2),[7,8] were relatively poor substrates for lipase-catalyzed transformations and underwent similar reaction that was much slower and with low stereoselectivity (e.g., for the CAL-B-catalyzed acetylation of **3c** the enantiomer ratio $E = 32$, while for **1c** $E = 3$).



rac-**3** (-)-(*R*)-**3** (+)-(*S*)-**4**

a, R=Me **b**, R=Et **c**, R=Pr^{i}

(2)

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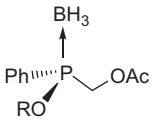
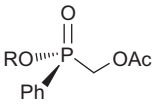
In contrast to the phosphine oxides **3**, whose absolute configurations were known,[7,8] the direct determination of the absolute configuration of **1** using X-ray analysis could not be performed since no crystals could be obtained. Therefore, a simple chemical correlation was performed, which was based on the reduction of enantiomerically enriched hydroxymethyl(*i*-propoxy)phenylphosphine oxide (−)-(*R*)-**3c** and acetoxymethyl(*i*-propoxy)phenylphosphine oxide (+)-(*S*)-**4c** with borane.[4] As a conclusion, the absolute configurations (+)-(*R*) and (−)-(*S*) were ascribed to the resulting **1c**, assuming, by analogy to the borane reduction of bicyclic phosphine oxides,[9,10] that the reaction proceeded with retention of configuration at the phosphorus center. On this basis, the stereochemistry of the lipase-catalyzed acetylation of **1** was considered to be as shown in Eq. 1.[4] Moreover, comparison of the stereochemistry of the two analogous enzymatic reactions, the acetylation of **1** (Eq. 1)[4] and the acetylation of **3** (Eq. 2),[7,8] indicated that the same enzymes recognized and preferentially transformed the enantiomers of **1** and **3** (and led to the corresponding acetates **2** and **4**) which had opposite spatial arrangement around the phosphorus.



(+)-(*R*)-**2**



(+)-(*S*)-**4**

This would mean that a simple replacement of the oxygen atom with the borane moiety at the phosphorus atom would result in an inversion of stereochemistry of the enzymatic reaction. Such different behavior of enzymes seemed very interesting. Attempting to explain this phenomenon, we decided to perform molecular modeling for the enzymatic reaction. The theoretical calculations cast doubt on this result, predicting the same stereochemical course of both reactions shown in Eqs. (1) and (2), which means that the replacement of oxygen by a borane group at the phosphorus stereogenic center does not influence the stereorecognition by the enzyme.[11] Since there is no doubt about the absolute configuration of the phosphine oxides **3** and **4**,[7,8] we have surmised that the absolute configuration of *P*-boranes **1** and **2** might have been wrongly ascribed[4] and decided to reinvestigate it using both theoretical calculations and a more detailed chemical correlation.

2. Results and discussion

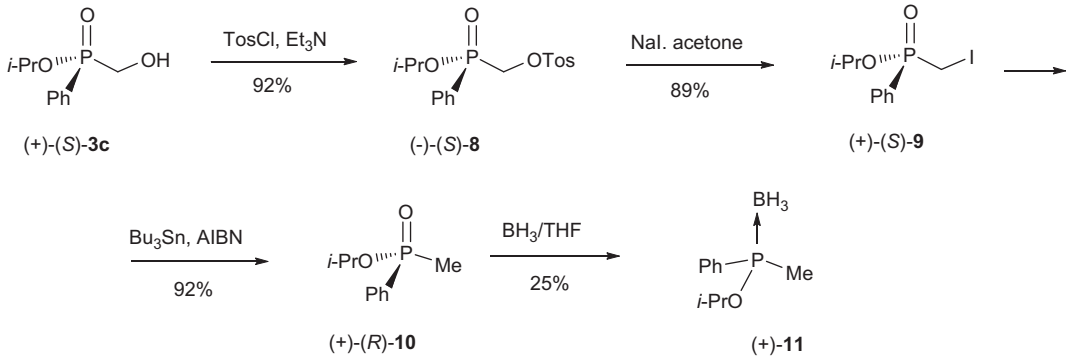
2.1. Synthesis of (hydroxymethyl)phenylphosphine *P*-boranes

Enantiomerically pure alkoxy(hydroxymethyl)phenylphosphine boranes **1** were synthesized by reduction of the corresponding enantiomerically pure phosphine oxides **3** or **4**, obtained via iterative enzymatic resolution (Eq. 2), with borane–THF complex (Eq. 3, Table 1, entries 1–4). The reaction proceeded smoothly, but unwanted by-products, a secondary phosphine borane **5** and hydroxyphosphine borane **6** were always formed. They were the products of a subsequent/simultaneous reduction of the alkoxy group and their content in the reaction mixture was higher in the case of lower alkyl substituents. For obvious reasons, no formation of these types of by-products was not observed in the reduction of *t*-butyl(hydroxymethyl)phenylphosphine **7** (Table 1, entry 5). It should be noted that **7** was synthesized according to the literature[12] and was not enantiomerically pure. When acetates **4** were subjected to the reaction with borane, the acetyl group was always removed.

Table 1
Borane reduction of (hydroxymethyl)phenylphosphine oxides

Entry	R^1	R^2	Phosphine oxide			Phosphine borane		
			Symbol	$[\alpha]_D$	Absol. config.	Symbol	Yield (%)	$[\alpha]_D$
1	MeO	H	**3a**	−24.7[a] −39.0[b]	(*R*)	**1a**	11	+80.2[a]
2	MeO	Ac	**4a**	+53.0[a]	(*S*)	**1a**	10	−80.2[a]
3	*i*-PrO	H	**3c**	−22.2[a] −58.3[b]	(*R*)	**1c**	60	+101.0[a]
4	*i*-PrO	Ac	**4c**	+38.8[a]	(*S*)	**1c**	45	−102[a]
5	*t*-Bu	H	**7**	−4.8[a,c]	(*S*)	**14**	95	+3.9[a,c]

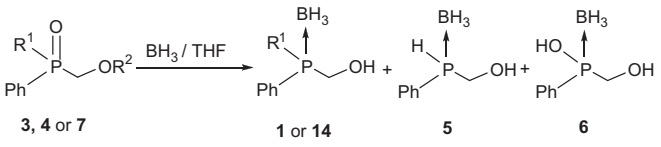
[a] In chloroform, *c* 1.
[b] In methanol, *c* 1.
[c] ee = 45%.



(+)-(*S*)-**3c** (-)-(*S*)-**8** (+)-(*S*)-**9**

(+)-(*R*)-**10** (+)-**11**

Scheme 1. Synthesis of phosphine oxide **10** and phosphine borane **11**.



