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A study toward understanding the role of a phosphorus stereogenic center in (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane derivatives as catalysts in the borane-mediated asymmetric reduction of prochiral ketones

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Abstract—Representative diastereomeric pairs of chiral catalysts, containing the (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane moiety, with different stereochemistry at the phosphorus stereogenic center, have been synthesized and their stereoselection in the borane-mediated asymmetric reduction of representative prochiral ketones has been described.

1. Introduction

In recent years, there has been increasing interest in the design, synthesis, and applications of new and different classes of chiral molecules containing the N–P=O structural framework as catalysts for the borane-mediated asymmetric reduction of prochiral ketones[1–14] particularly, after the ingenious demonstration of the importance of these molecules as chiral catalysts by Wills.[1–8] In a continuation of our interest in the development of appropriate chiral catalysts, containing the N–P=O structural framework,[11–14] in the borane-mediated asymmetric reduction of prochiral ketones, we herein report our studies toward understanding the role of a phosphorus stereogenic center in the catalysts, containing (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-(3.3.0)octane moiety **I**, in directing the stereochemical pathway in the borane-mediated asymmetric reduction of prochiral ketones.

2. Results and discussion

Over the last few years, we have been actively involved in the synthesis and applications of various chiral catalysts based on the N–P=O structural framework built mainly on a (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo(3.3.0)octane skeleton **I** for the borane-mediated asymmetric reduction of prochiral ketones, with a view to develop useful chiral catalysts for obtaining the corresponding secondary alcohols in high enantioselectivities.[11–14] In this regard, we have synthesized representative chiral catalysts **1**–**9** and examined their potential for performing the borane-mediated asymmetric reduction of representative prochiral ketones.[11–14]

We envisaged that understanding the actual role of the stereochemistry at the phosphorus center in these catalysts, would probably (a) throw some light on understanding the mechanism of the reduction as the stereochemistry of the resulting secondary alcohols would provide the stereochemical sense of direction of the reduction process and (b) help us in designing appropriate catalyst(s), which can provide high enantioselectivities. A careful literature search revealed that there are very few reports in this subject. Wills prepared catalysts **10** and **10A** and studied their catalytic potential in the borane-mediated asymmetric reduction of prochiral ketones (Eq. 1).[5]

Wills et al. have also reported that catalysts **13** and **13A** provide the same sense of stereoselectivity in the borane-mediated asymmetric reduction of acetophenone, while

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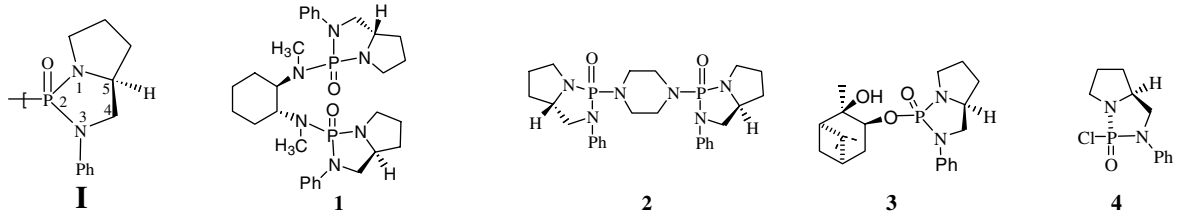
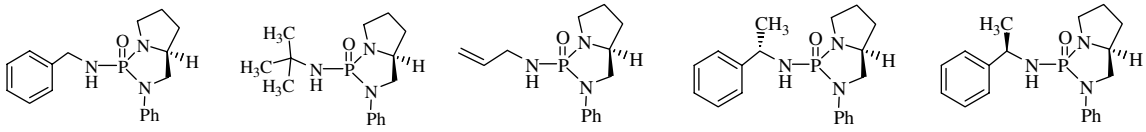
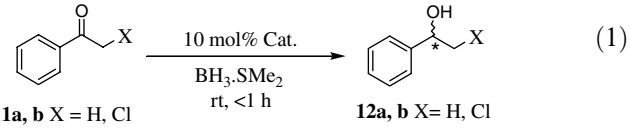


I 1 2 3 4



5 6 7 8 9

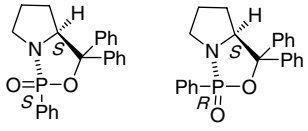
10 10A



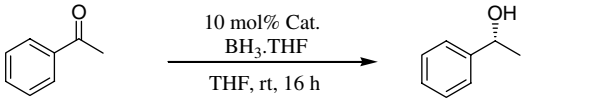
11a, b X = H, Cl — 10 mol% Cat., $BH_3.SMe_2$, rt, <1 h — 12a, b X= H, Cl (1)

Cat.	X = H	X = Cl
10	50% *ee* (*S*),	42% *ee* (*R*)
10A	5% *ee* (*R*),	4% *ee* (*R*)

catalyst **13** provides better enantioselectivities than **13A** (Eq. 2).[7]



13 13A



11a — 10 mol% Cat., $BH_3.THF$, THF, rt, 16 h — 12a

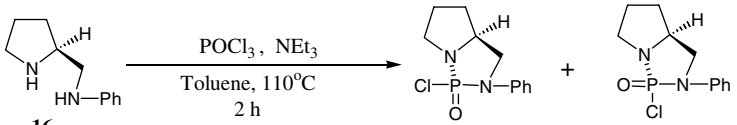
95% *ee* (with Cat. **13**)
75% *ee* (with Cat. **13A**) (2)

With this background information, we planned to examine the stereochemical sense of direction in the case of three representative diastereomeric pairs of catalysts **4** and **4A**; **14** and **14A** and **15** and **15A**, built mainly on skeleton **I**. We selected three representative prochiral ketones **11a–c** for our study.

