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Use of new chiral tricoordinated phosphorus borane complexes in enantioselective borane reduction of ketones: complexes structure and mechanistic studies

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Abstract

New tricoordinated phosphorus borane complexes were synthesized and their use as catalysts in enantioselective borane reduction of prochiral aromatic and aliphatic ketones was investigated. The structure of (2*R*,5*S*)-2-*o*-anisyl-3-oxa-1-aza phosphabicyclo[3.3.0]octane–borane complex **1b** and (2*R*,5*S*)-2,3-diphenyl-1,3-diazaphosphabicyclo[3.3.0]octane–borane complex **6a** was established by X-ray diffraction analysis. A relationship has been established between the structure of the oxazaphospholidine borane complexes and the enantioselectivity obtained in the reduction of acetophenone, both with 2 mol% and one equivalent of the catalyst. Among the different oxazaphospholidine borane complexes tested, only the complexes **1–3**, including 3-oxa-1-azaphosphabicyclo-[3.3.0]octane and 3-oxa-1-azaphosphabicyclo[4.3.0]nonane moieties, were efficient catalysts. A rational mechanism is proposed according to the experimental results, especially from a deuterium labelling study.

Keywords: Enantioselective; Borane; Reduction; Ketones; Organophosphorus–borane complexes; Oxazaphospholidines

1. Introduction

Based on the pioneering research of Itsuno's group [1], Corey discovered that the reduction of ketones by borane is efficiently catalyzed by chiral oxazaborolidine and provides alcohols with excellent enantioselectivity and predictable stereochemistry [2]. Since this discovery, new chiral and efficient oxazaborolidines have been prepared and applied in enantioselective synthesis [3,4].

1,3,2-Oxazaphospholidines are versatile reagents in asymmetric organophosphorus chemistry [5] and have been shown to be effective co-catalysts in enantioselective reactions [6–8]. Recently, we reported [9] a new method for the enantioselective reduction of ketones with either BH_3:THF or BH_3:SMe_2 catalyzed by (2*R*,5*S*)-2-phenyl-3-oxa-1-azaphosphabicyclo[3.3.0]octane–borane complex **1a** (Scheme 1).

This oxazaphospholidine borane complex **1a** can easily be prepared by action of 1.3 equivalents of BH_3:THF on (2*R*,5*S*)-2-phenyl-3-oxa-1-azaphosphabicyclo-[3.3.0]octane and further purification by flash chromatography on silica gel (eluent diethyl ether–pentane, 50/50) in 97% chemical yield (Scheme 2).

The use of a catalytic amount (2 mol%) of complex **1a** in the enantioselective borane reduction of various ketones led to the corresponding alcohols with enantioselectivities ranging from 33 to 92% and quantitative conversion at 110 °C, whereas the reduction proceeded with 99% enantiomeric excess under stoichiometric conditions. Furthermore, we have recently described an application of this complex in the catalytic enantioselective borane reduction of imines [10].

Herein, we report the synthesis of several new oxazaphospholidine and diazaphospholidine borane complexes and their use in the enantioselective borane reduction of acetophenone. The aim of these investigations is to establish a relationship between the structure of the oxazaphospholidine borane complex and the enantioselectivity obtained in the reduction of a prochiral ketone. Understanding the mechanism of this new

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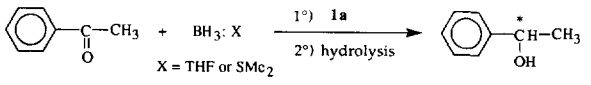


Scheme 1.

enantioselective reduction is a key component in designing new efficient chiral tricoordinated phosphorus borane catalysts. Consequently, we have studied the mechanism of this reduction reaction by both experimental and theoretical means.

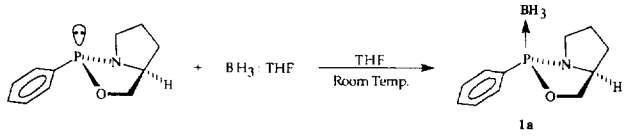
2. Results and discussion

2.1. Synthesis of borane complexes

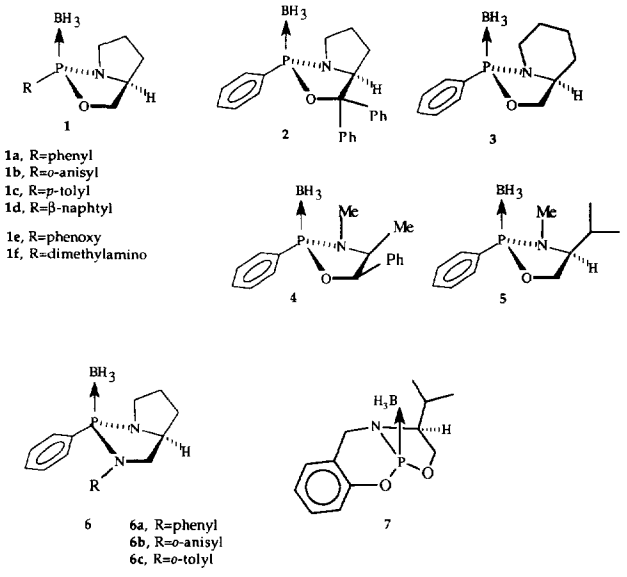
In order to ascertain the structural features which contribute to the enantioselectivity, a number of analogues of **1a** have been prepared by exchange reaction from several tricoordinated phosphorus compounds and either aminoalcohols, diamines or amino diol (Scheme 3).

A wide variety of diastereomerically pure oxazaphospholidines have been prepared from (*S*)-(+)-prolinol, by exchange reaction in refluxing toluene with $RP(NMe_2)_2$ (R = phenyl, *o*-anisyl, *p*-tolyl, β-naphthyl, dimethylamino) [6,11]. These ligands have been applied successfully in different enantioselective reactions such cycloaddition, carbonylation, amination catalyzed by different transition metal complexes [6,7]. These oxazaphospholidines react with 1.3 equivalents of BH_3:THF (or BH_3:SMe_2) in THF for 12 h at room temperature, yielding complexes **1a–d** and **1f**. Action of phenol on (2*R*,5*S*)-2-dimethylamino-3-oxa-1-azaphosphabicyclo[3.3.0]octane in refluxing toluene gave a mixture of two diastereomer *anti* and *syn* compounds, respectively (2*R*,5*S*)- and (2*S*,5*S*)-2-phenoxy-3-oxa-1-azaphosphabicyclo[3.3.0]octane in a ratio 90:10. From this mixture we have obtained only one crystallized diastereomer borane complex **1e**. Complex **2** was prepared in the same way as **1a**, from α,α′-diphenyl-2-pyrrolidinemethanol [12] in order to probe the influence of steric hindrance on the reaction.