(3)

The phosphine oxide (+)-(*R*)-**10** was synthesized according to the procedure previously described by us[7] and transformed into the corresponding borane **11** (Scheme 1).

2.2. Determination of the absolute configuration of *P*-boranes 1

2.2.1. Theoretical calculations

Since in a previous paper,[4] only the *O*-*i*-propyl derivatives **1c** and **2c** were examined, we limited our calculations to these derivatives. Although the absolute configuration of **3c** was known, we also performed calculations for this derivative, as this allowed us to verify the reliability of the methodology applied.

In order to estimate the value of the specific rotation for **1c** and **3c**, we calculated the specific rotation of each conformer using the B3LYP/6-311++G(2d,2p) method for the D line of Na (λ = 589 nm). The net specific rotation for the given compound was calculated as the population-weighted average of the rotations of individual conformations according to the equation shown below,[13]

$$[\alpha]_D = \sum_i x_i [\alpha]_D^i$$

where x_i is the fractional population of conformer i, whose specific rotation is $[\alpha]_D^i$.

The Boltzmann distribution of the conformers was calculated on the basis of the Gibbs free energies of the conformers obtained at the B3LYP/6-311++G(2d,2p)//B3LYP/6-31+G* level (Tables 2 and 3).

The lowest energy conformers of **1c** and **3c**, considered in optical rotation calculations are shown in Figures 1 and 2, respectively,

The specific rotation for particular conformers can adopt very different values and can even change the sign. This was particularly apparent for the **1c** conformers for which the specific rotation varied from −300 to +190 (see Table 2). However, among the numerous conformers, only a few have a determining effect on the specific rotation. There are two such essential conformers for **3c** and three for **1c**. Calculations predict that the enantiomers of **3c** and **1c** having analogous spacial arrangement should show specific rotations with the same sign, that is, calculated $[\alpha]_D$ for (*R*)-enantiomers **3c** and **1c** in the gas phase are −54.3 and −67.4, respectively. The predicted gas phase specific rotations show appreciable deviations from the experimental data, 32 for **3c** and 34 for **1c**. However, the specific rotation of **1c** calculated in $CHCl_3$ (−85.2), is much closer to the experimental value (−102.0) in terms of absolute numbers than the gas phase value. However, due to the convergence problems with optimization of some

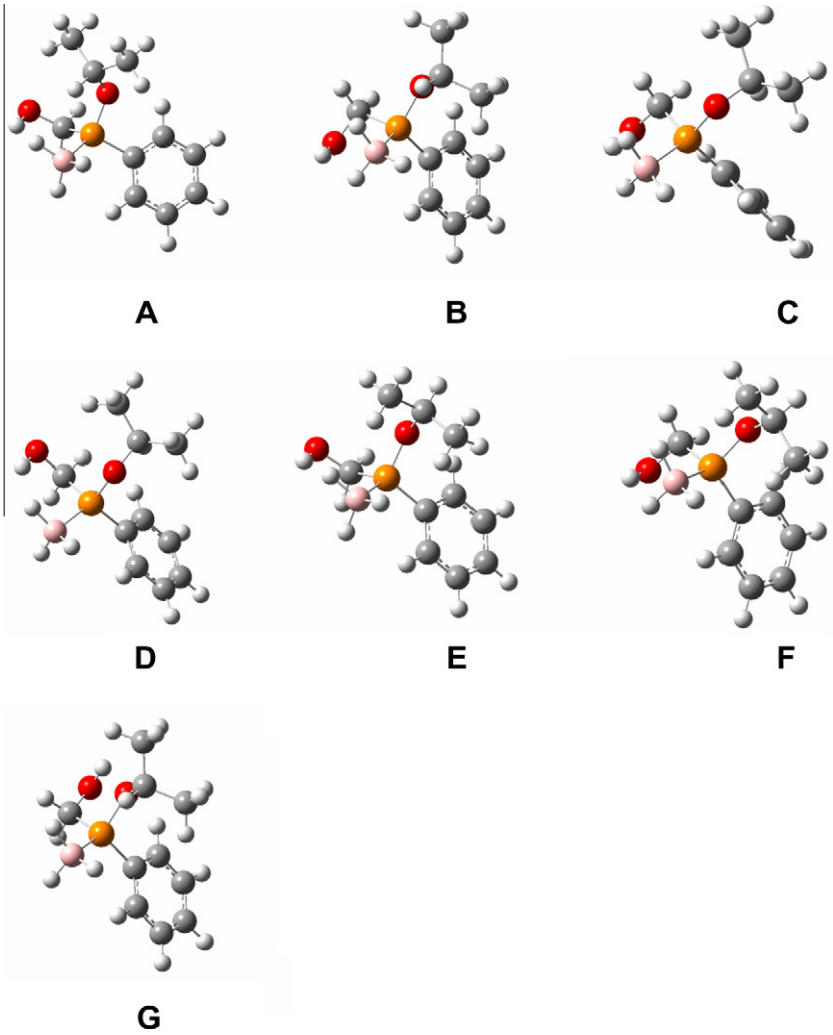


Figure 1. Seven lowest energy conformers of (*R*)-**1c**.

