Chiral (*o*-Hydroxyaryl)oxazaphospholidine Oxides: A New Class of Bifunctional Catalysts in the Enantioselective Borane Reduction of Ketones

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The synthesis of a new class of bifunctional organophosphorus catalysts for the asymmetric borane reduction of prochiral ketones has been investigated. Keys to the architecture of effective catalysts are an oxazaphospholidine structural unit and a hydroxyaryl moiety. These (*o*-hydroxyaryl)oxazaphospholidine oxides have been successfully applied to the catalytic (2 mol-%) asymmetric borane reduction of numerous prochiral ketones with enantiomeric excesses up to 84% *ee*.

Introduction

Asymmetric catalysis of the reduction of prochiral ketones to enantiomerically enriched alcohols remains a fundamental asymmetric transformation.[1] In the last few years, numerous methods have been reported for this process, most of which involve either asymmetric hydrogenation using an organometallic complex or modified hydride transfer reagents.[2] In this area, one of the most successful catalysts for this application are the oxazaborolidine family of compounds described by Itsuno[3] and Corey.[4] Although many of these methods give excellent results in terms of enantioselectivity, few are without some limitation or practical disadvantage.[5]

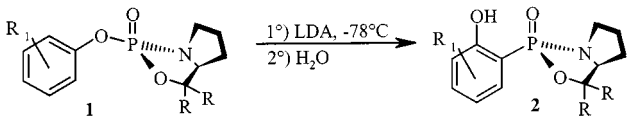
In 1992, we reported the first enantioselective borane reduction of ketones involving catalysts not based on the oxazaborolidine structure, but on an oxazaphospholidine−borane complex.[6] Although not as effective in terms of enantiomeric inductions, this compound has the advantage of high stability and simple preparation. Following this pioneering work, numerous asymmetric phosphorus catalysts such as phosphinamides and oxazaphospholidine oxides have been reported by Wills and our group, resulting in moderate to excellent enantiomeric excesses.[7] Thus, all these catalysts act essentially as Lewis bases, serving to increase the reactivity of borane by electron donation. Nevertheless, the most efficient catalysts present Lewis acid and Lewis base structural moieties that activate both ketone and borane during the stereochemical control of the asymmetric reduction. From this concept of multifunctional catalysis, we have envisioned the incorporation of a hydroxy group in the phosphonamide catalyst, including an oxazaphospholidine ring from (*S*)-prolinol and (*S*)-diphenylprolinol. The presence of such a group could provide an adjacent Lewis acid site upon reaction with borane, which could activate the carbonyl group and enhance the enantiomeric excesses.

In the context of our studies, we describe in this paper the synthesis of a new class of (*o*-hydroxyaryl)oxazaphospholidine oxides and their use as bifunctional catalysts in the enantioselective borane reduction of prochiral ketones.

Results and Discussion

Recently, we have reported a new general procedure for the preparation of various chiral (*o*-hydroxyaryl)diazaphospholidine oxides and (*o*-hydroxyaryl)phosphonates.[8] This method, based on the properties of the phosphoryl-directed metallation group (P-DMG), involves a totally stereospecific P−O to P−C rearrangement,[9−12] with a total retention of configuration on the phosphorus atom. An extension of this study has also demonstrated that this reaction is totally diastereoselective and regioselective.[13] These compounds featuring a basic (P=O) and an acidic (OH) site have found application as catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes,[14] and as ligands in an enantioselective trimethylsilylcyanation of aromatic aldehydes catalyzed by chiral titanium complexes.[15]

The synthesis of chiral (*o*-hydroxyaryl)oxazaphospholidine oxides **2**, derived from (*S*)-prolinol derivatives, may be achieved from precursors **1**. This can be done in a two-step sequence involving an unstable metallated intermediate that undergoes a fast 1,3-rearrangement with formation of a phosphorus−carbon bond[16] (Scheme 1).



Scheme 1. General procedure for the synthesis of (*o*-hydroxyaryl)-oxazaphospholidine oxides **2**

Precursors **1** were easily available from two different procedures as outlined in Scheme 2.

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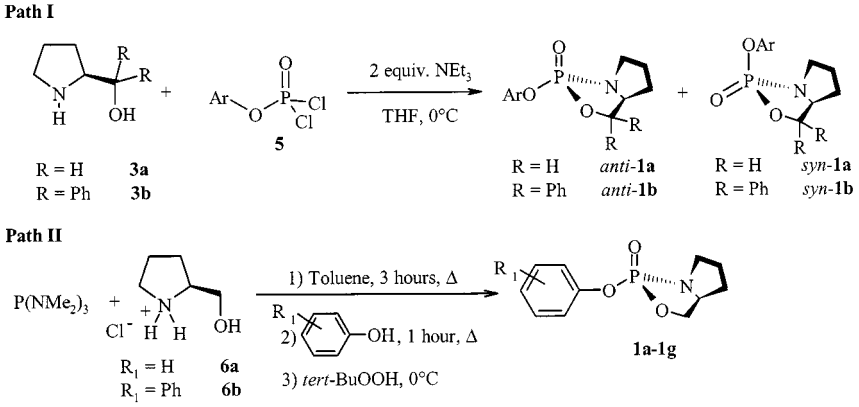


Scheme 2. General procedures for the synthesis of precursors **1**

Table 1. Synthesis of precursors **1**

Entry	Precursors	Yield (%)	diastereomeric ratio
1	*anti*-**1a** *syn*-**1a**	89[a]	50/50
2	*anti*-**1b** *syn*-**1b**	65[a]	70/30
3	*anti*-**1a**	82[b]	100/0
4	*anti*-**1b**	71[b]	100/0
5	*anti*-**1c**	67[b]	100/0
6	*anti*-**1d**	82[b]	100/0
7	*anti*-**1e**	62[b]	100/0
8	*anti*-**1f**	70[b]	100/0
9	*anti*-**1g**	71[b]	100/0

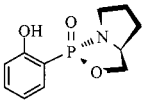
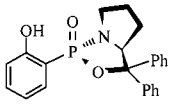
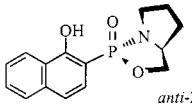
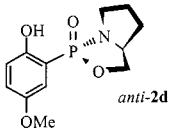
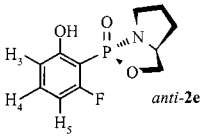
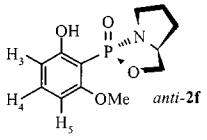
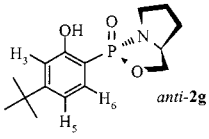
[a] Synthesized as outlined in Scheme 2, path I. – [b] Synthesized as outlined in Scheme 2, path II.