Molecule **4** is already known in the literature[15] and we have previously reported[12] the applications of catalyst **4** (5 mol %) in the borane-mediated asymmetric reduction of representative prochiral ketones (Table 1, entry 1). Molecule **4A** was obtained as a minor product in the preparation of **4** via treatment of the chiral diamine **16** with $POCl_3$.[15] With a view to obtaining **4A** in substantial quantities, we treated chiral diamine **16** with $POCl_3$ in toluene at 110 °C and thus obtained both the isomers **4** and **4A** in reasonable isolated yields, after separation through column chromatography (Eq. 3). The structure of molecule **4A** was also established from single crystal X-ray data (Fig. 1).

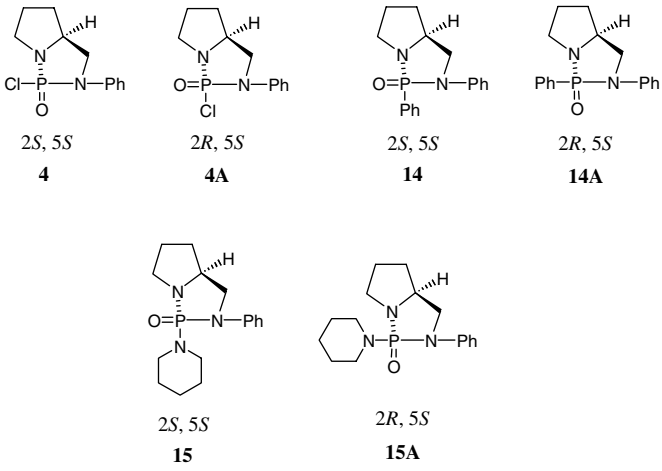
We have examined the borane-mediated asymmetric reduction of selected ketones **11a–c** with catalyst **4A** (5 mol %). The resulting secondary alcohols **12a–c** (Scheme 1) were obtained in similar enantioselectivities as in the case of catalyst **4**.[12] More interestingly, we noticed that the resulting secondary alcohols (with catalyst **4A**) have the same absolute configuration as in the case of catalyst **4** (Table 1, entries 1 and 2).

We next prepared the catalysts (diastereomeric pairs) **14** and **14A**,[16] and **15** and **15A**[16] in reasonable isolated yields via the reaction of diamine **16** with phenylphosphonicdichloride **17** and *N*-(dichlorophosphinyl)-piperidine **18**, respectively, followed by careful column chromatography (Scheme 2). The absolute configurations of all catalysts **14** and **14A**, and **15** and **15A** were



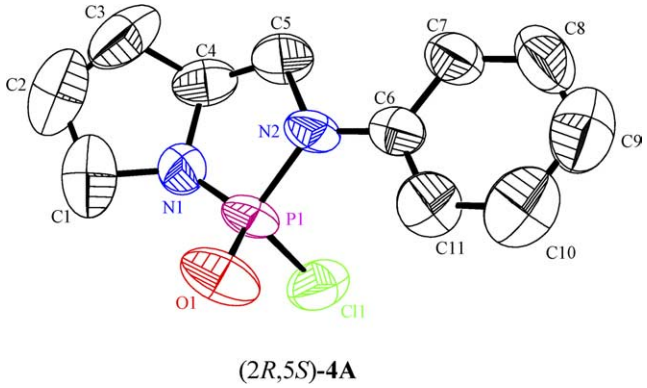
16 — $POCl_3$, NEt_3, Toluene, 110°C, 2 h — 2*S*, 5*S* **4** + 2*R*, 5*S* **4A** (3)

Isolated yields: 38% 26%



2*S*, 5*S* **4** 2*R*, 5*S* **4A** 2*S*, 5*S* **14** 2*R*, 5*S* **14A**

2*S*, 5*S* **15** 2*R*, 5*S* **15A**



(2*R*,5*S*)-**4A**

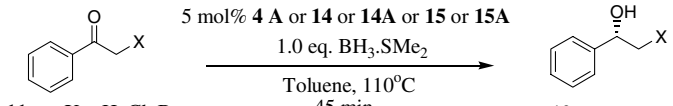
Figure 1. ORTEP diagram of (2*R*,5*S*)-**4A**. (Hydrogen atoms were omitted for clarity.)

also established by single crystal X-ray data (Figs. 2 and 3). We have then examined their catalytic potential in the borane-mediated asymmetric reduction of the three representative prochiral ketones **11a**–**c** (Eq. 4) (Table 1, entries 3–6). We also performed the reduction of phenacyl bromide **11c** with a combination of catalysts **15** and **15A** (2.5 mol % + 2.5 mol % = total 5 mol %) with a view to understand the effect, if any, on the stereodirection and we noticed that the resulting alcohol was obtained in almost similar enantioselectivity with the same configuration (Table 1, entry 7). All these results are presented in Table 1.