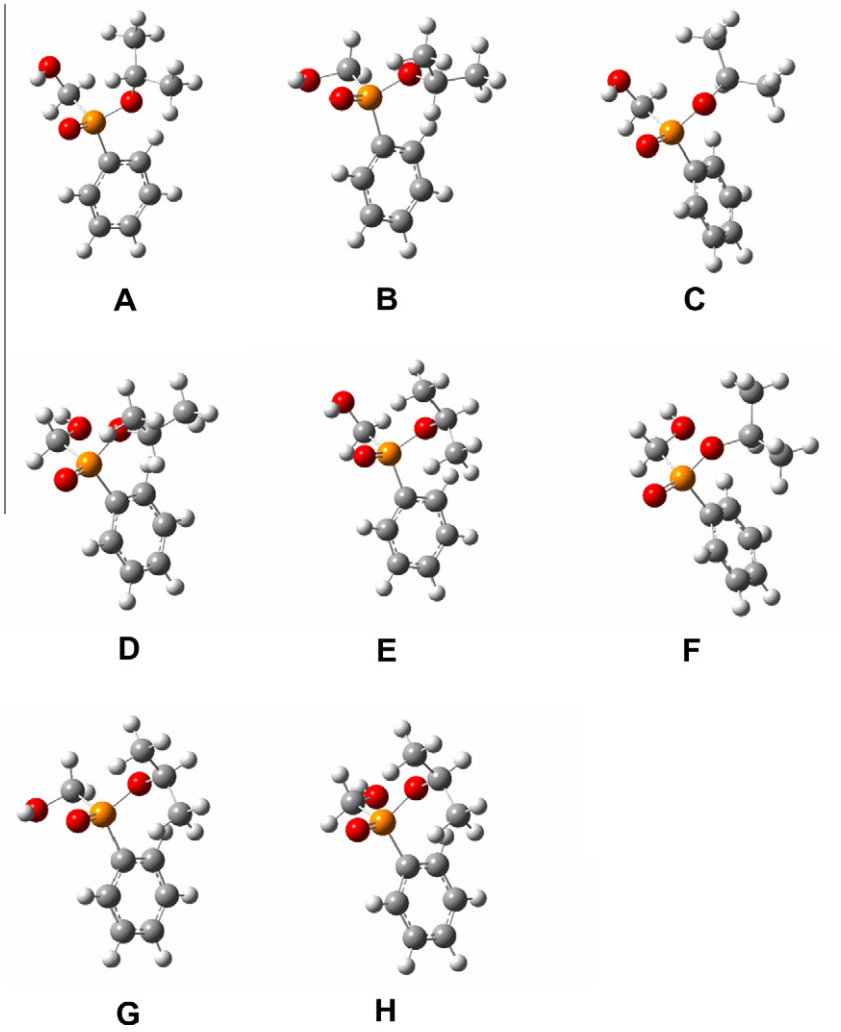


Figure 2. Eight lowest energy conformers of (*R*)-**3c**.

Table 2
Boltzmann distribution of conformers and the specific rotation calculated for (*R*)-hydroxymethyl(*i*-propoxy)phenylphosphine *P*-borane **1c** (in parentheses, specific rotations in $CHCl_3$ are given)

Conformer	$[\alpha]_D$	x_i	Molecular specific rotation
(*R*)-**1cA**	−141.2 (−148.6)	0.470 (0.528)	−66.3 (−78.4)
(*R*)-**1cB**	+39.6 (+43.4)	0.43 (0.37)	+17.05 (+16.0)
(*R*)-**1cC**	+189.4 (+196.1)	0.0004 (0.0)	+0.1 (0.0)
(*R*)-**1cD**	−4.7 (+23.1)	0.0004 (0.0014)	0.00 (+0.03)
(*R*)-**1cE**	−302.15 (−324.3)	0.0007 (0.0011)	−0.2 (−0.35)
(*R*)-**1cF**	−136.0 (−134.15)	0.0004 (0.0005)	−0.05 (−0.07)
(*R*)-**1cG**	−182.5 (−223.1)	0.098 (0.1003)	−17.8 (−22.37)
		Net specific rotation	−67.4 (−85.2)

conformer structures of **3c** in $CHCl_3$, the calculation of optical rotation of **3c** in solution could not be completed. Thus, we believe that the discrepancy between the experimental and calculated specific rotation of **3c** is mainly due to neglecting the solvent effect in the calculations.

2.2.2. Chemical correlation

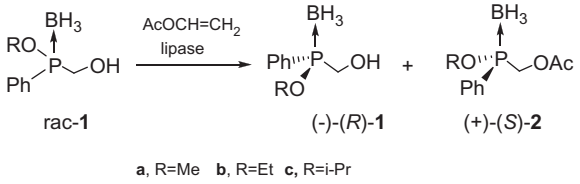
The detailed chemical correlation was performed using the phosphine oxides **3a** and **3c** and phosphine boranes **1a** and **1c** (Scheme 2). Since in each case the stereochemical course was the same, the transformations are presented using only the compound number. Thus, (−)-(*R*)-**3** was reacted with a complex of borane with THF or borane with dimethyl sulfide (in both cases the results were identical) to give (+)-**1** of unknown absolute configuration. If the reaction proceeded with retention of configuration, its absolute configuration should be (*R*) (Route A), if with inversion, its configuration should be (*S*) (Route B). The subsequent reaction, removal of the borane moiety by 1-octene followed by the addition of sulfur, leading to phosphine sulfide (+)-**12**, must proceed with retention of configuration.[14] Hence, the absolute configuration of (+)-**12** obtained was either (*S*) (Route A) or (*R*) (Route B). Finally, oxidation of (+)-**12** with iodoxybenzene gave the starting (−)-(*R*)-**3**. This means that either all of the transformations proceeded with retention of configuration (Route A) or two of the three reactions,

Table 3
Boltzmann distribution of conformers and the specific rotation calculated for (*R*)-hydroxymethyl(*i*-propoxy)phenylphosphine oxide **3c**

Conformer	$[\alpha]_D$	x_i	Molecular specific rotation
(*R*)-**3cA**	−86.3	0.43072	−37.16
(*R*)-**3cB**	−25.2	0.54204	−13.66
(*R*)-**3cC**	−23.2	0.00005	0.00
(*R*)-**3cD**	−145.8	0.01182	−1.72
(*R*)-**3cE**	−186.0	0.00658	−1.22
(*R*)-**3cF**	−27.2	0.00003	0.00
(*R*)-**3cG**	−58.1	0.00866	−0.50
(*R*)-**3cH**	−195.5	0.00011	−0.02
		Net specific rotation	−54.30

namely the reduction of **3** with borane and oxidation with iodoxybenzene, proceeded with inversion (Route B). As this sequence of reactions could not give an answer, (−)-(*R*)-**3** was independently transformed into phosphine sulfide **12**. The initial acetylation gave acetate (−)-(*R*)-**4**, which was treated with Lawesson reagent to afford the thiono derivative (−)-**13**. Removal of the acetyl group using sodium methoxide led to (−)-**12**, thus the opposite enantiomer to that obtained in the previous reaction. Since the Lawesson reagent is known to transform phosphine oxides into phosphine sulfides with retention of configuration at phosphorus,[15] the (*S*)-configuration was tentatively ascribed to (−)-**12**. Moreover, its oxidation with iodoxybenzene produced the opposite enantiomer of the starting **3**, that is, (+)-(*S*)-**3** with a diminished enantiomeric excess, which undoubtedly proved that this reaction proceeded with predominant inversion of the configuration at the phosphorus, the result being contrary to the earlier literature reports.[15–17] This overall result allowed us to discard Route A and to ultimately conclude that the reduction of the phosphine oxide **3** with borane, which leads to phosphine borane (+)-(*S*)-**1**, proceeds with inversion of configuration.

To sum up, the absolute configuration of **1** is (+)-(*S*)-**1a**,**c** and (−)-(*R*)-**1a**,**c**, which is in full agreement with the theoretical calculations presented above and which is contrary to the previous chemical correlation.[4] In this context, the stereochemistry of the enzymatic reaction shown in Eq. 1, must also be reversed and read as follows (Eq. (4)).