The first pathway involves the formation of the two expected diastereomers in a diastereomeric ratio varying from 50:50 to 70:30, depending on the nature of the considered chiral moiety (Table 1, Entries 1 and 2). On the other hand, diastereomerically pure precursors **1** were easily available by exchange reaction at 110 °C in toluene between tris(dimethylamino)phosphane and (*S*)-prolinol hydrochloride (**6a**) or (*S*)-diphenylprolinol (**6b**) followed by addition of the desired phenol. Oxidation of crude phosphanes by *tert*-butyl hydroperoxide afforded the expected compounds **1a**−**g** with chemical yields ranging from 62 to 82%. In all cases, nearly only one diastereomer was obtained, and characterized as the thermodynamic *anti* diastereomer (Table 1). The notations of the *syn* and *anti* diastereomers are according to the methylene substituent of the pyrrolidine ring with respect to the extracyclic aryl group. If they are on the same side of the five-membered phosphorus-containing ring, we call it a *syn* diastereomer; otherwise, it is an *anti* diastereomer.[18] A subsequent P−O to P−C rearrangement on treatment of precursors **1** with LDA in THF at −78 °C led to the stereoselective formation of the corresponding (*o*-hydroxyaryl)oxazaphospholidine oxides **2** (Table 2).

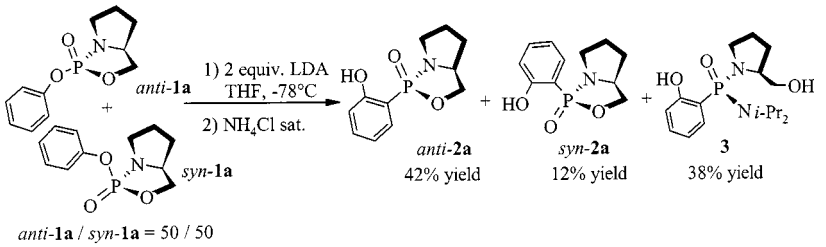
In all cases, this reaction proceeds with total retention of configuration at the phosphorus atom and with total regioselectivity. Precisely established that the stereochemistry of the 1,3-phosphorus migration operates with retention of configuration at the phosphorus atom, a mechanism proceeding via a trigonal bipyramidal intermediate (TBP) has been postulated.[8]

The *ortho*- and *para*-substituted precursors **1c** and **1d** led exclusively to the formation of the expected products by 1,3-migration of the phosphoryl group from the oxygen to the adjacent carbon atom on the *ortho* position in 80 and 67% chemical yield, respectively (Table 2, Entries 3 and 4).

Table 2. Stereoselective P−O to P−C rearrangement of precursors **1a**−**1g**

Entry	Precursor **1**	Product	Regioselectivity (%)[a]	Yield (%)[b]
1	*anti*-**1a**	 *anti*-**2a**	100/0	70 (100/0)[c]
2	*anti*-**1b**	 *anti*-**2b**	100/0	85 (100/0)[c]
3	*anti*-**1c**	 *anti*-**2c**	100/0	80 (100/0)[c]
4	*anti*-**1d**	 *anti*-**2d**	100/0	67 (100/0)[c]
5	*anti*-**1e**	 *anti*-**2e**	100/0	65 (100/0)[c]
6	*anti*-**1f**	 *anti*-**2f**	100/0	85 (100/0)[c]
7	*anti*-**1g**	 *anti*-**2g**	100/0	33 (100/0)[c]

[a] Regioselectivity determined by ^{31}P NMR spectroscopy. − [b] Isolated yield after column chromatography. − [c] A total diastereoselectivity was determined from ^{31}P NMR analysis.



Scheme 3

The structures of the final products obtained were determined by ^{1}H and ^{13}C NMR analysis. P−O to P−C rearrangement of *meta* precursors **1e**−**1g** led to the corresponding (*o*-hydroxyaryl)oxazaphospholidine oxides in chemical yields varying from 33 to 85% (Table 2, Entries 3−5). In all cases, only one regioisomer was obtained and fully characterized by NMR-spectroscopic analysis of coupling constants of aromatic protons on the phenol moiety. Thus, the ^{1}H NMR spectrum of *anti*-**2e** revealed two doublets of doublets attributed to 3-H and 5-H, respectively. A similar study of compounds *anti*-**2f** led to the same conclusion concerning the regioselectivity of this reaction. Due to the important steric hindrance of the *tert*-butyl group, rearrangement of precursor *anti*-**1g** occurred with total regioselectivity at the C-1 position. In this case, the ^{1}H NMR spectrum revealed two doublets of doublets, attributable to 3-H and 6-H, and a doublet of doublets of doublets attributable to 5-H.

On the other hand, although the rearrangement of diastereomerically pure *anti*-**1a** led to the expected product in 70% yield, the treatment of a mixture of the two diastereomers, *anti*-**1a** and *syn*-**1a**, in a 1:1 molar ratio, with 2 equiv. of LDA in THF at −78 °C led to the formation of three major products (Scheme 3).

Thus, the two expected products *anti*-**2a** and *syn*-**2a** were obtained in 42 and 12% yield, respectively, and a third product, **3**, was isolated in 38% yield. The exact structure of *anti*-**2a** and **3** have been unambiguously determined by NMR spectroscopy and X-ray diffraction analysis.

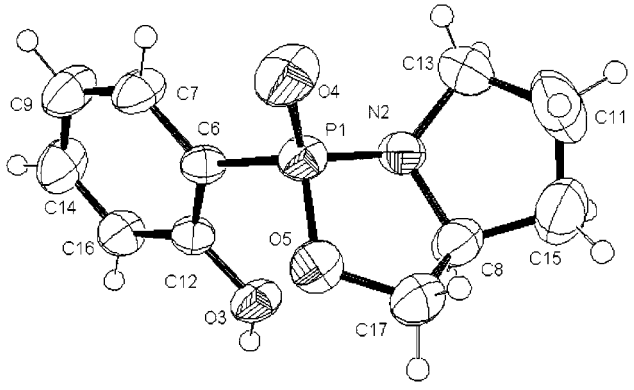
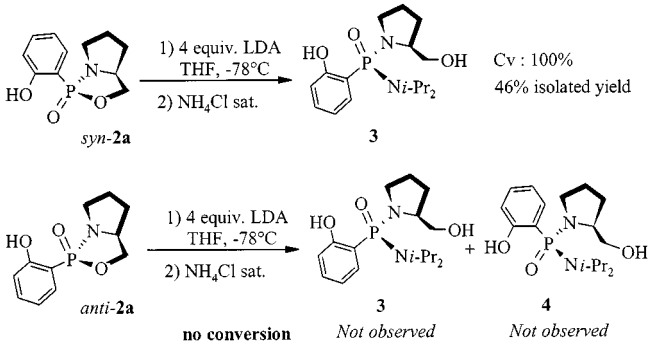


Figure 1. Structure of *anti*-**2a**, showing the labelling scheme; selected bond lengths [Å] and angles [°]: P1−O4 1.475(1), P1−N2 1.642(2), P1−O5 1.580(1), P1−C6 1.781(1), O3−C12 1.346(2); N2−P1−O4 115.3(1), N2−P1−O5 97.7(1), N2−P1−C6 111.8(1), O4−P1−O5 116.0(1), O4−P1−C6 108.7(1), O5−P1−C6 106.8(1), P1−N2−C8 111.1(1), P1−N2−C13 122.6(1), C8−N2−C13 109.5(2), P1−05−C17 111.5(1)



Scheme 4

In the case of *anti*-**2a**, it appears that the configuration at the phosphorus atom (R_P) was retained during the rearrangemen (see X-ray data) (Figure 1).