3. Fate of the phosphorus stereogenic center: possible explanation

From these results (Table 1, Eq. 4), it is quite clear that the diastereomeric pairs of catalysts (**4** and **4A**, **14** and

Table 1. Asymmetric reduction of prochiral ketones **11a**–**c** using catalysts **4A**, **14**, **14A**, **15**, **15A**, and **15** + **15A**



11a-c, X = H, Cl, Br

12a-c
59-84% *ee*

(4)

Entry[a]	Ketone	Catalyst	Conf. at phosphorus	X	Product	Yield (%)[b]	ee (%)[c]	Conf.[d]
1[e]	**11a**	**4**	*S*	H	**12a**	85	62	*R*
	11b	**4**	*S*	Cl	**12b**	93	81	*S*
	11c	**4**	*S*	Br	**12c**	89	87	*S*
2	**11a**	**4A**	*R*	H	**12a**	82	66	*R*
	11b	**4A**	*R*	Cl	**12b**	88	75	*S*
	11c	**4A**	*R*	Br	**12c**	91	84	*S*
3	**11a**	**14**	*S*	H	**12a**	79	65	*R*
	11b	**14**	*S*	Cl	**12b**	90	76	*S*
	11c	**14**	*S*	Br	**12c**	92	83	*S*
4	**11a**	**14A**	*R*	H	**12a**	83	62	*R*
	11b	**14A**	*R*	Cl	**12b**	88	79	*S*
	11c	**14A**	*R*	Br	**12c**	89	84	*S*
5	**11a**	**15**	*S*	H	**12a**	84	59	*R*
	11b	**15**	*S*	Cl	**12b**	85	78	*S*
	11c	**15**	*S*	Br	**12c**	80	81	*S*
6	**11a**	**15A**	*R*	H	**12a**	81	64	*R*
	11b	**15A**	*R*	Cl	**12b**	85	73	*S*
	11c	**15A**	*R*	Br	**12c**	91	79	*S*
7	**11c**	**15** + **15A** (1:1)	*S* + *R*	Br	**12c**	90	82	*S*

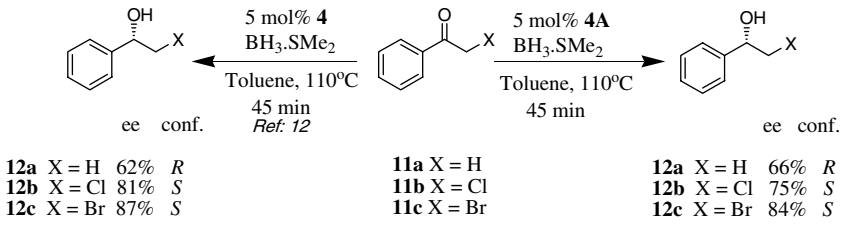
[a] All reactions were carried out on a 1 mM scale of ketone **11a**–**c** with 1 mM of $BH_3{\cdot}SMe_2$ in the presence of catalyst (5 mol %) in toluene for 45 min at 110 °C.

[b] Yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).

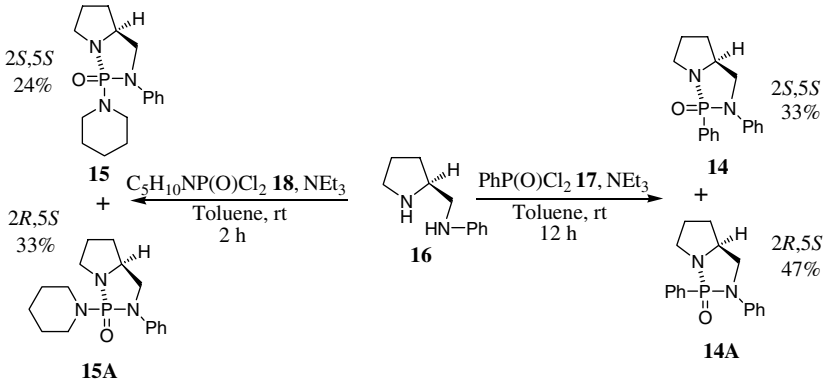
[c] Determined by HPLC analysis using the chiral column, Chiralcel-OD-H.

[d] Absolute configuration was assigned by the comparison of the sign of the specific rotation with that of the reported molecules.[17,18]

[e] These results were previously reported by us.[12]



Scheme 1.



Scheme 2.

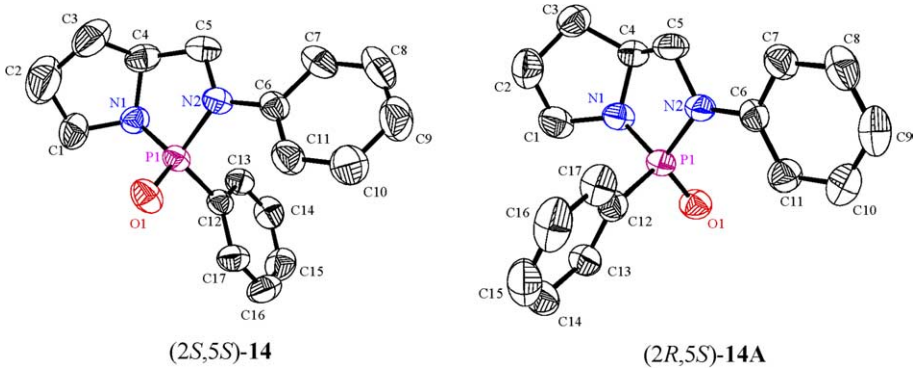


Figure 2. ORTEP diagrams of **14** and **14A**. (Hydrogen atoms were omitted for clarity.)