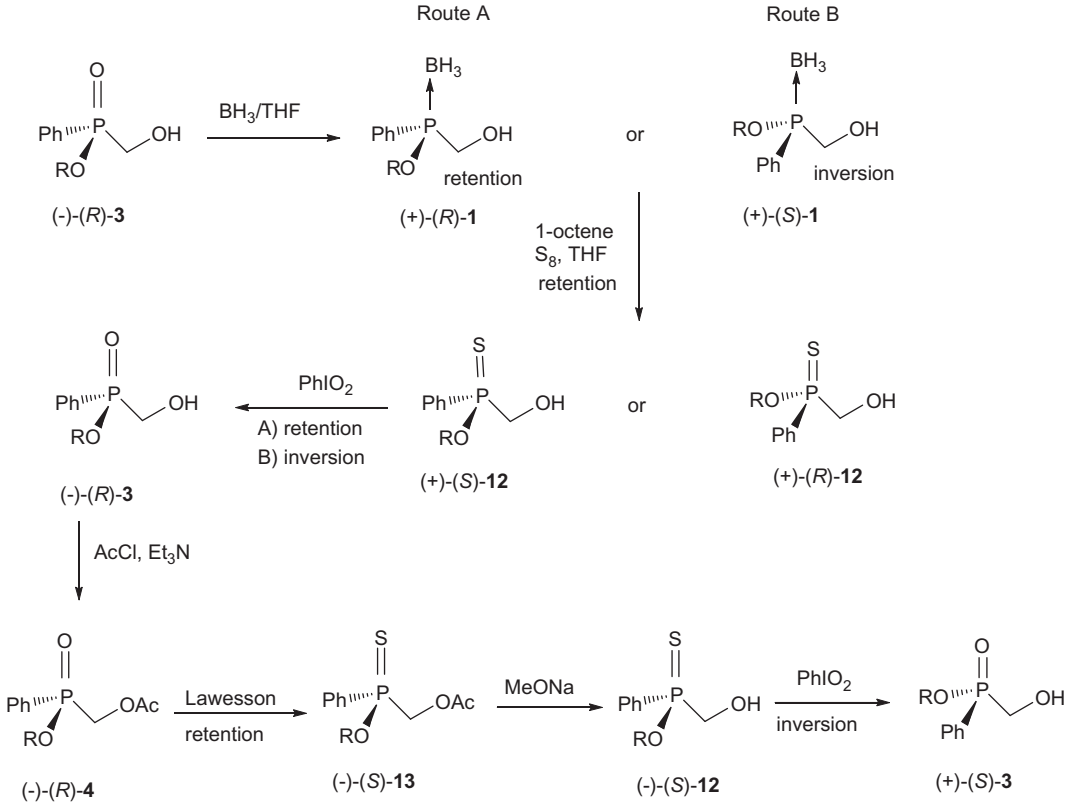


(4)

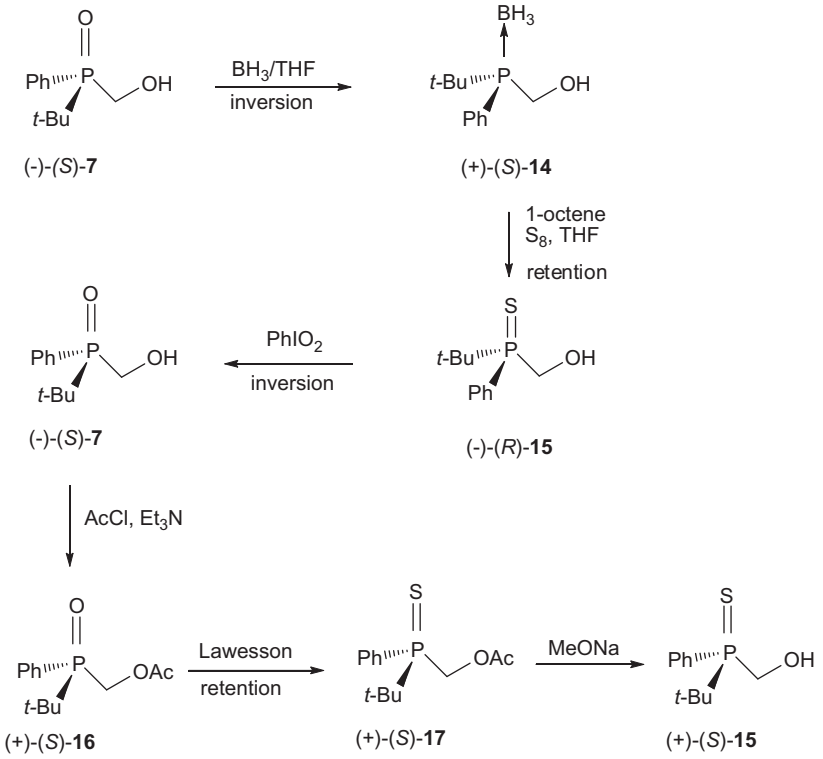
a, R=Me **b**, R=Et **c**, R=i-Pr

2.3. Stereochemistry of the reaction of various phosphine oxides with borane

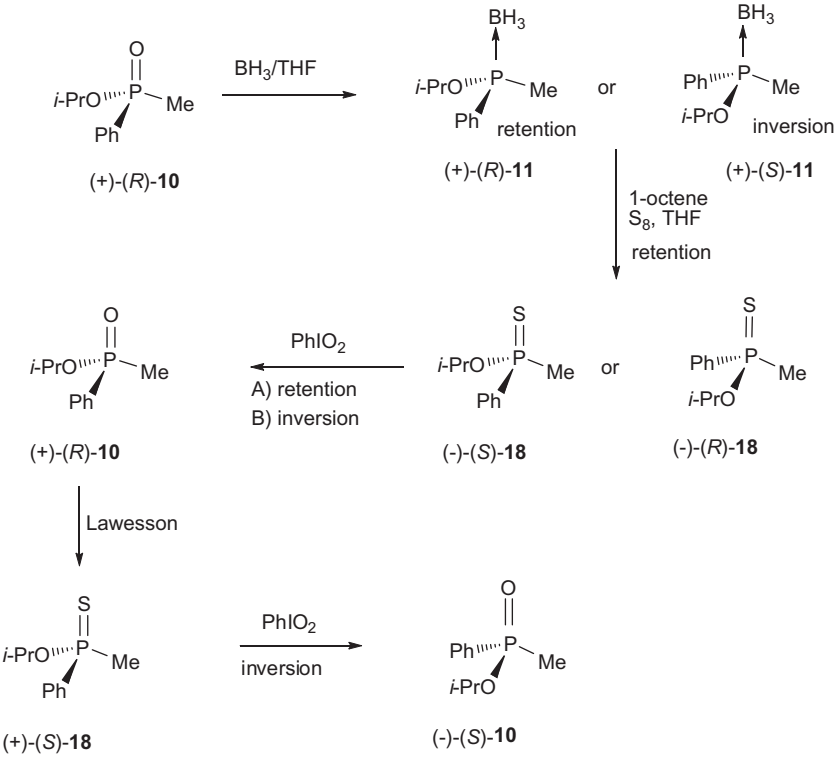
Since it has been found that the borane reduction of the phosphine oxides **3**, containing one C–O–P bond and the hydroxymethyl substituent, proceeds with different stereochemistry (inversion at phosphorus) than the reduction of the bicyclic phosphine oxides, which have only C–P bonds and are deprived of the hydroxymethyl substituent,[9,10] we decided to investigate the impact of the 'extra' oxygen atoms on the mechanism of the reduction. To this end, two sequences of transformations were performed. In the first one, the stereochemistry of the borane reduction of *t*-butyl(hydroxymethyl)phenylphosphine oxide **7** (thus having only direct C–P bonds and a pending hydroxymethyl substituent) was studied (Scheme 3). In the second one, *i*-propoxymethylphenylphosphine oxide **10** (thus having one C–O–P bond and no hydroxymethyl substituent) was used as the subject of analogous stereochemical investigations (Scheme 4).