The sum of the bond angles around the nitrogen atom of the pyrrolidine ring is 343.2°, showing a nonplanar configuration. Moreover, a strong intermolecular hydrogen bond between the hydroxy group and the oxygen atom on another phosphorus moiety may be noticed (1.64 Å).

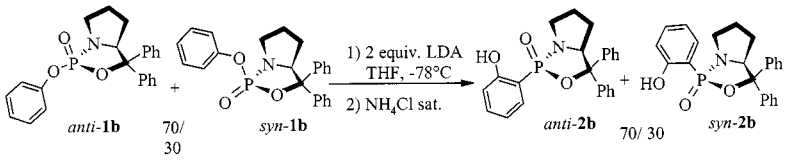
In order to rationalize the formation of compound **3**, several experiments were conducted (Scheme 4).

Thus, treatment of diastereomer *syn*-**2a** with 4 equiv. of LDA afforded only the expected product **3** in 46% yield, resulting from a nucleophilic attack of LDA on the phosphorus atom and subsequent opening of the oxazaphospholidine ring. It is noteworthy that a total conversion of diastereomer *syn*-**2a** into the expected compound **3** has been noticed by ^{31}P NMR analysis. The low chemical yield can be explained by the difficulty to isolate the product **3** by silica gel chromatography.

On the other hand, whatever the experimental conditions applied, no degradation of diastereomer *anti*-**2a** and no formation of any by-products was observed.Treatment of α,α′-diphenylprolinol diastereomers *anti*-**1b** and *syn*-**1b**, instead prolinol derivatives *anti*-**1a** and *syn*-**1a**, led exclusively to the formation of the expected compounds *anti*-**2b** and *syn*-**2b**. Thus, in this case, no by-products resulting from a nucleophilic attack of LDA on the phosphorus atom have been encountered (Scheme 5).

Analysis of the X-ray structure of **3** revealed that the phosphorus atom presents an (S_P) configuration, indicating that the nucleophilic attack proceeds with inversion of the configuration at the phosphorus atom (Figure 2).

Moreover, there are two strong intramolecular hydrogen bonds between the *o*-hydroxyaryl group with the oxygen



Scheme 5

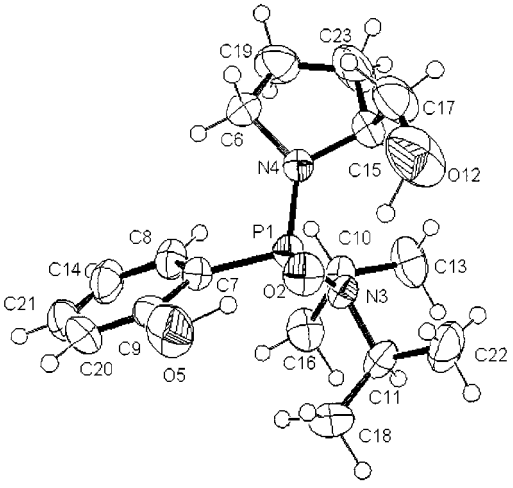
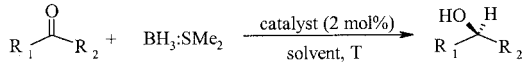


Figure 2. Structure of **3**, showing the labelling scheme; selected bond lengths [Å] and angles [°]: P1−O2 1.495(1), P1−N3 1.644(1), P1−N4 1.628(1), P1−C7 1.802(1), O5−C9 1.359(2), C17−O12 1.401(3), O12−H12 1.124(2), O2−H12 1.826(1), O5−H5 1.118(2), O2−H5 1.491(2); C7−P1−N3 111.9(1), C7−P1−N4 106.7(1), C7−P1−O2 108.0(1), N3−P1−N4 105.2(1), N3−P1−O2 109.6(1), N4−P1−O2 115.3(1), P1−N4−C6 129.3(1), P1−N4−C15 123.0(1), C6−N4−C15 107.0(2), P1−N3−C10 120.2(1), P1−N3−C11 122.7(1), C11−N3−C10 114.8(1), H5−O2−P1 100.6(1), H12−O2−P1 100.7(1), H5−O2−H12 148.7(1), O2−H5−O5 164.1(2), O2−H12−O12 154.2(1)

atom attached to the phosphorus moiety (1.491 and 1.826 Å, respectively).

We have also investigated the catalytic properties of these compounds in the enantioselective borane reduction of prochiral ketones (Scheme 6).



Scheme 6

We first examined the use of catalyst *anti*-**2a** in the enantioselective reduction of acetophenone in a variety of solvents and at various temperatures (Table 3).

The use of THF at 60 °C appears to give the best enantioselectivity, and leads to (*R*)-phenylethanol in 95% yield and 32% *ee* (Table 3, Entry 5).

Under the best experimental conditions, this study has been extended to a series of prochiral ketones. The results are summarized in Table 4.

In all cases, a total conversion into the corresponding alcohols was obtained in yield varying from 67 to 92%. Nevertheless, in all cases, moderate enantiomeric excesses have been encountered, except for 2-chloroacetophenone where the catalyst revealed high enantioface-differentiating ability (Entry 5, 68% *ee*). Moreover, the major enantiomers formed always had the same relative configurations.

Table 3. Influence of temperature and nature of the solvent on the enantiomeric excess in the enantioselective borane reduction of acetophenone catalyzed by 2 mol-% of *anti*-**2a**

Entry	Solvent	T [°C]	Yield [%][a]	ee [%][b]
1	CH_2Cl_2	20	28	10 (*R*)
		60	75	2 (*R*)
2	Toluene	20	85	3 (*R*)
		110	87	2 (*R*)
3	CH_3CN	20	88	6 (*R*)
		60	82	3 (*R*)
4	MTBE	20	89	8 (*R*)
		50	81	6 (*R*)
5	*THF*	20	85	10 (*R*)
		60	*95*	*32 (R)*

[a] Isolated yield. − [b] *ee* determined by HPLC analysis on a Daicel Chiralcel OD-H column at 254 nm; flow rate 0.5 mL/min; eluent: hexane/*i*PrOH/NEt_3 (90:10:0.01), t_R = 14.11 min, t_S = 15.97 min.

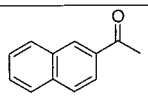
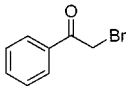
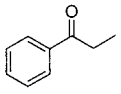
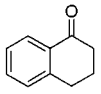
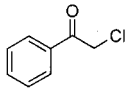
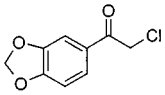
On the basis of these results, compounds **2a**−**2g** and **3** have been successfully employed as catalysts in the enantioselective borane reduction of 2-chloroacetophenone (Table 5).