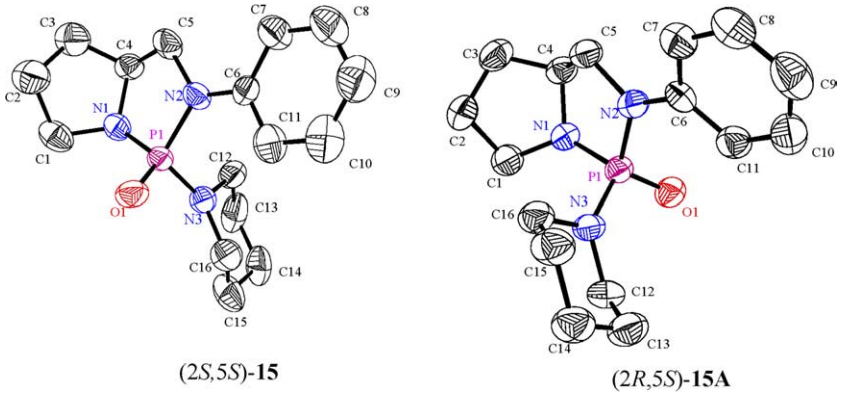
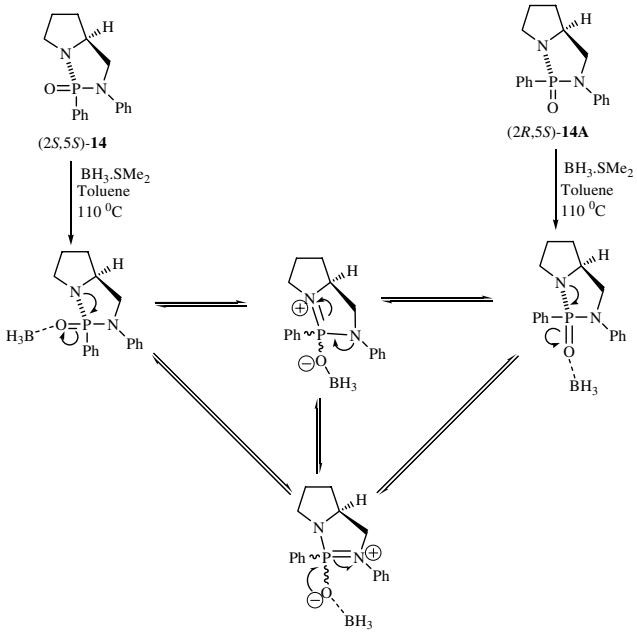


Figure 3. ORTEP diagrams of **15** and **15A**. (Hydrogen atoms were omitted for clarity.)

14A, and **15** and **15A**) containing the N–P=O structural framework, built mainly on skeleton **I** provided the resulting secondary alcohols **12a–c** with the same absolute configuration and also in almost similar enantioselectivities thus indicating that all the catalysts perform the reduction process with a similar sense of stereoselection. This would mean that both the diastereomeric catalysts (in all the cases) are forming either the same, or similar, types of species which essentially direct the reduction process. To understand this aspect, we have performed the following experiments using the diastereomeric catalysts (2*S*,5*S*)-**14** and (2*R*,5*S*)-**14A** as a representative case: (1) With a view to understand the effect of temperature on the stability of phosphorus stereogenic center, we heated catalyst **14** in toluene at 110 °C for 45 min and recorded the ^{31}P NMR spectrum in $CDCl_3$ (after removing toluene), which showed a peak at δ 26.59 (the original catalyst **14** showed a peak at δ 26.54). In a similar experiment, catalyst **14A** showed a peak at δ 21.16 in the ^{31}P NMR spectrum (the original catalyst **14A** showed a peak at δ 21.11). These results clearly indicate that both these catalysts **14** and **14A** are stable at 110 °C in toluene and that the stereochemistry at the phosphorus stereogenic center remains intact. (2) With a view to examine the stability of these catalysts in the presence of $BH_3{\cdot}SMe_2$, we first treated catalyst **14** (5 mol %, 0.030 g, 0.1 mM) in toluene with $BH_3{\cdot}SMe_2$ (0.152 g, 2 mM) [in the ratio of 1:20 as in the case of reaction conditions] at 110 °C for 45 min. The ^{31}P NMR spectrum of this mixture (in toluene containing 20% $CDCl_3$) showed many broad peaks in the region δ 60–140 (the prominent peaks at δ 76.48, 85.29, 133.64 and 138.66).[22] With a view to understand the optical nature of this (actual) catalytic species, we destroyed the $BH_3{\cdot}SMe_2$ with methanol and the solvent evaporated and recorded the specific rotation of the resulting mixture which had $[\alpha]_D^{25} = +9.9$ (*c* 1.87, MeOH). We also recorded the ^{31}P NMR spectrum (of this mixture) in $CDCl_3$, which showed many broad peaks in the region δ 55–110 (the prominent ones at δ 66.76, 84.14, 99.20, 101.50, 106.90, and 107.66).[22] Similar experiments were carried out with **14A**: ^{31}P NMR spectrum (in toluene with 20% $CDCl_3$ after treating with $BH_3{\cdot}SMe_2$ as in the case of catalyst **14**) showed many broad peaks in the region δ 60–140 (the prominent ones at δ 78.31, 85.93, 134.48, 135.99, and 138.40)[22] while the ^{31}P NMR spectrum in $CDCl_3$ (after the destruction of $BH_3{\cdot}SMe_2$ using methanol as in the case of catalyst **14**) showed broad peaks in the region δ 55–110 (the prominent ones at δ 66.36, 84.80, 99.07, 101.96, 107.65, and 108.39),[22] this mixture (as in the case of **14**) gave $[\alpha]_D^{25} = +10.75$ (*c* 1.60, MeOH). Specific rotations of the original catalysts showed that catalyst **14**, $[\alpha]_D^{25} = -31.4$ (*c* 1.02, $CHCl_3$), is levorotatory while catalyst **14A**, $[\alpha]_D^{25} = +107.6$ (*c* 0.98, $CHCl_3$), is dextrorotatory. Although it may not be appropriate (because of the presence of more than one catalytic species), the fact that both these diastereomers showed the same sense (sign) of specific (dextrorotatory) rotation may, to some extent, indicate the same configuration of the phosphorus stereogenic center (in the reduction process) in both cases. (3) With a view to understand the nature of catalyst after the reduction process, we recorded the ^{31}P NMR spectrum of the reaction mixture in $CDCl_3$ in the case of catalyst **14** (after the reduction of phenacyl bromide and destroying the excess $BH_3{\cdot}SMe_2$ with methanol and removing all the solvents), which showed many broad peaks in the region δ 55–110 [(prominent ones at δ 64.54, 94.43, 97.25, and 102.43) and also showed minor peaks at δ −1.20, −17.05, −58.80].[22] In a similar experiment, the ^{31}P NMR spectrum in the case of catalyst **14A** showed broad peaks in the region δ 55–110 [(prominent peaks at δ 64.85, 94.27, 97.47, and 102.63) and also showed minor peaks at δ −1.24, −58.90].[22]