Scheme 2. Chemical correlation of the absolute configurations of **1** and **3**.



Scheme 3. Chemical correlation of the absolute configurations of **7** and **14**.



Scheme 4. Chemical correlation of the absolute configurations of **10** and **11**.

Scheme 3 clearly shows that also in the case of *t*-butyl(hydroxymethyl)-phenylphosphine oxide **7**, the borane reduction proceeds with inversion of configuration. This can be undoubtedly concluded on the basis of the absolute configurations of **7** and **14**, which are known from the literature.[5,12,18] Nevertheless, some additional transformations, analogous to those presented in Scheme 2, have been performed and proved that their stereochemical course was identical as for **1** and **3**.

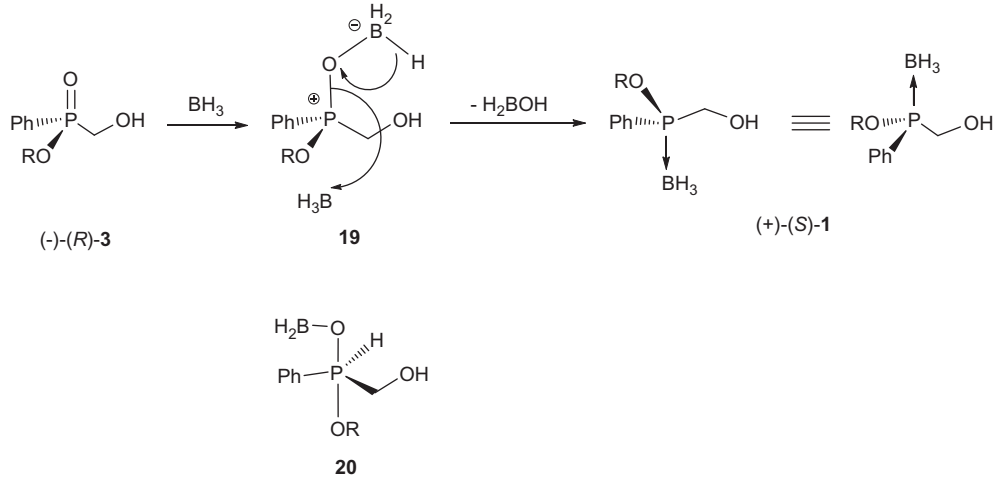
All of the discussions presented above for the correlation between **3** and **1** (Scheme 2) and **7** and **14** (Scheme 3) also proved valid for the correlation between **10** and **11** (Scheme 4).

It is noteworthy to add that the reaction sequence: transformation of a phosphine oxide into a phosphine sulfide by the Lawesson reagent (proceeding with retention of configuration) and oxidation of the resulting phosphine sulfide to the parent phosphine oxide with iodoxybenzene (proceeding with inversion of configuration) constitutes an example of a Walden cycle. The only drawback is the lack of full stereoselectivity during the oxidation step, which proceeds with a partial racemization and causes a loss of steric integrity of the compounds involved.

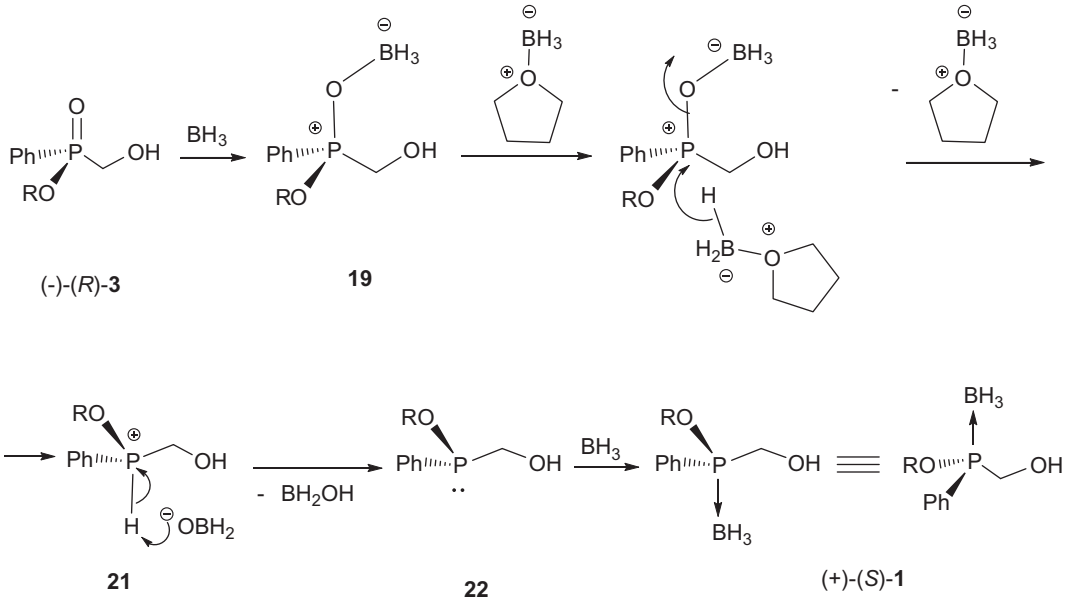
2.4. Mechanism of the reaction of phosphine oxides with borane

All the results presented above undoubtedly prove that the borane reduction of acyclic phosphine oxides proceeds with inversion of configuration, irrespective of the substituents at phosphorus. Therefore, the mechanism proposed by Keglevich et al. for bicyclic phosphine oxides[9,10] does not apply to this transformation. A proposal of a new mechanism is shown in Scheme 5 for the reduction of **3** to **1**, although it may be extended to the reduction of the remaining types of acyclic phosphine oxides. It seems reasonable to assume that instead of a hydride shift from boron to phosphorus in the initially formed *O*-boron-phosphine oxide **19**, which would lead to a pentacoordinate phosphorane **20**,[9,10] an attack of the hydride anion on the oxygen atom takes place. This causes breaking of the phosphorus–oxygen bond and an attack of the electron pair of this bond on the next borane molecule, which ultimately results in the inversion of configuration at the phosphorus (Scheme 5). Such a difference between the mechanisms of the reduction of bicyclic and acyclic phosphine oxides may be explained in terms of both the higher ability of cyclic phosphorus derivatives to form hypervalent pentacoordinate intermediates, and steric hindrance around phosphorus in bicyclic phosphine oxides.