Furthermore, we have synthesized an analogue of **1a** with a piperidine ring instead of the pyrrolidine ring to analyze the effect of the ring size on the enantioselectivity. Pure (*S*)-piperidine-2-methanol was obtained by enzymatic kinetic resolution from (*RS*)-piperidine-2-methanol [13] and led to complex **3** by the procedure



Scheme 2.



Scheme 3.

described above. Moreover, the acyclic β-amino alcohols (−)-ephedrine and (*S*)-*N*-methylvalinol were used for the synthesis of the 1,3,2-oxazaphospholidine borane complexes **4** [14] and **5** from exchange reaction with the bis(dimethylamino)phenylphosphine followed by treatment with a solution of BH_3:THF complex at room temperature. The 1,3,2-oxazaphospholidine prepared from (*S*)-*N*-methylvalinol was obtained in diastereomeric ratio of 85:15, but distillation of the oxazaphospholidine afforded nearly only one diastereomer with probably the (2*R*,5*S*) configuration [15]. Chiral diazaphospholidine borane complexes **6a–c** were prepared from the corresponding diamines to evaluate the role of the nature of the intracyclic heteroatom on the enantioselectivity. (*S*)-Glutamic acid was converted to (*S*)-5-oxopyrrolidine-2-carboxanilide in refluxing aniline, and subsequent reduction with lithium aluminum hydride afforded (*R*)-2-anilinomethylpyrrolidine [16]. Exchange reaction with bis(dimethylamino)phenylphosphine followed by treatment with a solution of BH_3:THF complex at room temperature led to the formation of complex **6a**. The other compounds **6b–c** were prepared according to this procedure.

The 3,4-benzo-7-isopropyl-2,9-dioxa-6-aza-1-phospha^{III}bicyclo[4.3.0] compound was synthesized by exchange reaction between tris(dimethylamino)phosphine and (*R*)-*N*-(*o*-hydroxybenzyl)valinol in refluxing toluene. This aminodiol has been prepared from (*S*)-(+)-valinol in a two-step sequence, involving formation of an imine with salicylaldehyde, followed by reduction with $AlLiH_4$. As shown, ^{31}P NMR spectroscopy (one signal at $\delta = 128.9$ ppm) this exchange reaction led to the formation of a single diastereomer bicyclic compound. This phosphane has three chiral centers: phos-

Table 1
NMR properties of borane complexes

Complex	$\delta^{31}P$ (ppm)	$\delta^{11}B$ (ppm)	$^1J_{P-B}$ (Hz)
1a (R = Phenyl)	139.9	−40.7	72.6
1b (R = *o*-Anisyl)	142.2	−40.1	69.2
1c (R = *p*-Tolyl)	140.1	−39.8	71.5
1d (R = β-Naphthyl)	125.2	−38.5	71.0
1e (R = Phenoxy)	133.5	−41.2	72.2
1f (R = Dimethylamino)	144.5	−42.3	75.3
2	139.9	−38.2	72.6
3	128.9	−39.7	68.1
4	134.2	−40.2	67.2
5	144.3	−40.4	68.2
6a (R = Phenyl)	101.9	−35.3	68.1
6b (R = *o*-Anisyl)	102.5	−36.8	72.3
6c (R = *o*-Tolyl)	101.7	−35.2	69.5
7	127.3	−41.2	68.3

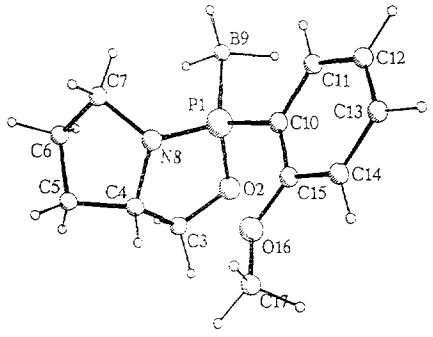


Fig. 1. X-ray diffraction analysis of complex **1b**. Selected bond lengths (Å) and angles (deg). B9–P1 1.917, O2–P1 1.602, N8–P1 1.661, C10–P1 1.802; (C4–N8–C7 110.6, C4–N8–P1 110.9, C7–N8–P1 121.4, sum 342.9); N8–P1–O2 97.5, B9–P1–O2 110.9, B9–P1–N8 115.9; C10–P1–N8 109.4, B9–P1–C10 113.7, C10–P1–O2 104.5.

phorus, nitrogen and carbon. Neglecting the highly constrained configuration in which the lone pairs on phosphorus and nitrogen are trans, it can be assumed that the absolute configurations on the chiral centers are (1*R*,6*R*,7*S*) with the isopropyl group is on a 'roof position' as shown by the molecular model. The treatment of this new chiral bicyclic phosphane by BH_3:THF solution led quantitatively to complex **7**.

These new complexes stable to air and moisture were isolated in almost quantitative chemical yields after flash chromatography on silica gel (eluent: diethyl ether–pentane, 50/50)(Table 1).

Chemical shifts of ^{11}B and coupling constants $^1J_{P-B}$ are in agreement with those already reported [17].

For example, for **1a** the coordination of a BH_3 group to a phosphorus atom was established by the presence of a quartet at $\delta = 139.9$ ppm in $^{31}P\{^1H\}$ spectra and by a doublet at $\delta = -40.7$ ppm in $^{11}B\{^1H\}$ spectra with a $^1J_{P-B} = 72.6$ Hz. The bicyclic aminophosphane borane complex **7** was interesting because its bicyclic structure and the pyramidal phosphorus atom force the nitrogen atom to stay pyramidal. We expected this to hinder the $p\pi$–$d\pi$ interaction and to restore the nitrogen atom's donor properties. However, in contrast to the observation reported by Riess and coworkers [18] on the bicyclicphosphanes, we have not observed the formation of the bis(borane)aminophosphane adduct revealing the strong basic character of the nitrogen atom bound to the phosphorus atom. In our case, the steric effect of the isopropyl group probably decreases the reactivity of the nitrogen atom with respect to the free borane.

The X-ray diffraction analyses of complexes **1b** and **6a** (Figs. 1 and 2) showed that the configuration at the phosphorus atom was retained during borane complexation [19,20]. In complexes **1b** and **6a**, the sum of the bond angles around the nitrogen atom of the pyrrolidine ring are respectively 342.9° and 344.7°, showing in both cases a non-planar configuration. In complex **6a**, the sum of the bond angles around the N5 atom is 356.8°, showing an almost planar configuration. Moreover, the phenyl ring (C16–C21) is almost coplanar with the atoms N5, P1, C4 and the bond distance N5C16 is short (1.40 Å), suggesting an interaction between the lone pair of the nitrogen atom and the aromatic system.