In all cases, a total conversion of 2-chloroacetophenone and enantioselectivities varying from moderate to high (Entries 1−9, 7 to 84% *ee*) were encountered. Catalyst *anti*-**2b**, possessing a diphenylprolinol moiety, afforded the best enantioselectivity (Entry 3, 84% *ee*). Moreover, depending on the configuration assigned at the phosphorus atom of the diastereomer used, the reaction afforded the expected chloro alcohol with the same (*S*) absolute configuration but with a significant decrease of the enantioselectivity using the *syn* diastereomer (Entries 1−4). It is also noteworthy that the use of catalyst **3** afforded the expected product in 80% yield, but with a total absence of enantioselectivity (Entry 10, 1% *ee*).

Conclusion

We have described the synthesis of various new chiral (*o*-hydroxyaryl)oxazaphospholidine oxides using a stereospecific migration-rearrangement procedure and proceeding with total regioselectivity. These compounds have been successfully used as bifunctional catalysts in the enantioselective borane reduction of prochiral ketones with enantiomeric excesses of up to 84% *ee*. Studies dealing with mechanistic features are currently in progress.

Table 4. Enantioselective borane reduction of various ketones with 2 mol-% of *anti*-**2a**

Entry	Ketone	Yield (%)[a]	ee (%)[b]
1		82	10 (*R*)[c]
2		81	11 (*S*)[d]
3		92	19 (*R*)[e]
4		75	18 (*R*)[f]
5		86	**68 (*S*)**[g]
6		67	**44 (*S*)**[h]

[a] Isolated yield. – [b] *ee* determined by HPLC analysis. – [c] Daicel Chiralcel OJ column at 254 nm; flow rate 1.0 mL/min; eluent: hexane/*i*PrOH (90:10), t_S = 14.70 min, t_R = 18.39 min. – [d] Daicel Chiralcel OD-H column at 254 nm; flow rate 0.5 mL/min; eluent: hexane/*i*PrOH/NEt_3 (95:5:0.01), t_S = 19.79 min, t_R = 23.24 min. – [e] Daicel Chiralcel OD-H column at 254 nm; flow rate 0.5 mL/min; eluent: hexane/EtOH/NEt_3 (95:5:0.01), t_R = 13.88 min, t_S = 15.51 min. – [f] Daicel Chiralcel OJ column at 254 nm; flow rate 0.5 mL/min; eluent: hexane/*i*PrOH (90:10), t_S = 13.40 min, t_R = 16.58 min. – [g] Daicel Chiralcel OD-H column at 254 nm; flow rate 0.5 mL/min; eluent: hexane/EtOH/NEt_3 (95:5:0.01), t_S = 18.97 min, t_R = 22.51 min. – [h] Daicel Chiralcel OD-H column at 254 nm; flow rate 0.7 mL/min; eluent: hexane/*i*PrOH (98:2), t_S= 33.80 min, t_R = 47.50 min.

Table 5. Influence of the nature of the catalysts in the enantioselective borane reduction of 2-chloroacetophenone

Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	*anti*-**2a**	86	68 (*S*)
2	*syn*-**2a**	80	47 (*S*)
3	*anti*-**2b**	83	*84 (S)*
4	*syn*-**2b**	79	59 (*S*)
5	*anti*-**2c**	86	47 (*S*)
6	*anti*-**2d**	80	56 (*S*)
7	*anti*-**2e**	91	67 (*S*)
8	*anti*-**2f**	89	7 (*S*)
9	*anti*-**2g**	82	36 (*S*)
10	**3**	80	1 (*S*)

[a] Isolated yield. – [b] *ee* determined by HPLC analysis on a Daicel Chiralcel OD-H column at 254 nm; flow rate 0.5 mL/min; eluent: hexane/EtOH/NEt_3 (95:5:0.01), t_S = 18.97 min, t_R = 22.51 min.

Experimental Section

^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and ^{19}F NMR spectra were recorded with Bruker AC100, AC200 and AC400 spectrometers in $CDCl_3$ as solvent. The chemical shifts (ppm) were determined relative to Me_4Si (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). Toluene and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl immediately prior to use. Ethyl acetate and petroleum ether (35–60 °C) were purchased from SDS and used without further purification. – Column chromatography was performed on SDS silica gel (70–230 mesh). LDA (2 M in THF) and *tert*-butyl hydroperoxide (5.5 M in decane) were purchased from Fluka.

General Procedure for the Preparation of Compounds *anti*-1a/*syn*-1a and *anti*-1b/*syn*-1b: To a solution of the corresponding chiral amino alcohol (10 mmol) and freshly distilled NEt_3 (3.8 mL, 30 mmol) in THF (25 mL) was added phenyl dichlorophosphate (1.64 mL, 11 mmol) dropwise at 0 °C. The mixture was stirred under nitrogen at room temperature overnight and then filtered to remove Et_3NHCl. The solvent was evaporated under reduced pressure and the crude product purified by flash chromatography.

(2*S*,5*S*)-2-Phenoxy-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*anti*-1a) and (2*R*,5*S*)-2-Phenoxy-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*syn*-1a): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 80:20) afforded an inseparable mixture of *anti*-**1a** and *syn*-**1a** (1:1) as a colorless oil in 89% yield; – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.61 (m, 1 H), 1.98 (m, 3 H), 3.08 (m, 1 H), 3.54 (m, 1 H, *syn*), 3.83 (m, 2 H + 1 H, *anti*), 4.18 (m, 1 H), 4.48 (ddd, J = 6.4 Hz, J = 8.7 Hz, J = 22.6 Hz, 1 H, *syn*), 3.50 (m, 5 H), 7.20 (m, 10 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5 (d, J = 2.9 Hz, *anti*), 27.5 (d, J = 3.3 Hz, *syn*), 29.8 (d, J = 3.0 Hz, *syn*), 30.5 (d, J = 3.8 Hz, *anti*), 45.0 (s, *syn*), 46.7 (d, J = 2.3 Hz, *anti*), 61.2 (d, J = 12.6 Hz, *anti*), 62.0 (d, J = 13.0 Hz, *syn*), 70.2 (d, J = 4.4 Hz, *anti*), 71.3 (d, J = 4.2 Hz, *syn*), 120.0 (d, J = 4.4 Hz, 2 C, *syn*), 120.6 (d, J = 4.6 Hz, 2 C, *anti*), 124.6 (s, *syn*), 124.8 (s, *anti*), 129.4 (s, 2 C, *anti*), 129.5 (s, 2 C, *syn*), 150.3 (d, J = 7.2 Hz, *syn*), 151.4 (d, J = 6.9 Hz, *anti*). – ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 21.2 (*anti*), 16.0 (*syn*).