For the sake of completeness, another possible explanation of the stereochemical course of the reaction investigated was taken into account (Scheme 6).[19] It assumes a simple nucleophilic attack of a hydride anion on the phosphonium derivative **19**, based on the



Scheme 5. Proposed mechanism of the reduction of acyclic phosphine oxides with borane.



Scheme 6. An alternative mechanism of the reduction of acyclic phosphine oxides with borane.

fact that the borane–THF complex is sufficiently activated to generate the hydride. The nucleophilic substitution with the hydride proceeds with inversion of the configuration at the phosphorus atom and produces the protonated phosphine **21**, with a simultaneous regeneration of the borane–THF complex. Abstraction of the proton from the phosphorus atom in **21** leads to phosphine **22**, which ultimately reacts with the next borane molecule to give the phosphine *P*-borane **1** with inversion of configuration. Nevertheless, at this stage, neither mechanism can be proven.

3. Conclusions

A reinvestigation of the sterical course of the borane reduction of acyclic phosphine oxides was performed using both theoretical calculations and a detailed chemical correlation. It allowed us to prove that the reduction proceeds with full inversion of configuration at the phosphorus and to correct the former wrongly ascribed absolute configurations of the resulting phosphine *P*-boranes. On this basis, the formerly established stereochemistry of the lipase-promoted kinetic resolution of a series of alkoxy(hydroxymethyl)phenylphosphine *P*-boranes was also corrected and ultimately determined. An interesting example of a Walden cycle was achieved via the reaction sequence: transformation of a phosphine oxide into a phosphine sulfide by the Lawesson reagent (proceeding with retention of configuration) and oxidation of the resulting phosphine sulfide to the parent phosphine oxide with iodoxybenzene (proceeding with a predominant inversion of configuration). A mechanism of the borane reduction of acyclic phosphine oxides explaining inversion of configuration at the phosphorus center has also been proposed.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker instrument at 200 MHz for ^{1}H and 81 MHz for ^{31}P with $CDCl_3$ as solvent. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter at 20 °C. Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. The enantiomeric excess (ee) values were determined by chiral HPLC (Varian Pro Star 210, Chiralpak OD). Enantiomerically pure **3a** and **3c** were obtained according to the literature,[7,8] respectively. Enantiomerically enriched **7** was also prepared according to the literature.[12]

4.2. Synthesis of phosphine oxide 10

4.2.1. Synthesis of isopropoxy(phenyl)tosyloxymethylphosphine oxide (−)-(*S*)-8

Enantiomerically pure (+)-(*S*)-**3c** (0.2576 g, 1.204 mmol), TosCl (0.235 g, 1.23 mmol) and Et_3N (0.1246 g, 1.23 mmol) were dissolved in CH_2Cl_2 (10 mL) and the solution was stirred at rt. After 4 days (^{31}P NMR control), the solvent was evaporated and the crude mixture was separated by column chromatography using CH_2Cl_2/MeOH 100:1 as eluent. Yield 0.4078 g (92%). $[\alpha]_D$ = −6.4 (*c* 1.46, $CHCl_3$). Ee = 100% [HPLC Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 52.08 min]. ^{31}P NMR ($CDCl_3$): δ 29.6. ^{1}H NMR ($CDCl_3$): δ 1.28 (1.24, d, *J* = 6.14 Hz, 3H), 1.38 (d, *J* = 6.14 Hz, 3H), 2.43 (s, 3H), 4.10–4.39 (d AB, 2H), 4.59–4.76 (m, 1H), 7.24–7.82 (m, 9H). MS (CI): *m/z* 369 (M+H).

4.2.2. Synthesis of iodomethyl(isopropoxy)phenylphosphine oxide (+)-(*S*)-9

Compound (−)-(*S*)-**8** (0.3852 g, 1.0467 mmol) and NaI (0.6280 g, 4 equiv, 4.187 mmol) were dissolved in acetone (10 mL) and the solution was refluxed for 2 weeks (^{31}P NMR control). The solvent was evaporated, and to the residue water was added and the mixture was extracted with CH_2Cl_2. The organic solution was washed with an aqueous solution of $Na_2S_2O_3$ and dried over $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by column chromatography using CH_2Cl_2 as eluent. Yield: 0.3022 g (89%). $[\alpha]_D$ = + 26.2 (*c* 1.12, $CHCl_3$). Ee = 100% [HPLC Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 39.09 min]. ^{31}P NMR ($CDCl_3$): δ 32.9. ^{1}H NMR ($CDCl_3$): δ 1.24 (1.24, d, *J* = 6.15 Hz, 3H), 1.45 (d, *J* = 6.15 Hz, 3H), 3.05–3.25 (m, 2H), 4.63–4.77 (m, 1H), 7.43–7.89 (m, 5H). MS: *m/z* 325 (M+H).

4.2.3. Synthesis of isopropoxy(methyl)phenylphosphine oxide (+)-(*R*)-10

Compound (+)-(*S*)-**9** (0.2883 g, 0.8898 mmol) and Bu_3SnH (0.3096 g, 1.0678 mmol) and AIBN (a few mg) were dissolved in benzene (20 mL) and refluxed for one week. The next sample of Bu_3SnH (0.060 g) and AIBN were added and the refluxing was continued for another day. After completion of the reaction (^{31}P NMR control), the solvent was evaporated and the residue was purified by column chromatography using CH_2Cl_2 as eluent. Yield: 0.616 g (92%). $[\alpha]_D$ = +40.0 (*c* 1.06, $CHCl_3$), ee = 100%. [HPLC, Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 20.3 min]. ^{31}P NMR ($CDCl_3$): δ 40.7. ^{1}H NMR ($CDCl_3$): δ 1.14 (d, *J* = 6.15 Hz, 3H), 1.37 (d, *J* = 6.15 Hz, 3H), 1.64 (d, *J* = 14.58 Hz, 3H), 4.43–4.59 (m, 1H), 7.41–7.87 (m, 5H). HRMS: calcd for $C_{10}H_{15}O_2P$ 198.080969, found 198.08101.