Although the borane complexation rate must depend upon the nature of atoms liganded to the phosphorus atom [21], we have found that the tricoordinated compounds **1a** and **6a** possessed the same reactivity with respect to BH_3:SMe_2 in benzene solution: in a competitive reaction, the relative rate of complexation determined by ^{31}P NMR spectroscopy was $k_{1a}/k_{6a} \approx 1$.

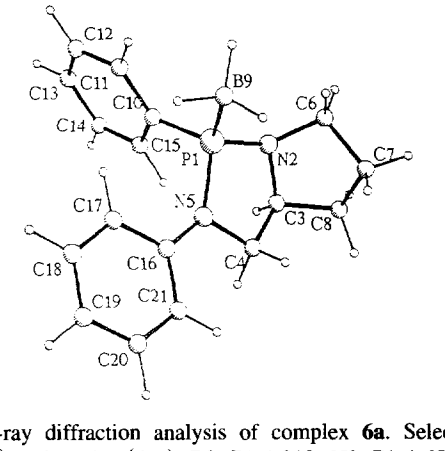


Fig. 2. X-ray diffraction analysis of complex **6a**. Selected bond lengths (Å) and angles (deg). B9–P1 1.910, N2–P1 1.659, N5–P1 1.684, C10–P1 1.806; (C3–N2–P1 111.2, C6–N2–P1 124.0, C3–N2–C6 109.5, sum 344.7); N5–P1–N2 95.3, B9–P1–N5 118.4, B9–P1–N2 114.8, C10–P1–N2 107.4, B9–P1–C10 114.5, N5–P1–C10 104.3; (C4–N5–P1 112.2, C16–N5–P1 124.5, C4–N5–C16 120.1, sum 356.8).

3. Relationship between catalyst structure and enantioselectivity in the reduction of acetophenone

We reported a peculiar behavior for the borane reduction towards ketones where the enantioselectivity increased with temperature [9]. Thus, the catalytic reduction of acetophenone in the presence of 2 mol% of complex **1a** gave the highest *e.e.* in refluxing toluene (Fig. 3). Under these conditions the acetophenone was totally transformed into the corresponding alcohol in less than 5 min. The enantioselectivity increased with the amount of catalyst, culminating in greater than 99% *e.e.* with one equivalent of complex **1a** (Fig. 4).

Complexes **1a–7** were used as catalysts in the reduction of acetophenone by BH_3:THF in refluxing toluene. All reactions were performed both with 2 mol% and one equivalent of complex **1a** (Table 2).

In every case, the (*R*)-1-phenylethanol was obtained as the major enantiomer. Enantioselectivity seems to be very sensitive to the structure of the catalyst. Complexes **1a–1f** gave low enantiomeric excesses (22–37%) when used in 2 mol% ratio. However, use of one equivalent of these complexes led to high levels of asymmetric induction (*e.e.* > 99%). Under catalytic conditions (2 mol%), a still lower *e.e.* was obtained, increasing the steric hindrance on the oxazaphospholidine ring (complex **2**). Replacement of the pyrrolidine ring by a piperidine one (complex **3**) had the same effect. However, the use of complexes **2** and **3** in stoichiometric amounts led to *e.e.* > 99%. The substitution of the oxazaphospholidine by a diazaphospholidine ring (complexes **6a–c**) proved to be detrimental towards the enantioselectivity. Catalysts derived from (−)-ephedrine and *N*-methylvalinol were inefficient (complexes **4** and **5**), as was also the case from the peculiar bicyclicphosphane (complex **7**). As a result, oxazaphospholidines derived from prolinol were demonstrated to be useful catalysts for enantioselective reduction of prochiral ketones. The 3-oxa-1-azaphosphabicyclo[3.3.0] moiety appeared to be crucial to obtain high *e.e.* in catalytic borane reductions,

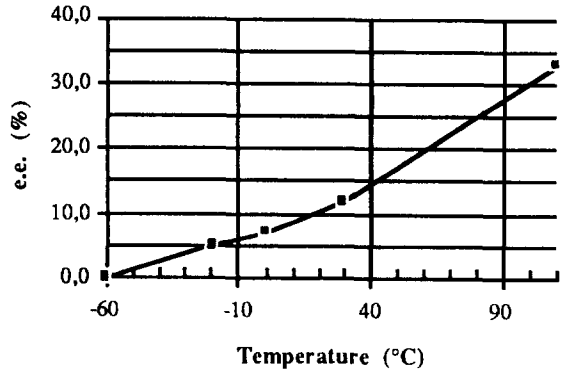


Fig. 3. Plot of enantioselectivity against temperature for borane reduction of acetophenone catalyzed by complex **1a** (2 mol.%).

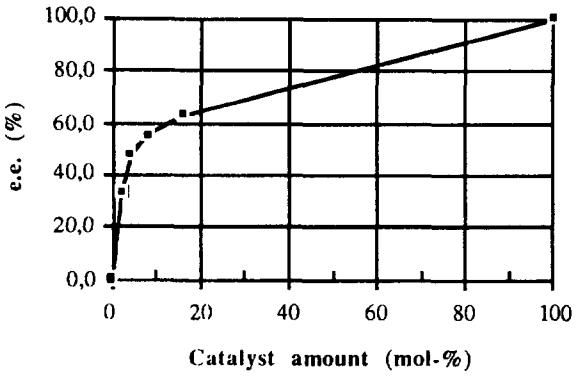


Fig. 4. Plot of enantioselectivity against amount of catalyst for borane reduction of acetophenone catalyzed by complex **1a**.

the extracyclic ligands of complexes **1** playing a secondary role on the enantioselectivity.

Complex **1a** was used as catalyst in the enantioselective reduction of several prochiral ketones. The enantioselectivity depends on the nature of the ketones (Table 3). Reduction of aromatic ketones (entries 1 and 2) gave low enantiomeric excesses, compared with the results obtained with aliphatic ketones (entries 4–7). The best result was obtained for *iso*-propyl methyl ketone (entry 4), which the reduction afforded in few minutes to (*S*)-2-methyl-3-propanol in 92% *e.e.* Ethyl acetoacetate was reduced in 76% *e.e.* (entry 8) and 2-acetyl furane gave the corresponding alcohol in 40%

Table 2
Reduction of acetophenone by BH_3:THF, catalyzed by oxazaphospholidine–borane complexes at 110 °C [a]

Entry	Complex	2 mol% [b]		One equivalent [c]		Abs. Conf. [d]
		e.e. (%) [e]	Yield (%) [f]	*e.e.* (%) [e]	Yield (%) [f]	
1	**1a**	33	75	> 99	74	*R*
2	**1b**	36	73	> 99	76	*R*
3	**1c**	31	76	> 99	69	*R*
4	**1d**	30	69	> 99	71	*R*
5	**1e**	22	72	> 99	76	*R*
6	**1f**	37	71	> 99	69	*R*
7	**2**	10	76	> 99	76	*R*
8	**3**	8	81	> 99	75	*R*
9	**4**	0	83	< 5	80	—
10	**5**	1	77	< 5	73	—
11	**6a**	2	74	< 5	70	—
12	**6b**	1	73	< 5	73	—
13	**6c**	4	68	< 5	71	—
14	**7**	3	78	< 5	75	—

[a] Reactions run in toluene; see the Section 6 for general procedures. [b] Ketone/borane/catalyst ratio 1:1:0.02. [c] Ketone/borane/catalyst ratio 1:1:1. [d] Absolute configuration based upon measurement of optical rotation. [e] Enantiomeric purity determined by ^{31}P NMR spectroscopy, using (4*R*,5*R*)-dicarboalkoxy-2-chloro-1,3,2-dioxaphospholane as a chiral derivatizing reagent [22]. [f] Isolated yield of distilled product.