(2*S*,5*S*)-2-Phenoxy-4,4-diphenyl-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-1b) and (2*R*,5*S*)-2-Phenoxy-4,4-diphenyl-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*syn*-1b): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 80:20) afforded an inseparable mixture of *anti*-**1b** and *syn*-**1b** (70:30) as a colourless oil in 65% yield; – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (m, 4 H), 3.09 (m, 1 H), 3.68 (m, 1 H), 4.31 (dt, J = 10.9 Hz, J = 6.0 Hz, 1 H, *anti*), 4.59 (ddd, J = 24.5 Hz, J = 10.5 Hz, J = 5.7 Hz, 1 H, *syn*), 7.24 (m, 15 H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.9 (s, *syn*), 25.6 (d, J = 4.2 Hz, *anti*), 29.5 (s, *syn*), 29.8 (d, J = 4.3 Hz, *anti*), 44.7 (s, *syn*), 46.0 (d, *anti*), 70.2 (d, J = 11.5 Hz, *anti*), 71.4 (d, J = 9.2 Hz, *syn*), 88.2 (d, J = 3.0 Hz, *syn*), 89.3 (d, J = 2.8 Hz, *anti*), 119.8 (d, J = 4.4 Hz, 2 C, *syn*), 120.5 (d, J = 4.7 Hz, 2 C, *anti*), 124.5 (s, *anti*), 125.3 (s, *syn*), 126.1 (s, 4 C, *anti*), 126.5 (s, 4 C, *syn*), 127.4 (s, 2 C, *syn*), 127.8 (s, 2 C, *anti*), 127.9 (s, 4 C, *syn*), 128.0 (s, 4 C, *anti*), 129.0 (s, 2 C, *anti*), 129.5 (s, 2 C, *syn*), 140.6 (d, J = 5.6 Hz, *anti*), 140.9 (d, J = 5.8 Hz, *syn*), 142.5 (d, J = 4.3 Hz, *anti*), 143.7 (s, *syn*), 150.7 (d, J = 7.2 Hz, *syn*), 151.1 (d, J = 6.9 Hz, *anti*). – ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 17.1 (*anti*), 14.3 (*syn*).

General Procedure for the Preparation of Compounds *anti*-1a–*anti*-1g: An equimolar mixture of tris(dimethylamino)phosphane (5 mmol, 0.82 g) and (*S*)-(+)-prolinol hydrochloride (**6a**) (5 mmol, 0.51 g) was placed in dry toluene (10 mL) in a two-necked round flask under argon and warmed at 110 °C for 3 h; 1 equiv. of desired phenol was then added at room temperature, and the mixture was warmed at 110 °C for 1 h. The mixture was allowed to cool to room temperature and the toluene was removed in vacuo. The crude phosphane was diluted with dichloromethane (15 mL) and the mixture was cooled at 0 °C. *tert*-Butyl hydroperoxide (0.9 mL,

5.5 M, decane) was slowly added and the mixture was stirred for additional 3 h. After removing the solvent in vacuo, the crude product was purified by flash chromatography.

(2*S*,5*S*)-2-(1-Naphthyloxy)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-1c): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 75:25) afforded *anti*-**1c** as a white solid in 67% yield; − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 (m, 1 H), 1.81 (m, 3 H), 2.88 (m, 1 H), 3.67 (m, 3 H), 4.10 (m, 1 H), 7.39 (m, 4 H), 7.59 (m, 1 H), 7.77 (d, *J* = 7.6 Hz, 1 H), 8.15 (d, *J* = 8.5 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4 (d, *J* = 3.5 Hz), 30.3 (d, *J* = 3.4 Hz), 46.5 (d, *J* = 2.7 Hz), 61.2 (d, *J* = 12.1 Hz), 70.0 (d, *J* = 4.6 Hz), 115.5 (d, *J* = 3.0 Hz), 121.7, 124.7, 125.2, 126.0, 126.3, 126.7 (d, *J* = 4.8 Hz), 127.5, 134.5, 146.6 (d, *J* = 8.7 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 21.4. − $C_{15}H_{16}NO_3P$ (289.27): calcd. C 62.28, H 5.58, N 4.84, P 10.71; found C 62.10, H 5.61, N 4.75, P 10.55.

(2*S*,5*S*)-2-(4-Methoxyphenoxy)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-1d): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 80:20) afforded *anti*-**1d** as a colourless oil in 82% yield; − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.52 (m, 1 H), 1.83 (m, 3 H), 2.91 (m, 1 H), 3.64 (m, 2 H), 3.65 (s, 3 H), 4.02 (m, 2 H), 6.72 (d, *J* = 9.1 Hz, 2 H), 7.00 (dd, *J* = 9.1 Hz, *J* = 1.2 Hz, 2 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4 (d, *J* = 2.8 Hz), 30.4 (d, *J* = 4.3 Hz), 46.6 (d, *J* = 2.7 Hz), 55.3, 61.3 (d, *J* = 12.9 Hz), 70.2 (d, *J* = 5.3 Hz), 114.3 (s, 2 C), 121.4 (d, *J* = 4.2 Hz, 2 C), 144.2 (d, *J* = 8.6 Hz), 156.4. − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 21.2. − $C_{12}H_{16}NO_4P$ (269.23): calcd. C 53.53, H 5.99, N 5.20, P 11.5; found C 53.60, H 5.8, N 5.19, P 11.47.

(2*S*,5*S*)-2-(3-Fluorophenoxy)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-1e): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 80:20) afforded *anti*-**1e** as a colourless oil in 62% yield; − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.53 (m, 1 H), 1.89 (m, 3 H), 2.85 (m, 1 H), 3.67 (m, 3 H), 4.14 (ddd, *J* = 15.8 Hz, *J* = 8.1 Hz, *J* = 5.9 Hz, 1 H), 6.46 (m, 1 H), 6.89 (m, 2 H), 7.19 (dd, *J* = 14.7 Hz, *J* = 7.9 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4 (d, *J* = 3.7 Hz), 30.4 (d, *J* = 4.3 Hz), 46.6 (d, *J* = 2.7 Hz), 61.2 (d, *J* = 12.1 Hz), 70.3 (d, *J* = 4.8 Hz), 108.4 (dd, *J* = 178.8 Hz, *J* = 24.4 Hz), 111.8 (d, *J* = 21.4 Hz), 116.3 (d, *J* = 3.0 Hz), 130.2 (d, *J* = 9.5 Hz), 151.4 (d, *J* = 7.4 Hz), 162.7 (d, *J* = 247.3 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 21.1. − ^{19}F NMR (94.2 MHz, $CDCl_3$): δ = −81.1. − $C_{11}H_{13}FNO_3P$ (257.20): calcd. C 51.37, H 5.09, N 7.39, P 12.04; found C 51.20, H 5.10, N 7.32, P 11.82.