Although it is difficult to ascertain the actual nature of the catalytic species from these studies, it is quite clear that catalysts are not stable and undergo changes during the reduction process. On the basis of the ^{31}P NMR spectra and specific rotation studies it may, to some extent, be possible to say that both the catalysts (diastereomeric pairs) may be converting into similar species although we do not have any concrete evidence. It may be possible to speculate that both the catalysts may be undergoing some changes in the presence of $BH_3{\cdot}SMe_2$ due to scrambling of the stereochemistry of phosphorus center as shown in Scheme 3.



Scheme 3. Possible pathway for the scrambling of the phosphorus stereogenic center.

4. Conclusion

In conclusion, we have demonstrated that the phosphorus stereochemistry, in all these catalysts containing the N–P=O structural framework built mainly on skeleton **I**, has no significant role in directing the stereochemical pathway of the reduction process. These results also support, to some extent, our earlier studies that the different groups on the phosphorus in the catalysts built on skeleton **I**, have little or no significant influence on the enantioselectivities.[14]

5. Experimental

All melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected. IR spectra were recorded on Jasco-FT-IR model 5300. ^{1}H NMR (200 or 400 MHz) and ^{13}C NMR (50 or 100 MHz) spectra were recorded in deuterochloroform ($CDCl_3$) on a Bruker-AC-200 or Bruker-Avance-400 spectrometer using tetramethylsilane (TMS, $\delta = 0$) as an internal standard. ^{31}P NMR (81 or 162 MHz) spectra were recorded on Bruker-AC-200 or Bruker-Avance-400 spectrometer using 85% H_3PO_4 ($\delta = 0$ ppm) as external standard. Elemental analyses were recorded on a Thermo Finnigan Flash 1112 analyzer. Mass spectra were recorded on Shimadzu LCMS 2010A mass spectrometer. The X-ray diffraction measurements were carried out at 298 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Kα ($\lambda = 0.71073$ Å) radiation with CAD-4 software or at 298 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube ($\lambda = 0.71073$ Å). HPLC analyses were carried out on a Shimadzu LC-10AD instrument using chiral column (Chiralcel-OD-H). Optical rotations were measured on Jasco DIP 370 digital polarimeter.

We have provided the details of the experimental procedures, specific rotations, and enantiomeric purities of the secondary alcohols using HPLC, with catalyst **14** as a representative case, since the remaining data are given in Table 1. We have previously prepared molecules **12a–c** and reported their spectral data.[11,13] The present spectral data (IR, ^{1}H NMR, and ^{13}C NMR) of these molecules are in agreement with the earlier data.

5.1. Preparation of catalysts

5.1.1. (2*S*,5*S*)- and (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octanes 4 and 4A. To a stirred solution of (*S*)-2-anilinomethylpyrrolidine **16** (1.058 g, 6 mM) and triethylamine (1.214 g, 12 mM) in toluene (20 mL) at 110 °C was added phosphorusoxychloride (0.920 g, 6 mM). After 2 h (monitored by TLC) stirring at the same temperature, the reaction mixture was cooled to room temperature and filtered to remove the salts. The filtrate was concentrated in vacuo and the residue, thus obtained, purified by column chromatography (silica gel, 15% ethyl acetate in hexanes) to afford the less polar (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane **4A**, and more polar (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane **4**.