4.3. Synthesis of phosphine boranes—general procedure

A phosphine oxide **3**, **7,** or **10** was dissolved in a solution of BH_3 in THF (1 M, 6 equiv) and the mixture was stirred at room temperature. The reaction was monitored by ^{31}P NMR and was stopped when the substrate was consumed. The solvent was removed under vacuum. The residue was separated by column chromatography using dichloromethane as solvent to give **1**, **14,** or **11**, respectively.

4.3.1. For compound (+)-(*S*)-14 see the literature[5]

4.3.1.1. Compound (+)-(S)-1a. Yield: 11%. $[\alpha]_D$ = +80.2 (*c* 1.15, $CHCl_3$), ee = 100% [HPLC: Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 31.6 min]. ^{31}P NMR ($CDCl_3$): δ 112.85 (q, $J_{P\text{-}B}$ = 63.04 Hz). ^{1}H NMR ($CDCl_3$): δ 0.75 (br q, $J_{B\text{-}H}$ = 94.71 Hz, 3H, BH_3), 1.90 (br s, 1H, OH), 3.72 (d, 2H, *J* = 11.67 Hz), 4.12 (s, 2H, CH_2OH), 7.46–7.92 (m, 5H, Ph). MS (CI): *m/z* 183 (M−H).

4.3.1.2. Compound (+)-(S)-1c. Yield: 60%. $[\alpha]_D$ = +101 (*c* 1.15, $CHCl_3$), ee = 100%. For analytical data see the literature.[4]

4.3.1.3. Compound (+)-(S)-11. Yield 25%, $[\alpha]_D$ = +68.4 (*c* 2.25, $CHCl_3$), ee = 100% (HPLC: Chiralpak OD; Hexan: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 8.59 min); ^{31}P NMR ($CDCl_3$): δ 107.33 (q, $J_{P\text{-}B}$ = 67.22 Hz); ^{1}H NMR ($CDCl_3$): δ 0.80 (br q, $J_{B\text{-}H}$ = 94.67 Hz, 3H, BH_3), 1.12 (d, *J* = 6.14 Hz, 3H, $(CH_3)_2$CHO), 1.31 (d, *J* = 6.14 Hz, 3H, $(CH_3)_2$CHO), 1.67 (d, *J* = 9.18 Hz, 3H, CH_3), 4.41–4.48 (m, 1H, $(CH_3)_2CH$O), 7.45–7.82 (m, 5H, Ph). MS (CI): *m/z* 195 (M+H).

4.3.1.4. Compound 5. Compound **5** was isolated from the reaction of (−)-(*R*)-**3c** with borane (Scheme 3). Yield: 15%. $[\alpha]_D$ = +6.4 (*c* 1.01, $CHCl_3$), ^{31}P NMR ($CDCl_3$): δ 0.1 (q, $J_{P\text{-}B}$ = 41.53 Hz); ^{1}H NMR ($CDCl_3$): δ 0.8 (br q, *J* = 92.27 Hz, 3H, BH_3), 1.85 (br s, 1H), 4.27 (s, 2H), 5.57 (double m, $J_{P\text{-}H}$ = 376 Hz), 7.35–7.84). MS (CI) *m/z* 155 (M+H).

4.3.1.5. Compound 6. Isolated as above. Yield 10%. ^{1}P NMR ($CDCl_3$): δ 16.5 (q, $J_{P\text{-}B}$ = 48.62 Hz); ^{1}H NMR ($CDCl_3$): δ 0.64 (br q,

J = 94.97 Hz, 3H, BH_3), 1.56 (br s, 1H), 2.19 (br s, 1H), 4.38 (s, 2H), 7.36–7.91 (m, 5H). MS (CI): *m/z* 171 (M+H).

4.4. Transformation of phosphine boranes into phosphine sulfides; general procedure

To a suspension of sulfur (67 mg, 2.094 mmol) in THF (3 mL) under argon was added 1-octene (235 mg, 2.094 mmol) and a solution of **1a**, **1c**, **14,** or **11** (0.524 mmol) in THF (3 mL). The mixture was refluxed until the substrate was consumed (^{31}P NMR control). The solvent was removed under vacuum and the residue was purified by column chromatography in dichloromethane to give phosphine sulfides **12a**, **12c**, **15,** or **18**, respectively.

4.4.1. Compound (+)-(*R*)-12a

Yield 32%, $[\alpha]_D$ = +23.4 (*c* 1.17, $CHCl_3$), ee = 100% (HPLC: Chiralpak OD; Hexane : (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 31.7 min (major), t_R = 35.3 min (minor). ^{31}P NMR ($CDCl_3$): δ 91.56. ^{1}H NMR ($CDCl_3$): δ 1.96 (br s, 1H, OH), 3.55 (d, J = 13.21 Hz, 3H, CH_3), 3.93 (AB, 2H, CH_2OH), 7.45–7.95 (m, 5H, Ph); MS (CI): *m/z* 203 (M+H); HRMS: calcd for $C_8H_{12}O_2PS$: 203.029566, found: 203.02954.

4.4.2. Compound (+)-(*R*)-12c

Yield 92%, $[\alpha]_D$ = +26.1 (*c* 1.57, $CHCl_3$), ee = 100% (HPLC: Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 16 min). ^{31}P NMR ($CDCl_3$): δ 86.68. ^{1}H NMR ($CDCl_3$): δ = 1.20 (d, J = 6.2 Hz, 3H, CH_3), 1.39 (d, J = 6.2 Hz, 3H, CH_3), 2.45 (br s, 1H, OH), 3.96 (AB, 2H, CH_2OH), 4.74–4.86 (m, 1H, $(CH_3)_2CH$O), 7.35–7.99 (m, 5H, Ph); MS (CI): *m/z* = 231 (M+H); HRMS: calcd for $C_{10}H_{15}O_2PS$: 230.053011, found: 230.05345.

4.4.3. Compound (−)-(*R*)-15

Yield 92%, $[\alpha]_D$ = −5.7 (*c* 1.02, $CHCl_3$), ee = 45% (HPLC: Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 24.4 min for (−)-(*R*), t_R = 28.4 min for (+)-(S); ^{31}P NMR ($CDCl_3$): δ 64.63; ^{1}H NMR ($CDCl_3$): δ 1.20 (d, J = 16.47 Hz, 9H, *t*-Bu), 3.06 (br s, 1H, OH), 4.27 (AB, 2H, CH_2OH), 7.44–7.85 (m, 5H, Ph); MS (CI): *m/z* 229 (M+H); HRMS: calcd for $C_{11}H_{18}$PSO 229.081602 found 229.08156.