Table 3
Reduction of ketones with 2 mol% of **1a** at 110 °C [a]

Entry	Ketone	*e.e.* (%) [b]	Abs. Conf. [c]	Yield (%) [d]
1	Acetophenone	33	*R*	80
2	Propiophenone	38	*R*	63
3	Benzyl methyl ketone	55	*S*	81
4	*iso*-Propyl methyl ketone	92 [e]	*S*	75
5	*tert*-Butyl methyl ketone	36	*R*	67
6	2-Butanone	42	*R*	58
7	2-Hexanone	50	*S*	73
8	Ethyl acetoacetate	76	*R*	76
9	2-Acetyl furane	40	*R*	70

[a] Reactions run in toluene; see Section 6 for general procedures. [b] Unless otherwise noted, enantiomeric purity determined by ^{31}P NMR spectroscopy, using (4*R*-5*R*)-dicarboalkoxy-2-chloro-1,3,2-dioxaphospholane as a chiral derivatizing reagent. [c] Absolute configuration based upon measurement of optical rotation. [d] Isolated yield of distilled product. [e] Enantiomeric excess was determined by CPG analysis of the isopropylurethane derivatives, on a chiral capillary column XE-S-60-(*S*)-valine-(*S*)-α-phenyl-ethylamide.

e.e. (entry 9). Nevertheless, in all cases the use of one equivalent of complexes **1a** led to *e.e.* > 99%.

4. Mechanistic studies of the enantioselective borane reduction of acetophenone catalyzed by complex 1a

In order to propose a mechanistic rationale, several experimental features have to be taken into account:

- the enantioselectivity of the borane reduction towards ketones increased with temperature;
- concurrently with the catalytic enantioselective reduction of acetophenone by BH_3:THF, there was a non-catalyzed reduction of the ketone by free borane;
- the stoichiometric reaction between acetophenone and **1a** did not yield 1-phenylethanol, even at elevated temperatures. Addition of one equivalent of BH_3:THF changes significantly the outcome of the reaction, leading to high chemical yields and *e.e.* of the corresponding alcohols. Considering these facts, the question arises as to the origin of the transferred hydride to the carbonyl group.

In the reaction between an oxazaphospholidine–BD_3 complex **8** (analogous to **1a**), acetophenone and BH_3:THF in a molar ratio 1:1:1, quantitative transfer of deuterium atoms was observed and (*R*)-1-^{2}H-1-phenylethanol was obtained in *e.e.* > 99% in refluxing toluene.

This fact was confirmed using complex **1a**, acetophenone and BD_3:THF in a molar ratio 1:1:1, which afforded only non-deuterated (*R*)-1-phenylethanol. Under these conditions, no exchange reaction between the deuterated borane complex and free borane was observed. Therefore, in the stoichiometric reaction, the hydride transfer on the carbonyl group proceeded only from the BH_3 unit complexed to the phosphorus atom.

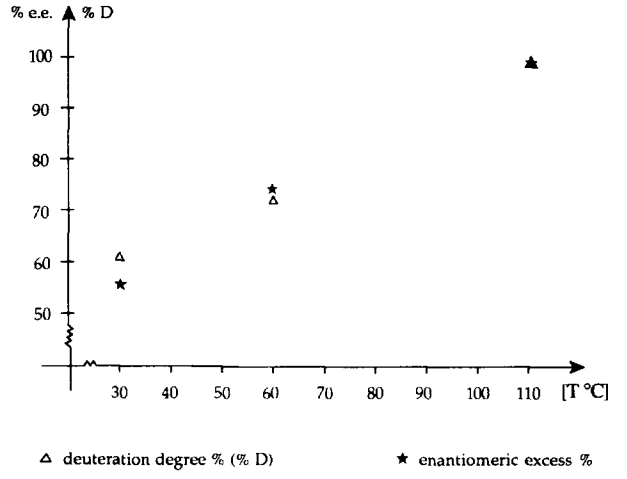
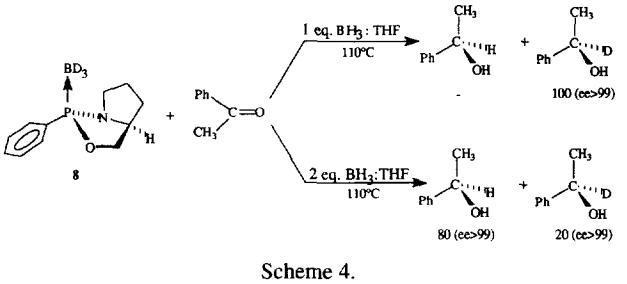


Fig. 5. Plots of enantiomeric excess and deuteration degree against temperatures for borane reduction of acetophenone catalyzed by complex **8** (one equivalent).

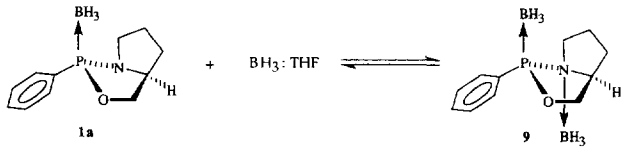
At 30 and 60 °C, reaction of complex **8**, BH_3:THF and acetophenone (molar ratio 1:2:1) led to a mixture of 1-^{2}H-1-phenylethanol and 1-phenylethanol (Fig. 5). Assuming that there was no isotopic effect on the determination of *e.e.*, we found a direct correlation between *e.e.* and deuterated compound percentage. This suggests that in the case of the stoichiometric reaction the enantioselectivity results only from the transfer from the coordinated BH_3–P^{III} on the *si* enantiotopic face of the acetophenone to give rise to (*R*)-1-phenylethanol. Under either catalytic conditions or excess of borane vs. **1a**, the hydrogen transfer proceeds following a more complex mechanism. In fact, the use of complex **8**, BH_3:THF and acetophenone in a molar ratio 1:2:1 in refluxing toluene led to a mixture of (*R*)-1-^{2}H-1-phenylethanol and (*R*)-1-phenylethanol in a 20/80 ratio with an *e.e.* > 99% (Scheme 4).