(2*S*,5*S*)-2-(3-Methoxyphenoxy)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-1f): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 75:25) afforded *anti*-**1f** as a pale yellow oil in 70% yield; − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.51 (m, 1 H), 1.80 (m, 3 H), 2.91 (m, 1 H), 3.64 (s, 3 H), 3.66 (m, 3 H), 4.09 (ddd, *J* = 15.5 Hz, *J* = 7.9 Hz, *J* = 5.6 Hz, 1 H), 6.62 (m, 3 H), 7.09 (td, *J* = 8.1 Hz, *J* = 0.6 Hz, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.3 (d, *J* = 2.9 Hz,), 30.3 (d, *J* = 3.3 Hz), 46.5 (d, *J* = 2.6 Hz), 55.0, 61.1 (d, *J* = 12.9 Hz), 70.0 (d, *J* = 5.3 Hz), 106.5 (d, *J* = 4.4 Hz), 110.2, 112.3 (d, *J* = 4.3 Hz), 129.6, 151.5 (d, *J* = 7.3 Hz), 160.2. − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 21.1. − $C_{12}H_{16}NO_4P$ (269.23): calcd. C 53.53, H 5.99, N 5.20, P 11.5; found C 53.90, H 5.76, N 5.12, P 11.49.

(2*S*,5*S*)-2-(3-*tert*-Butylphenoxy)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-1g): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 75:25) afforded *anti*-**1g** as a colourless oil in 71% yield; − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (s, 9 H), 1.52 (m, 1 H), 1.85 (m, 3 H), 2.92 (m, 1 H), 3.68 (m, 3 H), 4.05 (m, 1 H), 7.00 (d, *J* = 8.6 Hz, 2 H), 7.22 (d, *J* = 8.6 Hz, 2 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.4, 30.4 (d, *J* = 3.3 Hz), 31.2 (s, 3 C), 34.1, 46.6, 61.2 (d, *J* = 12.8 Hz), 70.1 (d, *J* = 5.0 Hz), 119.7 (d, *J* = 4.4 Hz, 2 C), 126.2 (s, 2 C), 147.4, 148.4 (d, *J* = 7.4 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 21.4. − $C_{15}H_{22}NO_3P$ (295.31): calcd. C 61.01, H 7.51, N 4.74, P 10.49; found C 61.20, H 7.48, N 4.75, P 10.10.

General Procedure for the Preparation of Compounds 2a−2g: To a stirred solution of the corresponding compounds **1a−1g** (2.5 mmol) in dry THF (25 mL) under argon was slowly added, at −78 °C, a solution of LDA (5 mmol, 2M in THF, 2.5 mL). The mixture was allowed to warm to room temperature (45 min) and quenched by addition of a saturated solution of NH_4Cl (15 mL). The product was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column.

(2*R*,5*S*)-2-(2-Hydroxyphenyl)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-2a) and (2*S*,5*S*)-2-(2-Hydroxyphenyl)-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*syn*-2a): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 50:50) afforded *anti*-**2a** and *syn*-**2a** as white solids in 41% yield. − *anti*-**2a:** m.p. 120 °C. − $[\alpha]_D^{20}$ = +50.7 (*c* = 1.02, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78 (m, 1 H), 2.01 (m, 3 H), 2.90 (m, 1 H), 3.67 (ddd, *J* = 15.5 Hz, *J* = 10.4 Hz, *J* = 5.3 Hz, 1 H), 3.93 (ddd, *J* = 8.7 Hz, *J* = 8.5 Hz, *J* = 1.8 Hz, 1 H), 4.19 (m, 1 H), 4.40 (m, 1 H), 6.89 (m, 2 H), 7.30 (m, 2 H), 10.50 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.8, 29.8 (d, *J* = 2.9 Hz,), 44.9, 63.4 (d, *J* = 8.6 Hz), 70.1, 110.6 (d, *J* = 180.0 Hz), 117.5 (d, *J* = 11.8 Hz), 119.3 (d, *J* = 13.5 Hz), 131.9 (d, *J* = 6.8 Hz), 134.8, 162.2 (d, *J* = 8.1 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 43.0. − $C_{11}H_{14}NO_3P$ (239.07): calcd. C 55.2, H 5.9, N 5.9, P 12.9; found C 55.4, H 5.6, N 6.2, P 12.7. − *syn*-**2a:** m.p. 122 °C. − $[\alpha]_D^{20}$ = −35.2 (*c* = 1.05, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.63 (m, 1 H), 2.01 (m, 3 H), 2.99 (m, 2 H), 4.02 (td, *J* = 8.7 Hz, *J* = 3.4 Hz, 1 H), 4.28 (m, 1 H), 4.67 (ddd, *J* = 15.4 Hz, *J* = 8.8 Hz, *J* = 6.4 Hz, 1 H), 6.97 (m, 2 H), 7.35 (m, 2 H), 10.88 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.1 (d, *J* = 5.3 Hz), 30.48 (d, *J* = 5.4 Hz), 44.1 (d, *J* = 5.9 Hz), 61.7 (d, *J* = 14.4 Hz), 70.2, 107.4 (d, *J* = 159.9 Hz), 118.4 (d, *J* = 11.3 Hz), 119.4 (d, *J* = 14.4 Hz), 130.8 (d, *J* = 8.8 Hz), 134.8 (d, *J* = 2.6 Hz), 163.9 (d, *J* = 5.9 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 38.0. − $C_{11}H_{14}NO_3P$ (239.07): calcd. C 55.2, H 5.9, N 5.9, P 12.9; found C 55.6, H 6.4, N 5.4, P 12.2.

(2*R*,5*S*)-2-(2-Hydroxyphenyl)-4,4-diphenyl-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*anti*-2b) and (2*S*,5*S*)-2-(2-Hydroxyphenyl)-4,4-diphenyl-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*syn*-2b): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 25:75) afforded *anti*-**2b** and *syn*-**2b** as white solids in 77% yield. − *anti*-**2b:** m.p. 64 °C. − $[\alpha]_D^{20}$ = −198.7 (*c* = 1.17, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.62 (m, 2 H), 1.77 (m, 2 H), 2.99 (m, 1 H), 3.66 (m, 1 H), 4.79 (ddd, *J* = 12.9 Hz, *J* = 6.6 Hz, *J* = 6.3 Hz, 1 H), 6.60 (tdd, *J* = 7.8 Hz, *J* = 3.6 Hz, *J* = 1.0 Hz, 1 H), 6.75 (ddd, *J* = 15.8 Hz, *J* = 7.8 Hz, *J* = 1.8 Hz, H_{11}), 6.92 (dd, *J* = 8.0 Hz, *J* = 7.2 Hz, 1 H), 7.39 (m, 11 H), 10.73 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.6, 30.3, 44.5, 71.7 (d, *J* = 8.6 Hz), 89.8, 110.9 (d, *J* = 180.0 Hz), 117.5 (d, *J* = 11.7 Hz), 119.2 (d, *J* = 14.5 Hz), 126.5 (s, 2 C), 126.7 (s, 2 C.), 127.7, 128.2 (s, 2 C.), 128.4, 128.6 (s, 2 C), 131.9 (d, *J* = 7.4 Hz), 134.7, 140.7 (d, *J* = 2.4 Hz), 142.4 (d, *J* = 5.1 Hz), 162.3 (d, *J* =