5.1.2. (2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane 4. Crystalline solid, yield: 0.590 g, (38%); mp: 138–140 °C (lit.[15] 135 °C); $[\alpha]_D^{25} = +121.8$ (*c* 1.00, $CHCl_3$) [lit.[12] $[\alpha]_D^{25} = +127.2$ (*c* 2.1, $CHCl_3$)]. We have previously reported the spectral data of **4**[12] and the present spectral data are in agreement with the reported data. In fact the single crystal X-ray data of (2*R*,5*R*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane has already been reported in the literature.[19]

5.1.3. (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane 4A. Crystalline solid, yield: 0.393 g, (26%); mp: 126–128 °C (lit.[15] 130 °C); $[\alpha]_D^{25} = -145.6$ (*c* 1.04, $CHCl_3$); IR (KBr): 2970, 1602, 1502, 1265, 1118 cm^{-1}; ^{1}H NMR (200 MHz): δ 1.61–2.26 (m, 4H), 3.11–3.32 (m, 1H), 3.46–3.65 (m, 1H), 3.70–4.00 (m, 3H), 7.05–7.16 (m, 1H), 7.21–7.45 (m, 4H); ^{13}C NMR (50 MHz): δ 26.03 (d, $J = 4.9$ Hz), 32.29, 45.78, 47.93 (d, $J = 15.8$ Hz), 57.07 (d, $J = 10.9$ Hz), 117.39 (d, $J = 4.9$ Hz), 123.06, 129.35, 139.84 (d, $J = 3.6$ Hz); ^{31}P NMR: δ 25.32; LCMS (*m*/*z*): 257 $(M+H)^+$, 259 $(M+2+H)^+$; Anal. Calcd for $C_{11}H_{14}N_2OPCl$: C, 51.47; H, 5.50; N, 10.91. Found: C, 51.51; H, 5.56; N, 10.80.

5.1.4. Crystal data for 4A. Empirical formula: $C_{11}H_{14}N_2OPCl$; formula weight: 256.66; crystal color and habit: colorless and plate; crystal dimensions: $0.52 \times 0.22 \times 0.20$ mm; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 6.7889(19)$ Å, $b = 12.646(4)$ Å, $c = 14.253(4)$ Å; $\alpha = 90.00$; $\beta = 90.00$; $\gamma = 90.00$; $V = 1223.6(6)$ Å^3; space group, $P2_12_12_1$ (no. 19); $Z = 4$; $D_{calcd} = 1.393$ g/cm^3; $F_{000} = 536$; λ(Mo K$_\alpha$) = 0.71073 Å; $R(I \geqslant 2\sigma_1) = 0.0827$, $wR^2 = 0.1832$. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **4A** CCDC # 261368).

5.1.5. (2*S*,5*S*)- and (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octanes 14 and 14A. To a stirred solution of (*S*)-2-anilinomethylpyrrolidine **16** (0.705 g, 4 mM) and triethylamine (0.809 g, 8 mM) in CH_2Cl_2 (10 mL) at room temperature was added phenylphosphonicdichloride **17** (0.780 g, 4 mM) dropwise. After 12 h stirring at room temperature (monitored by TLC), the reaction mixture was filtered to remove the salts. The solvent, from the filtrate, was removed in vacuo and the residue thus obtained, purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford less polar (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane **14** and more polar (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane **14A**. Molecules **14** and **14A** are known in the literature.[20] However their spectral data were not reported.

5.1.6. (2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane 14. Crystalline solid, yield: 0.390 g, (33%); mp: 162–164 °C; $[\alpha]_D^{25} = -31.4$ (*c* 1.02, $CHCl_3$); IR (KBr): 2964, 1602, 1506, 1261, 1103 cm^{-1}; ^{1}H NMR (200 MHz): δ 1.70–2.28 (m, 4H), 2.85–3.10 (m, 1H), 3.48–3.63 (m, 1H), 3.72–4.17 (m, 3H), 6.78–6.94 (m, 1H), 7.00–7.57 (m, 7H), 7.71–7.94 (m, 2H); ^{13}C NMR (100 MHz): δ 26.39, 32.19, 44.69, 49.19 (d, $J = 14.3$ Hz), 59.32 (d, $J = 5.0$ Hz), 116.20 (d, $J = 4.0$ Hz), 121.00, 128.28 (d, $J = 14.5$ Hz), 128.93, 131.39, 131.70 (d, $J = 9.5$ Hz), 133.15 (d, $J =$ 165.8 Hz), 141.68 (d, $J = 6.0$ Hz); ^{31}P NMR: δ 26.59; LCMS (*m*/*z*): 299

$(M+H)^+$; Anal. Calcd for $C_{17}H_{19}N_2OP$: C, 68.44; H, 6.42; N, 9.39. Found: C, 68.51; H, 6.40; N, 9.47.

5.1.7. Crystal data for 14. Empirical formula: $C_{17}H_{19}N_2OP$; formula weight: 298.31; crystal color, habit: colorless, block; crystal dimensions: $0.60 \times 0.52 \times 0.52$ mm; crystal system: hexagonal; lattice type: primitive; lattice parameters: $a = 9.0023(11)$ Å, $b = 9.0023(13)$ Å, $c = 33.331(13)$ Å; $\alpha = 90.00$; $\beta = 90.00$; $\gamma = 120.00$; $V = 2338.6(10)$ Å^3; space group, P65 (no. 170); $Z = 6$; $D_{calcd} = 1.271$ g/cm^3; $F_{ooo} = 948$; λ(Mo K_α) = 0.71073 Å; $R(I \geqslant 2\sigma_1) = 0.0368$, $wR^2 = 0.0870$. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **14** CCDC # 261369).