These results allow one to suggest the existence, at elevated temperature, of two possible enantioselective mechanisms depending on the amount of borane used.

It is well known that a nitrogen atom bound to a phosphorus atom loses most or all of its donor character and the nitrogen adopts a coplanar arrangement with its substituents. This fact is usually interpreted as resulting from the involvement of the nitrogen lone pair into π bonding with the π-acid phosphorus atom. Therefore,



Scheme 4.

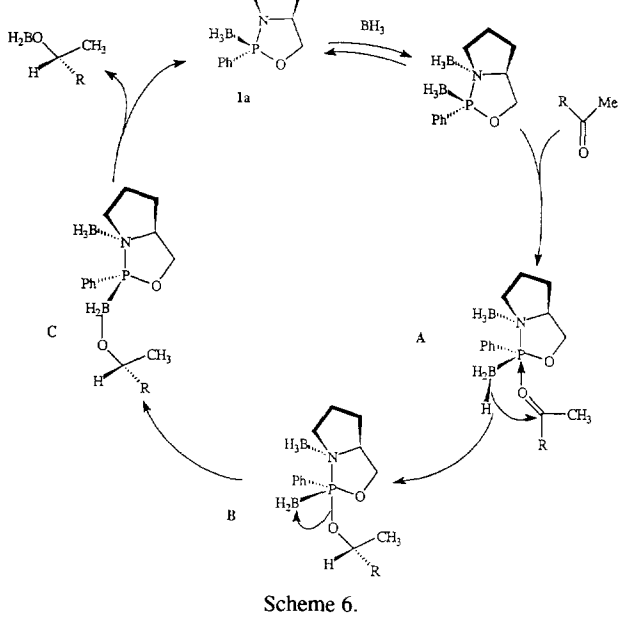


Scheme 5.

when aminophosphanes are allowed to react with borane, only one BH_3 group is coordinated to the phosphorus atom. The very few exceptions known to this general behavior concern a constrained structure in which the nitrogen atom is forced to stay pyramidal [18,23,24]. As revealed by X-ray analysis, the bicyclic nitrogen atoms of compounds of **1b** and **6a** have a non-planar configuration increasing their ligating ability with respect to the borane. This assumption was supported by observations of the ^{31}P NMR spectra of mixtures of **1a** and BH_3:THF. Addition of increasing amounts of BH_3:THF to a toluene solution of **1a**, showed the emergence of a broadened signal at $\delta = 162.3$ ppm, due to the likely formation of complex **9**, and the concomitant decrease of the **1a** signal (quartet, $\delta = 139.9$ ppm) (Scheme 5). This complexation was reversible and returned to the original complex **1a** by removing borane under vacuum. Nevertheless, complex **9** could not be isolated; neither could its structure be established unambiguously.

From these different experimental observations, a mechanism for the enantioselective borane reduction of ketones promoted by **1a** can be proposed (Scheme 6).

Anti approach of the ketone to the P–N bond is favored by borane coordination to the non-planar nitrogen atom increasing the electrophilic character of the tetracoordinated phosphorus atom. This approach leads to a trigonal bipyramidal (TBP) intermediate **A** in which



Scheme 6.

the five-membered oxazaphospholane ring is placed in a favorable apical equatorial position with the nitrogen atom coordinated by borane in apical positions. In this TBP intermediate the oxygen of the ketone is in an apical position and the intracyclic oxygen, the phenyl and the borane groups are in equatorial positions. The intramolecular hydride transfer occurs in **A** from the equatorial borane group to the *si* face of the ketone *via* a five-membered cyclic process to form an intermediate TBP **B**. This TBP intermediate is transformed into a tetracoordinated complex **C** by the apical oxygen transfer from the phosphorus atom to the electrophilic boron atom according to a three center mechanism. The TBP **C** leads, by dissociation, to the alkoxyborane and complex **1a**.

This proposed mechanism accounts for experimental observations:

(1) the hydrogen transfer to the ketone from the borane group coordinated to the phosphorus atom;

(2) the importance of the non-planar configuration of the nitrogen atom: the oxazaphospholidine complexes **4** and **5**, in which the nitrogen atom must be nearly planar such as the N5 nitrogen in **6a**, are ineffective in the enantioselective borane reduction of ketones;

(3) the analogous diazaphospholidine–borane complexes **6a–c** were shown to be inefficient in the enantioselective borane reduction of ketones. However, we have seen that the relative rate of oxazaphospholidine and diazaphospholidine complexation by the borane leading to **1a** and **6a** is $k_{1a}/k_{6a} \approx 1$. The complex **6a**, which is less reactive than **1a** for electrophilic and steric reasons, should react slowly with the ketone, and thus the non-catalyzed reduction of the ketone by free borane is favored;

(4) the enantioselectivity could be interpreted from the TBP **B** intermediate according to the relative positions of the substituents of the ketone with respect to the oxazaphosphabicyclo[3.3.0]octane moiety. In the case of the stoichiometric reaction a total enantioselectivity was observed, but the activity of **1a** is not sufficient to maintain this high level of enantioselectivity in catalytic conditions. The use of complex **1a** as a catalyst (2 mol%) in the enantioselective reduction of ketones showed clearly that the enantioselectivity depended mainly on the relative rates between the catalyzed and non-catalyzed reductions. The variation of enantioselectivity reported in Table 3 might be related to these relative rates, since in stoichiometric conditions high enantioselectivity was obtained (*e.e.* > 99%) for different ketones.

5. Conclusion

In the present paper we report a new class of catalysts in the enantioselective borane reduction of ke-

tones: the 1,3,2-oxazaphospholidine borane complexes. Although not as effective as oxazaborolidine catalyst [2] in terms of enantiomeric inductions, these compounds have the advantage of high stability and simple preparation.

Among the different oxazaphospholidine borane complexes studied in enantioselective borane reduction, only the complexes **1–3** with a bicyclic structure were effective. Under stoichiometric conditions in refluxing toluene did the complex **1a** present a high level of enantioselectivity for the reduction of several ketones (*e.e.* > 99%). A significant effect of temperature on selectivity was observed and the best results were obtained at elevated temperature. Such an effect has already been reported for the enantioselective borane reduction of ketones [25,26]. Here, this effect is essentially due to a competition between the catalyzed and non-catalyzed reduction. At the end of the reduction the complex **1a** can be recovered and reused without any loss of activity.

For this stoichiometric reaction an original mechanism has been proposed, taking into account experimental observations, and confirmed by theoretical studies [27]. Based on this, different new effective BH_3–P^{III} complexes could be conceived.