7.9 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 39.8. − $C_{23}H_{22}NO_3P$ (391.14): calcd. C 70.6, H 5.7, N 3.6, P 7.9; found C 70.2, H 5.9, N 3.4, P 7.5. − *syn*-**2b:** m.p. 188 °C. − $[\alpha]_D^{20}$ = −109.2 (*c* = 0.33, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (m, 1 H), 1.85 (m, 3 H), 3.15 (m, 2 H), 4.84 (ddd, *J* = 15.6 Hz, *J* = 10.8 Hz, *J* = 4.8 Hz, 1 H), .6.89 (m, 1 H), 7.02 (m, 1 H), 7.13 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 1 H), 7.39 (m, 9 H), 7.64 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 2 H), 11.07 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.0 (d, *J* = 2.6 Hz), 30.9, 44.4 (d, *J* = 4.4 Hz), 72.3 (d, *J* = 9.8 Hz), 90.2, 106.4 (d, *J* = 160.1 Hz), 118.4 (d, *J* = 10.9 Hz), 119.3 (d, *J* = 14.4 Hz), 125.4 (s, 2 C), 126.5 (s, 2 C), 127.7, 128.2 (s, 2 C), 128.4, 128.6 (s, 2 C.), 131.8 (d, *J* = 8.8 Hz), 135.5 (d, *J* = 2.4 Hz), 141.3 (d, *J* = 7.2 Hz), 144.5, 164.6 (d, *J* = 7.1 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 39.8. − $C_{23}H_{22}NO_3P$ (391.14): calcd. C 70.6, H 5.7, N 3.6, P 7.9; found C 70.5, H 5.8, N 3.7, P 7.9.

(S_P)-[(2*S*)-2-Hydroxymethylpyrrolidino]-(2-hydroxyphenyl)-(diisopropylamino)phosphane Oxide (3): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 75:25) afforded **3** as a pale yellow solid in 46% yield; m.p. 206 °C. − $[\alpha]_D^{20}$ = −3.8 (*c* = 0.26, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.7 Hz, 6 H), 1.31 (d, *J* = 6.7 Hz, 6 H), 1.83 (m, 4 H), 3.04 (m, 2 H), 3.60 (m, 5 H), 4.05 (br, 1 H), 6.85 (m, 2 H), 7.26 (m, 2 H), 11.65 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (s, 2 C), 24.0 (s, 2 C), 24.9 (d, *J* = 8.6 Hz), 29.9 (d, *J* = 7.2 Hz), 47.4 (d, *J* = 4.9 Hz, 2 C), 48.5 (d, *J* = 6.1 Hz), 60.7 (d, *J* = 2.4 Hz), 64.4 (d, *J* = 2.8 Hz), 114.7 (d, *J* = 145.3 Hz), 118.1 (d, *J* = 10.2 Hz), 118.6 (d, *J* = 12.9 Hz), 131.2 (d, *J* = 6.6 Hz), 133.7 (d, *J* = 2.5 Hz), 161.5 (d, *J* = 6.19 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 30.5. − $C_{17}H_{29}N_2O_3P$ (340.40): calcd. C 59.90, H 8.59, N 8.23, P 9.10; found C 60.15, H 8.61, N 8.15, P 9.22.

(2*R*,5*S*)-2-(1-Hydroxy-2-naphthyl)-1-aza-3-oxa-2-phosphabicyclo-[3.3.0]octan-2-one (*anti*-2c): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 75:25) afforded *anti*-**2c** as a white solid in 80% yield; m.p. 156 °C. − $[\alpha]_D^{20}$ = +19.6 (*c* = 0.54, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.70 (m, 1 H), 1.94 (m, 3 H), 2.84 (m, 1 H), 3.65 (m, 1 H), 3.88 (td, *J* = 8.6 Hz, *J* = 1.3 Hz, 1 H), 4.13 (m, 1 H), 4.35 (m, 1 H), 7.25 (m, 2 H), 7.51 (m, 2 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 8.38 (d, *J* = 7.8 Hz, 1 H), 11.66 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.7, 29.8 (d, *J* = 3.5 Hz), 44.7, 63.3 (d, *J* = 8.6 Hz), 70.0, 100.2 (d, *J* = 181.6 Hz), 118.8 (d, *J* = 14.1 Hz), 123.3, 124.8 (d, *J* = 12.8 Hz), 125.7, 125.9 (d, *J* = 7.1 Hz), 127.3, 128.8, 136.6 (d, *J* = 2.4 Hz), 160.9 (d, *J* = 7.5 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 44.4. − $C_{15}H_{16}NO_3P$ (289.27): calcd. C 62.28, H 5.58, N 4.84, P 10.71; found C 62.01, H 5.49, N 4.82, P 10.51.

(2*R*,5*S*)-2-(2-Hydroxy-5-methoxyphenyl)-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*anti*-2d): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 50:50) afforded *anti*-**2d** as a white solid in 67% yield; m.p. 160 °C. − $[\alpha]_D^{20}$ = +71.2 (*c* = 0.08, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.68 (m, 1 H), 1.89 (m, 3 H), 2.79 (m, 1 H), 3.55 (m, 1 H), 3.66 (s, 3 H), 3.82 (td, *J* = 8.7 Hz, *J* = 1.8 Hz, 1 H), 4.08 (m, 1 H), 4.31 (ddd, *J* = 15.0 Hz, *J* = 8.5 Hz, *J* = 6.5 Hz, 1 H), 6.89 (m, 2 H), 7.30 (m, 2 H), 10.00 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.7, 29.8 (d, *J* = 2.8 Hz), 44.9, 55.8, 63.4 (d, *J* = 8.3 Hz), 70.0, 110.4 (d, *J* = 180.0 Hz), 115.0 (d, *J* = 7.4 Hz), 118.4 (d, *J* = 14.4 Hz), 121.8 (d, *J* = 2.5 Hz), 152.1 (d, *J* = 17.4 Hz), 156.3 (d, *J* = 6.7 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 42.4. − $C_{12}H_{16}NO_4P$ (269.23): calcd. C 53.53, H 5.99, N 5.20, P 11.50; found C 54.20, H 5.86, N 5.14, P 12.03.