5.1.8. (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane 14A. Crystalline solid, yield: 0.560 g, (47%); mp: 164–165 °C; $[\alpha]_D^{25} = +107.6$ (*c* 0.98, $CHCl_3$); IR (KBr): 2972, 1601, 1500, 1234, 1122 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.61–2.02 (m, 3H), 2.16–2.27 (m, 1H), 2.81–2.94 (m, 1H), 3.08–3.17 (m, 1H), 3.56–3.66 (m, 1H), 4.03–4.13 (m, 1H), 4.24–4.38 (m, 1H), 6.81–6.90 (m, 1H), 7.11–7.22 (m, 4H), 7.39–7.54 (m, 3H), 7.65–7.76 (m, 2H); ^{13}C NMR (50 MHz): δ 26.75 (d, $J = 6.1$ Hz), 31.48 (d, $J = 3.6$ Hz), 44.15 (d, $J = 7.3$ Hz), 54.10 (d, $J = 9.7$ Hz), 57.77 (d, $J = 9.7$ Hz), 115.66 (d, $J = 4.9$ Hz), 120.52, 128.45 (d, $J = 14.6$ Hz), 128.74, 129.12 (d, $J = 149.2$ Hz), 131.75, 132.46 (d, $J = 10.9$ Hz), 142.13 (d, $J = 7.3$ Hz); ^{31}P NMR: δ 21.36; LCMS (*m*/*z*): 299 $(M+H)^+$; Anal. Calcd for $C_{17}H_{19}N_2OP$: C, 68.44; H, 6.42; N, 9.39. Found: C, 68.58; H, 6.41; N, 9.29.

5.1.9. Crystal data for 14A. Empirical formula: $C_{17}H_{19}N_2OP$; formula weight: 298.31; crystal color, habit: colorless, needle; crystal dimensions: $0.32 \times 0.24 \times 0.21$ mm; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 16.4550(9)$ Å, $b = 8.5013(5)$ Å, $c = 10.7642(6)$ Å; $\alpha = 90.00$; $\beta = 90.00$; $\gamma = 90.00$; $V = 1505.79(15)$ Å^3; space group, $P2_12_12_1$ (no. 19); $Z = 4$; $D_{calcd} = 1.316$ g/cm^3; $F_{ooo} = 632$; λ(Mo K_α) = 0.71073 Å; $R(I \geqslant 2\sigma_1) = 0.0356$, $wR^2 = 0.0914$. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **14A** CCDC # 261370).

5.1.10. (2*S*,5*S*)- and (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-piperidinyl-3-phenylbicyclo(3.3.0)octanes 15 and 15A. To a stirred solution of (*S*)-2-anilinomethylpyrrolidine **16** (0.352 g, 2 mM) and triethylamine (0.404 g, 4 mM) in toluene (10 mL) at room temperature was slowly added *N*-(dichlorophosphinyl)piperidine **18** (0.505 g, 2.5 mM). After stirring for 2 h at the same temperature (monitored by TLC), the reaction mixture was filtered to remove the salts. The solvent from the filtrate was removed in vacuo and the residue, thus obtained, was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford the less polar (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-piperidinyl-3-phenylbicyclo(3.3.0)octane **15** and the more polar (2*R*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-piperidinyl-3-phenylbicyclo(3.3.0)octane **15A**. Molecules **15** and **15A** have already been reported[21] as well as the spectral (IR, ^{1}H NMR, ^{31}P NMR and mass) data of these molecules.[21] Our spectral data are in agreement with that of the reported data.

5.1.11. (2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-piperidinyl-3-phenylbicyclo(3.3.0)octane 15. Crystalline solid, yield: 0.146 g (24%); mp: 108–110 °C, [lit.[21] 117.6–118.3]; $[\alpha]_D^{25} = -21.2$ (*c* 0.84, $CHCl_3$) {lit.[21] $[\alpha]_D^{25} = -21.8$ (*c* 1.10, $CHCl_3$)}; IR (KBr): 2932, 1601, 1502, 1226, 1122 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.20–2.15 (m, 10H), 2.82–3.15 (m, 5H), 3.32–3.47 (m, 1H), 3.60–3.90 (m, 3H), 6.85–6.97 (m, 1H), 7.02–7.18 (m, 2H), 7.20–7.36 (m, 2H); ^{13}C NMR (100 MHz): δ 24.53, 25.99 (d, $J = 3.9$ Hz),[†] 32.10, 44.92, 44.99, 48.78 (d, $J = 16.5$ Hz), 57.83 (d, $J = 7.7$ Hz), 116.06 (d, $J = 5.0$ Hz), 120.54, 128.77, 142.02 (d, $J = 6.8$ Hz). ^{31}P NMR: δ 21.00; LCMS (*m*/*z*): 306 $(M+H)^+$; Anal. Calcd for $C_{16}H_{24}N_3OP$: C, 62.93; H, 7.92; N, 13.76. Found: C, 62.92; H, 8.00; N, 13.65.

5.1.12. Crystal data for 15. Empirical formula: $C_{16}H_{24}N_3OP$; formula weight: 305.35; crystal color, habit: colorless, needle; crystal dimensions: $0.45 \times 0.32 \times 0.30$ mm; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 6.6671(3)$ Å, $b = 13.4035(7)$ Å, $c = 18.0477(9)$ Å; $\alpha = 90.00$; $\beta = 90.00$; $\gamma = 90.00$; $V = 1612.79(14)$ Å^3; space group, $P2_12_12_1$ (no. 19); $Z = 4$; $D_{calcd} = 1.258$ g/cm^3; $F_{ooo} = 656$; λ(Mo K_α) = 0.71073 Å; $R(I \geqslant 2\sigma_1) = 0.0446$, $wR^2 = 0.1194$. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **15** CCDC # 261371).