In the case of excess of borane, since the reaction led to a mixture of deuterated and non-deuterated alcohol in a 20:80 ratio with an *e.e.* > 99%, a second totally enantioselective reduction mechanism must be envisaged. As shown by preliminary ^{31}P NMR spectroscopic studies, at the end of the reduction the complex **1a** was partially transformed into new phosphorus–borane species. We are now investigating these new catalysts, and further structural, mechanistic, theoretical and synthetic studies are in progress.

Finally, this study demonstrates that the tricoordinated organophosphorus compounds can be used as enantioselective catalysts without transition metal complexes. Similarly, we have recently reported [28] that the oxazaphospholidine oxide prepared from (*S*)-prolinol is a efficient catalyst in the enantioselective borane reduction of ketones. Chloroacetophenone was reduced into the corresponding chlorhydrine in 94% *e.e.* and 92% yield at 60 °C in the presence of 2 mol% of catalyst in THF solution. These researches open the way for the synthesis of new chiral organophosphorus compounds in different coordination states and their use as catalysts [15,29–31] in enantioselective reactions.

6. Experimental section

All reactions were carried out under nitrogen. Tetrahydrofurane (THF) was dried over sodium wires and distilled over lithium aluminum hydride ($LiAlH_4$) immediately before use. Borane deuteride (BD_3) was prepared by reaction of sodium borohydride deuteride with boron trifluoride–diethyl ether complex according to the procedure of Brown [32]. The purities of all reagents were checked by NMR spectroscopy.

All melting points were taken on a Büchi apparatus, and are uncorrected. NMR spectra were taken on Bruker AC 100 MHz and AC 400 MHz spectrometers. IR spectra were measured with a Perkin–Elmer 298 IR spectrophotometer. Optical rotations were taken on a Perkin–Elmer 241 MC polarimeter.

All (2*R*,4*S*)-1,3,2-oxazaphospholidines were synthesized according to the previously described procedure [6,7].

6.1. General procedure for the synthesis of diastereomerically pure (2R,5S)-2-phenyl-3-aryl-1,3-diazaphosphabicyclo[3.3.0]octane

To a 25 ml two-necked round flask under nitrogen containing 6 ml of dry THF were dropped 5 mmol of the desired chiral diamine and 5.2 mmol of bis(dimethylamino)phenyl phosphine, each dissolved in 5 ml of dry THF. The solution was heated to reflux and the reaction was monitored by ^{31}P NMR spectroscopy. After completion of the reaction, the solvent was removed in vacuo and the resulting yellow oil subjected to fractional distillation under reduced pressure. In all cases, only one diastereomer of the product was obtained, as revealed by ^{31}P NMR spectroscopy.

6.1.1. (2R,5S)-2,3-Diphenyl-1,3-diazaphosphabicyclo-[3.3.0]octane

B.p. 155 °C (0.03 mm Hg). ^1H NMR ($CDCl_3$) δ (ppm): 1.8–1.9 (m, 3H), 2.0–2.1 (m, 1H), 3.0 (m, 1H), 3.2 (m, 1H), 3.4 (m, 2H), 4.0 (m, 1H), 6.8–7.4 (m, 10H); ^{31}P NMR (C_6D_6) δ (ppm): 98.1; $[\alpha]_{25}^{D} = +84.2$ ($c = 1$, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2980, 2860 (C–H), 1430 (P–Phenyl), 700.

6.1.2. (2R,5S)-2-Phenyl-3-o-tolyl-1,3-diazaphosphabicyclo[3.3.0]octane

Viscous oil; b.p. 150 °C (0.01 mm Hg); ^1H NMR ($CDCl_3$) δ (ppm): 1.6–2.1 (m, 6H), 2.3–2.4 (m, 1H), 3.2 (m, 1H), 3.5–3.7 (m, 3H), 4.0 (m, 1H), 7.0–7.2 (m, 9H); ^{31}P NMR (C_6D_6) δ (ppm): 98.3; $[\alpha]_{25}^{D} = +100.1$ ($c = 1$, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2980, 2860 (C–H), 1430 (P–Phenyl), 700.

6.1.3. (2R,5S)-2-Phenyl-3-o-anisyl-1,3-diazaphosphabicyclo[3.3.0]octane

B.p. 165 °C (0.01 mm Hg); ^1H NMR ($CDCl_3$) δ (ppm): 1.2–1.5 (m, 3H), 2.1 (s, 3H), 2.4–2.5 (m, 1H), 3.4 (m, 1H), 3.7–3.9 (m, 3H), 4.3 (m, 1H), 7.1–7.5 (m, 9H); ^{31}P NMR: (C_6D_6) δ (ppm): 99.3; $[\alpha]_{25}^{D} = +79.2$ ($c = 1$, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2980, 2860 (C–H), 1430 (P–Phenyl), 700.

6.2. General procedure for the synthesis of diastereomerically pure (2R,4S)-1,3,2-oxazaphospholidine–borane complexes (1–5)

To a stirred solution of (2*R*,4*S*)-1,3,2-oxazaphospholidine (500 mg) in THF was added 1.3 equivalents of BH_3:SMe_2 (2 M in THF). The mixture was allowed to stand with stirring at room temperature overnight. The solvent and the excess of borane were removed in vacuo, affording the corresponding complex oxazaphospholidine borane in quantitative yields.

Purification of all complexes was performed by chromatography on silica gel (eluent: diethyl ether–pentane, 50/50).

6.2.1. (2R,5S)-2-Phenyl-3-oxa-1-azaphosphabicyclo-[3.3.0]octane–borane complex ***1a***

Solid; m.p. 134 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.2–2.1 (m, 4H), 2.3–2.6 (m, 1H), 3.7–4.6 (m, 4H), 7.1–7.9 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.4 (d, $^3J_{CP}$ = 2.4 Hz), 31.0 (d, $^3J_{CP}$ = 1.7 Hz), 48.3 (d, $^2J_{CP}$ = 6.9 Hz), 62.4 (d, $^2J_{CP}$ = 1.3 Hz), 72.1 (d, $^2J_{CP}$ = 6.2 Hz), 128.4 (d, $^2J_{CP}$ = 10.7 Hz), 130.1 (d, $^3J_{CP}$ = 10.7 Hz), 131.7 (d, $^4J_{CP}$ = 2.7 Hz), 130.5 (m, $^1J_{CP}$ = 83.9 Hz, $^2J_{CB}$ = 33.6 Hz); ^{31}P NMR ($CDCl_3$) δ (ppm): 139.9 (q, $^1J_{PB}$ = 72.6 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −40.7 (d, $^1J_{PB}$ = 77.6 Hz); $[\alpha]_{25}^{D}$ = +103.5 (c = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2940, 2860 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1090 (C–O), 950 (P–O–C), 700, 666.