(2*R*,5*S*)-2-(2-Fluoro-6-hydroxyphenyl)-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*anti*-2e): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 50:50) afforded *anti*-**2e** as an orange syrup in 65% yield. − $[\alpha]_D^{20}$ = +47.5 (*c* = 0.06, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.67 (m, 1 H), 1.94 (m, 3 H), 2.85 (m, 1 H), 3.59 (m, 1 H), 3.84 (td, *J* = 8.3 Hz, *J* = 2.5 Hz, 1 H), 4.14 (m, 1 H), 4.36 (m, 1 H), 6.46 (ddd, *J* = 14.3 Hz, *J* = 8.9 Hz, *J* = 5.59 Hz, 1 H), 6.65 (dd, *J* = 8.3 Hz, *J* = 5.4 Hz, 1 H), 7.26 (dd, *J* = 15.3 Hz, *J* = 8.3 Hz, 1 H), 11.09 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.9 (d, *J* = 2.4 Hz), 30.2 (d, *J* = 4.0 Hz), 44.8 (d, *J* = 2.4 Hz), 62.2 (dd, *J* = 10.8 Hz, *J* = 3.4 Hz), 70.6, 100.0 (dd, *J* = 178.8 Hz, *J* = 20.3 Hz), 105.6 (dd, *J* = 23.0 Hz, *J* = 6.6 Hz), 113.4 (dd, *J* = 10.6 Hz, *J* = 3.0 Hz), 135.2 (d, *J* = 12.0 Hz), 163.4 (dd, *J* = 5.8 Hz, *J* = 3.2 Hz), 164.0 (d, *J* = 247.2 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 38.4. − ^{19}F NMR (94.2 MHz, $CDCl_3$): δ = −87.7. − $C_{11}H_{13}FNO_3P$ (257.20): calcd. C 51.37, H 5.09, N 7.39, P 12.04; found C 52.01, H 5.26, N 7.36, P 11.95.

(2*R*,5*S*)-2-(2-Hydroxy-6-methoxyphenyl)-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*anti*-2f): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 50:50) afforded *anti*-**2f** as an orange syrup in 85% yield; − $[\alpha]_D^{20}$ = +43.0 (*c* = 0.1, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.89 (m, 4 H), 2.89 (m, 1 H), 3.82 (s, 3 H), 3.89 (m, 1 H), 4.16 (m, 1 H), 4.38 (m, 1 H), 6.33 (dd, *J* = 8.2 Hz, *J* = 5.9 Hz, 1 H), 6.53 (dd, *J* = 8.3 Hz, *J* = 5.8 Hz, 1 H), 7.30 (dd, *J* = 8.5 Hz, *J* = 8.3 Hz, 1 H), 11.48 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.6 (d, *J* = 2.0 Hz,), 30.6 (d, *J* = 3.0 Hz), 44.9, 55.8, 62.2 (d, *J* = 11.1 Hz), 70.6 (d, *J* = 2.1 Hz), 99.8 (d, *J* = 180.0 Hz), 101.0 (d, *J* = 8.6 Hz), 110.2 (d, *J* = 12.4 Hz), 135.0, 161.9, 163.7 (d, *J* = 4.9 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 43.2. − $C_{12}H_{16}NO_4P$ (269.23): calcd. C 53.53, H 5.99, N 5.20, P 11.50; found C 53.20, H 5.80, N 5.14, P 11.36.

(2*R*,5*S*)-2-(4-*tert*-Butyl-2-hydroxyphenyl)-1-aza-3-oxa-2-phosphabicyclo[3.3.0]octan-2-one (*anti*-2g): Purification by column chromatography (silica gel; ethyl acetate/petroleum ether, 50:50) afforded *anti*-**2g** as a white solid in 33% yield; m.p. 144 °C. − $[\alpha]_D^{20}$ = +58.7 (*c* = 1.05, CH_2Cl_2). − ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.76 (m, 1 H), 1.99 (m, 3 H), 2.90 (m, 1 H), 3.62 (m, 1 H), 3.89 (td, *J* = 8.7 Hz, *J* = 1.9 Hz, 1 H), 4.17 (m, 1 H), 4.39 (ddd, *J* = 21.1 Hz, *J* = 8.6 Hz, *J* = 6.5 Hz, 1 H), 6.85 (dd, *J* = 8.7 Hz, *J* = 7.2 Hz, 1 H), 7.23 (dd, *J* = 16.5 Hz, *J* = 2.5 Hz, 1 H), 7.43 (ddd, *J* = 8.8 Hz, *J* = 2.5 Hz, *J* = 0.9 Hz, 1 H), 10.32 (s, 1 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.7 (d, *J* = 1.9 Hz), 29.8 (d, *J* = 2.8 Hz), 31.3 (s, 3 C), 32.4, 45.1, 63.4 (d, *J* = 7.5 Hz), 70.1, 109.5 (d, *J* = 179.1 Hz), 117.2 (d, *J* = 13.0 Hz), 127.4 (d, *J* = 8.2 Hz), 132.6, 141.8 (d, *J* = 13.2 Hz), 160.1 (d, *J* = 7.6 Hz). − ^{31}P NMR (40.5 MHz, $CDCl_3$): δ = 43.7. − $C_{15}H_{22}NO_3P$ (295.31): calcd. C 61.01, H 7.51, N 4.74, P 10.49; found C 60.90, H 7.42, N 4.58, P 10.61.

General Procedure for the Enantioselective Borane Reduction of Ketones: A solution of $BH_3{\cdot}SMe_2$ (2 M in THF) was added dropwise to a stirred and pre-warmed solution of 2 mol-% of the catalyst and ketone (1 equiv.) in degassed THF (5 mL) at 65 °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 with $MgSO_4$ and then distilled in a Kugelrohr apparatus to afford the expected alcohol. Enantiomeric excesses were determined by HPLC analysis.

X-ray Analyses: *anti*-**2a:** A plate white monocrystal of $C_{12}H_{17}N_1O_3P$, obtained by recrystallization in ethyl acetate, with approximate dimensions 0.5 × 0.4 × 0.4 mm was mounted on a glass capillary. All measurements were made with a Rigaku dif-

fractometer with Mo-K_α radiation. Cell constants and the orientation matrix for data collection were obtained from a least-squares refinement using setting angles of 30 reflections in the range θ = 1−25°, which corresponded to a monoclinic cell with dimensions: a = 7.0136(6), b = 8.0819(5), c = 10.5564(9) Å. For Z = 2 and M = 254.25, $\rho_{calcd.}$ = 1.41 g cm^{-3}. The space group was determined to be $P2_1$ from the systemic absences. A total of 1149 reflections were collected at T = 298 K. The standards were measured after every 144 reflections. Among the first 200 pairs of reflections, the signs of the corresponding calculated differences, establishing that the molecule is described with the correct absolute configuration (R_P). − **3:** A plate white monocrystal of $C_{17}H_{29}N_2O_3P$, obtained by recrystallization in ethyl acetate, with approximate dimensions 0.4 × 0.3 × 0.3 mm was mounted on a glass capillary. All the measurements were made with a Rigaku diffractometer with Mo-K_α radiation. Cell constants and the orientation matrix for data collection were obtained from a least-squares refinement using setting angles of 30 reflections in the range θ = 1−25°, which corresponded to an orthorhombic cell with dimensions: a = 9.3766(2), b = 11.0703(3), c = 17.8257(5) Å. For Z = 4 and M = 340.34, $\rho_{calcd.}$ = 1.19 g cm^{-3}. The space group was determined to be $P2_12_12_1$ from the systemic absences. A total of 2157 reflections were collected at T = 298 K. The standards were measured after every 208 reflections. Among the first 200 pairs of reflections, the signs of the corresponding calculated differences, establishing that the molecule is described with the correct absolute configuration (S_P). − Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145276 (*anti*-**2a**) and -145277 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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