Table 4
Oxidation of phosphine sulfides with iodoxybenzene

Entry	Substrate			Product			
	Symbol	$[\alpha]_D$[a]	ee (%)	Symbol	Yield (%)	$[\alpha]_D$[a]	ee (%)
1	(+)-(*S*)-**12a**	+18.0	77	(−)-(*R*)-**3a**	32	−10.7	45
2	(+)-(*S*)-**12c**	+26.1	>99	(−)-(*R*)-**3c**	68	−13.5	66
3	(−)-(*R*)-**12c**	−22.2	85	(+)-(*S*)-**3c**	50	+10.2	60
4	(−)-(*R*)-**15**	−5.7	45	(−)-(*S*)-**7**	30	−1.9	17
5	(−)-(*R*)-**18**	−25.2	100	(+)-(*R*)-**10**	30	−29.8	70

[a] In chloroform, *c* 1.

4.4.4. Compound (−)-(*R*)-18

Yield 40%, $[\alpha]_D$ = −25.2 (*c* 1, $CHCl_3$), 100% ee ^{31}P NMR ($CDCl_3$): δ 84.73. ^{1}H NMR ($CDCl_3$): δ 1.08 (d, J = 6.18 Hz, 3H, $(CH_3)_2$CHO), 1.36 (d, J = 6.18 Hz, 3H, $(CH_3)_2$CHO), 1.98 (d, J = 13.63 Hz, 3H, CH_3), 4.61–4.79 (m, 1H, $(CH_3)_2CH$O), 7.41–8.01 (m, 5H, Ph). MS (CI): *m/z* 215 (M+H).

4.5. Oxidation of phosphine sulfides with iodoxybenzene—general procedure

To a solution of **12**, **15,** or **18** (0.226 mmol) in chloroform (5 mL), iodoxybenzene (53 mg, 1.2 equiv = 0.271 mmol) and a few milligrams of Montmorillonite K-10 as an activator were added. The suspension was stirred at room temperature. The reaction was monitored by TLC (CH_2Cl_2/MeOH 20:1) or ^{31}P NMR. After filtration of the solid material, the solvent was removed under vacuum and the residue was purified by column chromatography using dichloromethane/methanol in gradient as solvent. Analytical data for the products were identical with those for the starting substrates. The yields, specific rotations and ee values are given in Table 4.

4.6. Sulfuration of (+)-(*R*)-10 with Lawesson reagent

To a solution of (+)-(*R*)-**10** {$[\alpha]_D$ = +40 (*c* 1.06, $CHCl_3$), ee = 100% (51 mg, 0.260 mmol)} in benzene (5 mL), Lawesson's reagent (105 mg, 0.260 mmol) was added. The reaction mixture was refluxed until the substrate was consumed (^{31}P NMR control). The solvent was removed under vacuum and the residue was purified by column chromatography using dichloromethane as solvent to give pure product (+)-(*S*)-**18**. Yield 58%, $[\alpha]_D$ = +25.2 (*c* 0.81, $CHCl_3$), ee = 100% (HPLC: Chiralpak OD; Hexane: (*i*-PrOH/EtOH 4:1) 98:2; fl. 0.5 mL/min; t_R = 7.96 min). For analytical data see (−)-(*R*)-**18**.

4.7. Transformation of hydroxymethylphosphine oxides into hydroxymethylphosphine sulfides with Lawesson's reagent

The hydroxymethylphosphine oxides **3a**, **3c,** and **7** were first acetylated using acetyl chloride–triethylamine under standard conditions to obtain **4a**, **4c**, and **16**. The sulfuration of the latter was performed as for (+)-(*R*)-**10** (vide supra). The resulting acetoxymethylphosphine sulfides **13a**, **13c,** and **17**, respectively, were then treated with sodium methoxide in methanol to give **12a**, **12c,** and **15**, respectively (see Schemes 2 and 3). The results are shown in Table 5.

4.8. Computational details

Full conformation analysis of both hydroxymethyl(*i*-propoxy)phenylphosphine *P*-borane **1c** and hydroxymethyl(*i*-propoxy)-phenylphosphine oxide **3c** was performed using the Spartan '08 program and the PM3 semiempirical method.[20] Sixteen and ten conformers were found for **1c** and **3c**, respectively. All conformers were further optimized at the B3LYP/6-31+G* level with

Table 5
Reactions of hydroxymethylphosphine oxides with Lawesson's reagent

Substrate, phosphine oxide				Product, phosphine sulfide					
CH_2OH		CH_2OAc		CH_2OAc			CH_2OH		
Symbol	$[\alpha]_D$[a] (ee [%])	Symbol	$[\alpha]_D$[a] (ee [%])	Symbol	Yield (%)	$[\alpha]_D$[a] (ee [%])	Symbol	Yield (%)	$[\alpha]_D$[a] (ee [%])
(−)-(*R*)-**3a**	−21.0 (85)	(−)-(*R*)-**4a**	−45.2 (85)	(−)-(*S*)-**13a**	83	−31.4 (85)	(−)-(*S*)-**12a**	100	−18.0 (77)[b]
(−)-(*R*)-**3c**	−17.5 (79)	(−)-(*R*)-**4c**	−30.5 (79)	(−)-(*S*)-**13c**	70	−18.2 (79)	(−)-(*S*)-**12c**	100	−9.3 (80)
(−)-(*S*)-**7**	−4.8 (43)	(+)-(*S*)-**16**	+13.2	(+)-(*S*)-**17**	75	+27.8	(+)-(*S*)-**15**	93	+5.2 (45)

[a] In chloroform, *c* 1.
[b] Partial racemization due to the MeO–MeO exchange at the phosphorus atom upon treatment with MeONa/MeOH.

tight convergence criteria using the GAUSSIAN 03 program,[21] yielding only seven and eight different structures for **1c** and **3c**, respectively, since some individual conformations found at the PM3 level converged to the same conformation at the DFT level. The stationary point nature of all of the obtained structures was verified by the vibrational analysis. Vibrational analysis also provided thermal corrections to calculated Gibbs free energies of conformers at 298 K. SCRF calculations of conformer distribution and optical rotation have been performed using the CPCM method[22] with UAKS atomic radii assuming $CHCl_3$ as solvent. The specific rotation was calculated using the B3LYP/6-311++G(2d,2p) method for D line of Na (λ = 589 nm) as the population-weighted average of the rotations of individual conformations according to Boltzmann distribution at the B3LYP/6-311++G(2d,2p)//B3LYP/6-31+G* level.

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