6.2.2. (2R,5S)-2-o-Anisyl-3-oxa-1-azaphosphabicyclo-[3.3.0]octane–borane complex ***1b***

Solid; m.p. 178 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.1 (s, 3H), 1.5–2.0 (m, 3H), 2.8–2.9 (m, 1H), 3.3–3.5 (m, 6H), 3.7–4.0 (m, 2H), 6.5–7.2 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.8 (d, $^3J_{CP}$ = 2.3 Hz), 30.8 (d, $^3J_{CP}$ = 3.1 Hz), 4 8.6 (d, $^2J_{CP}$ = 8.0 Hz), 55.7, 62.8 (d, $^2J_{CP}$ = 2.0 Hz), 72.9 (d, $^2J_{CP}$ = 6.0 Hz), 111.5 (d, $^2J_{CP}$ = 4 Hz), 120.6 (d, $^2J_{CP}$ = 10.0 Hz), 124.1 (d, $^1J_{CP}$ = 57.0 Hz), 133.0 (d, $^3J_{CP}$ = 7.0 Hz), 133.6, 161.5 (d, $^2J_{CP}$ = 4.0 Hz); ^{31}P NMR ($CDCl_3$) δ (ppm): 142.2 (q, $^1J_{PB}$ = 69.2 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −40.1 (d, $^1J_{PB}$ = 72.1 Hz); $[\alpha]_{25}^{D}$ = +115.3 (c = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2940, 2860 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1410, 1380 (CH_3), 1090 (C–O), 950 (P–O–C), 700.

6.2.3. (2R,5S)-2-p-Tolyl-3-oxa-1-azaphosphabicyclo-[3.3.0]octane–borane complex ***1c***

Solid; m.p. 106 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.2–1.4 (m, 4H), 2.8 (s, 3H), 3.1–4.2 (m, 8H), 6.8–7.4 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.7, 27.1, 33.2, 54.1 (d, $^2J_{CP}$ = 30.0 Hz), 63.1 (d, $^2J_{CP}$ = 4.0 Hz), 73.1 (d, $^2J_{CP}$ = 10.0 Hz), 121.3, 131.3, 153.1 (d, $^2J_{CP}$ = 24.0 Hz); ^{31}P NMR ($CDCl_3$) δ (ppm): 140.1 (q, $^1J_{PB}$ = 71.5 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −39.8 (d, $^1J_{PB}$ = 75.4 Hz); $[\alpha]_{25}^{D}$ = +98.1 (c = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3060, 2930 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1410, 1380 (CH_3), 1090 (C–O), 950 (P–O–C), 700.

6.2.4. (2R,5S)-2-β-Naphthyl-3-oxa-1-azaphosphabicyclo[3.3.0]octane–borane complex ***1d***

Solid; m.p. 122 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.3–1.4 (m, 4H), 2.3–2.5 (d, 2H), 3.1–4.2 (m, 6H), 6.4–7.5 (m, 7H); ^{31}P NMR ($CDCl_3$) δ (ppm): 125.2 (q, $^1J_{PB}$ = 71.0 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −39.6 (d, $^1J_{PB}$ = 73.5 Hz); $[\alpha]_{25}^{D}$ = +123.3 (c = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3060, 2930 (C–H), 2350 (B–H), 1430 (P–Arom.), 1090 (C–O), 950 (P–O–C).

6.2.5. (2R,5S)-2-Dimethylamino-3-oxa-1-azaphosphabicyclo[3.3.0]octane–borane complex ***1e***

Solid; m.p. 83 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.3–1.8 (m, 4H), 2.1 (s, 6H), 2.3–2.5 (quint., 1H), 3.7–4.3 (m, 7H); ^{13}C NMR ($CDCl_3$) δ (ppm): 26.1 (d, $^3J_{CP}$ = 3.0 Hz), 31.3, 36.3 (d, $^2J_{CP}$ = 17.4 Hz), 48.2 (d, $^2J_{CP}$ = 32.3 Hz), 62.1, 73.4 (d, $^2J_{CP}$ = 10.0 Hz); ^{31}P NMR ($CDCl_3$) δ (ppm): 144.5 (q, $^1J_{PB}$ = 75.3 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −42.3 (d, $^1J_{PB}$ = 76.1 Hz); $[\alpha]_{25}^{D}$ = +121.2 (c = 1, CH_2Cl_2); IR (neat, cm^{-1}): 2960 (C–H), 2350 (B–H), 1410, 1380 (CH_3), 1090 (C–O), 950 (P–O–C), 830.

6.2.6. (2R,5S)-2-Phenoxy-3-oxa-1-azaphosphabicyclo-[3.3.0]octane–borane complex ***1f***

Solid; m.p. 134 °C. ^{13}C NMR ($CDCl_3$) δ (ppm): 26.8, 31.3, 47.2 (d, $^2J_{CP}$ = 35.0 Hz), 62.1, 73.4 (d, $^2J_{CP}$ = 10.0 Hz), 121.3, 124.2, 129.5, 155.1; ^{31}P NMR ($CDCl_3$) δ (ppm): 133.5 (q, $^1J_{PB}$ = 72.2 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −41.2 (d, $^1J_{PB}$ = 74.3 Hz); $[\alpha]_{25}^{D}$ = +132.2 (c = 1, CH_2Cl_2).

6.2.7. (2R,5S)-2,4,4-Triphenyl-3-oxa-1-azaphosphabicyclo[3.3.0]octane–borane complex ***2***

α,α′-Diphenyl pyrrolidine methanol was obtained following the procedure reported in the literature [12]. The corresponding oxazaphospholidine–borane complex **2** was synthesized by the previously described method. Solid; m.p. 163 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.3–2.2 (m, 4H), 3.1–3.5 (m, 3H), 4.2–4.4 (m, 3H), 7.0–7.7 (m, 15H); ^{31}P NMR ($CDCl_3$) δ (ppm): 139.9 (q, $^1J_{PB}$ = 72.6 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −38.2 (d, $^1J_{PB}$ = 76.9 Hz); $[\alpha]_{25}^{D}$ = +83.8 (c = 1.2, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2860 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1090 (C–O), 960 (P–O–C), 745, 700.