5.1.13. (2*R*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-piperidinyl-3-phenylbicyclo(3.3.0)octane 15A. Crystalline solid, yield: 0.202 g, (33%); mp: 119–121 °C [lit.[21] 128.5–130.3 °C]; $[\alpha]_D^{25} = +64.9$ (*c* 1.55, $CHCl_3$) [lit.[21] $[\alpha]_D^{25} = +66.5$ (*c* 1.91, $CHCl_3$)]; IR (KBr): 2932, 1599, 1494, 1234, 1122 cm^{-1}; ^{1}H NMR (200 MHz): δ 1.15–2.33 (m, 10H), 2.85–3.47 (m, 7H), 3.62–3.80 (m, 1H), 3.96–4.18 (m, 1H), 6.82–7.00 (m, 1H), 7.09–7.40 (m, 4H); ^{13}C NMR (50 MHz): δ 24.51, 26.18 (d, $J = 4.9$ Hz), 27.48 (d, $J = 6.1$ Hz), 31.64 (d, $J = 4.9$ Hz), 43.79 (d, $J = 4.9$ Hz), 45.46, 52.99 (d, $J = 12.1$ Hz), 56.45 (d, $J = 13.3$ Hz), 115.55 (d, $J = 4.9$ Hz), 120.30, 129.01, 142.89 (d, $J = 6.1$ Hz); ^{31}P NMR: δ 15.34; LCMS (*m*/*z*): 306 $(M+H)^+$; Anal. Calcd for $C_{16}H_{24}N_3OP$: C, 62.93; H, 7.92; N, 13.76. Found: C, 63.00; H, 7.90; N, 13.88.

5.1.14. Crystal data for 15A. Empirical formula: $C_{16}H_{24}N_3OP$; formula weight: 305.35; crystal color, habit: colorless, needle; crystal dimensions: $0.27 \times 0.24 \times 0.13$ mm; crystal system: orthorhombic; lattice type: primitive; lattice parameters: $a = 8.9004(7)$ Å,

[†] It looks that one of the pyrrolidine ring carbon and two of the piperidine ring carbons (β- to nitrogen) might be merging and appearing as a doublet at δ 25.99 (total three carbons).

$b = 9.8833(8)$ Å, $c = 17.7994(15)$ Å; $\alpha = 90.00$; $\beta = 90.00$; $\gamma = 90.00$; $V = 1565.7(2)$ Å^3; space group, $P2_12_12_1$ (no. 19); $Z = 4$; $D_{calcd} = 1.295$ g/cm^3; $F_{ooo} = 656$; λ(Mo K_α) = 0.71073 Å; $R(I \geqslant 2\sigma_1) = 0.0503$, $wR^2 = 0.1030$. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **15A** CCDC # 261372).

5.2. Application of the catalysts

5.2.1. Representative procedure: asymmetric reduction of acetophenone 11a using catalyst 14: synthesis of (*R*)-1-phenylethanol 12a. To a stirred solution of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2,3-diphenylbicyclo(3.3.0)octane **14** (0.0149 g, 0.05 mM) in toluene (3 mL) was added borane-dimethyl sulfide (0.076 g, 1.0 mM) at room temperature and the reaction mixture heated to 110 °C. Once the temperature was stabilized at 110 °C, acetophenone **11a** (0.120 g, 1.0 mM) in toluene (2 mL) was added dropwise over 10 min and stirring continued for further 45 min (monitored by TLC) at 110 °C. Then, the reaction mixture was allowed to cool to room temperature and quenched with methanol. The solvent was then removed under reduced pressure and the residue thus obtained, purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*R*)-1-phenylethanol **12a** in 79% yield (0.096 g) as a colorless oil; $[\alpha]_D^{25} = +29.2$ (*c* 0.99, MeOH) {lit.[17] $[\alpha]_D^{25} = +44.1$ (*c* 3.0, MeOH), (*R*)-configuration, 97% ee} 65% ee, the enantiomeric purity was determined by HPLC using a chiral column [Chiralcel-OD-H, 95:5 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm, retention times: 9.04 min (*R*) and 10.75 min (*S*)].

5.2.2. (*S*)-2-Chloro-1-phenylethanol 12b. Colorless oil; 90% yield; $[\alpha]_D^{25} = +38.5$ (*c* 1.01, cyclohexane) {lit.[18] $[\alpha]_D^{25} = -48.1$ (*c* 1.73, cyclohexane), (*R*)-configuration, 100% ee} 76% ee, enantiomeric purity was determined by HPLC using chiral column [Chiralcel-OD-H, 90:10 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm, retention times: 8.77 min (*S*) and 9.59 min (*R*)].

5.2.3. (*S*)-2-Bromo-1-phenylethanol 12c. Colorless oil; 92% yield; $[\alpha]_D^{25} = +36.1$ (*c* 1.02, $CHCl_3$) {lit.[18] $[\alpha]_D^{25} = -39.0$ (*c* 8.00, $CHCl_3$), (*R*)-configuration, 93% ee} 83% ee, the enantiomeric purity was determined by HPLC using chiral column [Chiralcel-OD-H, 90:10 hexanes/*i*-PrOH, 1.0 mL/min, 254 nm, retention times: 8.70 min (*S*) and 9.54 min (*R*)].

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22. Peaks intensities in the case of **14** and **14A** are different in ^{31}P NMR spectra (162 MHz).