6.2.8. (2R,5S)-2-Phenyl-3-oxa-1-azaPhosphabicyclo-[3.4.0]nonane–borane complex ***3***

Enantiomerically pure (*S*)-(−)-2-hydroxymethylpiperidine was obtained via a kinetic enzymatic resolu-

tion of racemic compound, using *Pig Pancreatic Lipase* [13]. The corresponding oxazaphospholidine–borane complex **3** was synthesized by the previously described method. Solid; m.p. 88 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.3–1.7 (m, 6H), 2.2 (m, 1H), 2.6 (m, 2H), 3.4–3.7 (m, 4H), 7.4–7.8 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.3, 25.2, 28.3, 42.5 (d, $^2J_{CP}$ = 11.0 Hz), 54.1 (d, $^2J_{CP}$ = 7.5 Hz), 75.3 (d, $^2J_{CP}$ = 10.0 Hz), 122.1, 127.6, 130.6; ^{31}P NMR ($CDCl_3$) δ (ppm): 128.9(q, $^1J_{PB}$ = 68.1 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −39.7 (d, $^1J_{PB}$ = 70.3 Hz); $[\alpha]_{25}^{D}$ = +136.2 (*c* = 1, CH_2Cl_2); IR (neat, cm^{-1}) 3050, 2860 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1090 (C–O), 950 (P–O–C), 700, 666.

6.2.9. (2R,4S,5R)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidine–borane complex ***4***

Solid; m.p. 107 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.2–1.7 (m, 3H), 1.8 (d, 3H), 5.6 (m, 1H), 7.3–8.0 (m, 10H); ^{31}P NMR ($CDCl_3$) δ (ppm): 134.2 (q, $^1J_{PB}$ = 67.2 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −40.2 (d, $^1J_{PB}$ = 71.2 Hz); $[\alpha]_{25}^{D}$ = +4.5 (*c* = 4, $CHCl_3$); IR (neat, cm^{-1}): 3060, 2930 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1410, 1380 (CH_3), 1090 (C–O), 950 (P–O–C), 700.

6.2.10. (2R,4S)-3-Methyl-4-isopropyl-2-phenyl-1,3,2-oxazaphospholidine–borane complex ***5***

Solid; m.p. 110 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.9–1.0 (dd, 6H), 2.1 (m, 1H), 2.4–2.5 (d, 3H), 3.4–3.7 (m, 1H), 4.3–4.5 (m, 5H), 7.3–7.8 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (ppm): 14.7, 15.2, 18.4 (d, $^2J_{CP}$ = 9.0 Hz), 28.2, 30.9, 63.8 (d, $^2J_{CP}$ = 9.0 Hz), 127.9, 128.4, 130.9, 132.1; ^{31}P NMR ($CDCl_3$) δ (ppm): 137.3 (q, $^1J_{PB}$ = 68.1 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −39.8 (d, $^1J_{PB}$ = 70.3 Hz); $[\alpha]_{25}^{D}$ = +20.3 (*c* = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3060, 2930 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1410, 1380 (CH_3), 1090 (C–O), 950 (P–O–C), 700.

6.2.11. (2R,5S)-2,3-Diphenyl-1,3-diazaphospha-bicyclo[3.3.0]octane–borane complex ***6a***

Solid; m.p. 156 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.8–1.9 (m, 3H), 2.0–2.2 (m, 1H), 3.2 (m, 1H), 3.3–3.8 (m, 6H), 4.2 (m, 1H), 6.7–7.3 (m, 10H); ^{31}P NMR ($CDCl_3$) δ (ppm): 101.9 (q, $^1J_{PB}$ = 68.1 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −35.3 (d, $^1J_{PB}$ = 73.2 Hz); $[\alpha]_{25}^{D}$ = +103.5 (*c* = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2950 (C–H), 2350 (B–H), 1430 (P–Phenyl), 700.

6.2.12. (2R,5S)-2-Phenyl-3-o-tolyl-1,3-diazaphosphabicyclo[3.3.0]octane–borane complex ***6b***

Solid; m.p. 148 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.7–2.1 (m, 6H), 2.3–2.4 (m, 1H), 3.3 (m, 1H), 3.5–3.7 (m, 6H), 4.0 (m, 1H), 7.0–7.3 (m, 9H); ^{31}P NMR ($CDCl_3$) δ (ppm): 101.7 (q, $^1J_{PB}$ = 69.5 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −35.2 (d, $^1J_{PB}$ = 74.2 Hz); $[\alpha]_{25}^{D}$ = +103.4 (*c* = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2950 (C–H), 2350 (B–H), 1430 (P–Phenyl), 700.

6.2.13. (2R,5S)-2-Phenyl-3-o-anisyl-1,3-diazaphospha-bicyclo[3.3.0]octane–borane complex ***6c***

Solid; m.p. 164 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.3–1.6 (m, 3H), 2.1 (s, 3H), 2.3–2.5 (m, 1H), 3.4 (m, 1H), 3.6–3.8 (m, 6H), 4.2 (m, 1H), 7.0–7.4 (m, 9H); ^{31}P NMR ($CDCl_3$) δ (ppm): 102.5 (q, $^1J_{PB}$ = 72.3 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −36.8 (d, $^1J_{PB}$ = 77.8 Hz); $[\alpha]_{25}^{D}$ = +95.2 (*c* = 1, CH_2Cl_2); IR (neat, cm^{-1}): 3050, 2950 (C–H), 2350 (B–H), 1430 (P–Phenyl), 700.

6.2.14. 3,4-Benzo-7-isopropyl-2,9-dioxa-6-aza-1-phospha^{III}bicyclo[4.3.0]–borane complex ***7***

Solid; m.p. 124 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.9–1.1 (m, 5H), 1.3–1.4 (m, 3H), 1.7–1.9 (m. 1H), 2.3–3.1 (m, 4H), 3.7 (d, 2H), 6.8–7.3 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm): 20.1, 21.2, 29.8, 33.1, 47.1, 63.5, 140.7, 142.2, 145.3; ^{31}P NMR ($CDCl_3$) δ (ppm): 127.3 (q, $^1J_{PB}$ = 68.3 Hz); ^{11}B NMR (C_6D_6) δ (ppm): −41.2 (d, $^1J_{PB}$ = 72.6 Hz); $[\alpha]_{25}^{D}$ = −35.3 (*c* = 1, CH_2Cl_2); IR (neat, cm^{-1}) 3050, 2980 (C–H), 2350 (B–H), 1430 (P–Phenyl), 1410, 1380 (CH_3), 1090 (C–O), 950 (P–O–C), 700.

6.3. General procedure for asymmetric reduction of acetophenone by borane in refluxing toluene, using 2 mol% (respectively one equivalent) of chiral tricoordinated phosphorus borane complexes ***1–7*** *as catalyst*

A solution of BH_3:SMe_2 (2 M in THF) was added dropwise to a stirred and pre-warmed solution of 2 mol% (respectively one equivalent) of the catalyst and acetophenone (one equivalent) in degassed toluene (5 ml) at 110 °C. After 10 min, the solution was cooled to room temperature and then a saturated solution of $NaHCO_3$ was added slowly to the mixture. After decanting, the organic layer was dried over $MgSO_4$ and then distilled on a Kügelrohr apparatus to afford 1-phenylethanol in an average yield of 80%.

The same procedure was used to reduce all the ketones.

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