ΞJ52-1999-797
Journal of the Chinese Chemical Society, **1999**, *46*, 797-810

Preparation of Chiral Phosphorus(V) Reagents and Their Uses with Borane in the Enantioselective Reduction of Ketones

Guo-Hsian Chen (陳國祥), Jue-Liang Hsu (徐睿良), Wen-Bin Yang (楊文彬),
Jim-Min Fang* (方俊民), Gene-Hsiang Lee (李錦祥),
Yi-Hung Liu (劉怡弘) and Yu Wang (王 瑜)
Department of Chemistry, National Taiwan University, Taipei 106, Taiwan, R.O.C.

Chiral pentavalent phosphorus reagents **5-17** were prepared from $POCl_3$ and ephedrine (or the related α-amino alcohols), followed by substitution with nucleophiles of phenylmagnesium bromide, alcohols, amines, diamines and triamines. The substitution reactions occurred in a stereospecific manner with retention of the configuration at the phosphorus center. The structures of these phosphorus(V) reagents were determined by spectral methods and verified by X-ray diffraction in several instances. These phosphorus(V) reagents were used with borane/dimethylsulfide complex in the enantioselective reduction of aromatic, aliphatic and heterocyclic ketones. The phosphorus(V) reagents likely functioned as Lewis bases to react with borane, forming *in situ* zwitterionic species as the chiral reducing agents. The reactions were generally carried out at 0 °C in tetrahydrofuran solution with a molar ratio of ketone/borane/phosphoramidate = 1:1:0.2 to afford secondary alcohols with modest enantioselectivity, up to 67% ee in the reduction of 4′-methylacetophenone.

INTRODUCTION

Hexamethylphosphoramide (HMPA) is a dipolar reagent widely used to promote a variety of organometallic reactions.[1] Chiral phosphorus(V) reagents can be considered as the substitutes of HMPA to induce asymmetric organometallic reactions. Indeed, chiral phosphorus(V) reagents have been used as resolving agents,[2] auxiliaries[3] and ligands[4] to promote various asymmetric reactions. We have recently carried out the asymmetric cyanosilylation of benzaldehydes promoted by $SmCl_3$ and a *bis*-phosphoramidate reagent (**12**).[5] As a continuation of this study, we report herein the preparation of the chiral phosphorus(V) reagents **5-17** (Fig. 1) and their uses together with borane for the reduction of ketones.[6] The related work was also previously explored by other two research teams using different phosphorus(V) reagents.[4e,4g,7]

RESULTS AND DISCUSSION

Preparation of chiral phosphorus(V) reagents (Fig. 1)[8]

The commercially available (1*R*,2*S*)-(-)-ephedrine hydrochloric salt (**1**) was treated with $POCl_3$ in the presence of Et_3N at 0 °C to give the (2*R*,4*S*,5*R*)-chlorophosphoramidate **3** and its (2*S*,4*S*,5*R*)-isomer **3′** in a ratio of 87:13. The ratio could be increased to 93:7 when the condensation was conducted at -20 °C. These two isomers were rather stable and successfully separated by silica gel chromatography. Treatment of (1*R*,2*S*)-(-)-norephedrine with 2,2-dimethoxypropane gave 2,2,4-trimethyl-5-phenyloxazolidine, which was reduced by $LiAlH_4$ to afford (1*R*,2*S*)-2-isopropylamino-1-phenyl-1-propanol (**2**) in 86% overall yield.[9] The α-amino alcohol **2** reacted with $POCl_3$ at 0 °C to give predominantly the (2*R*,4*S*,5*R*)-clorophosphoramidate **4** (95%) along with a small amount of the (2*S*,4*S*,5*R*)-isomer **4′**. Compound **3** and its C-2 epimer, differing at the phosphorus center, showed distinct differences in the NMR spectra.[8a,8d] For example, the (2*R*,4*S*,5*R*)-isomer **3′** displayed H-4 and H-5 at δ 3.68 (m) and 5.53 (t, J = 7.3 Hz), whereas compound **3** exhibited the corresponding protons at lower fields of δ 3.82 (m) and 5.83 (d, J = 6.1 Hz) due to the deshielding effect of the P=O group on the same side. The H-5 of **3** appeared as a doublet, whereas the H-5 of the isomer **3′** displayed as a triplet due to couplings with both H-4 and the phosphorus atom. A similar trend was also shown in the ^1H NMR spectra of **4** and its (2*S*,4*S*,5*R*)-isomer. In the ^{31}P NMR spectra, the phosphorus signals of **3** and **4** occurred at higher fields than the corresponding signals of the (2*S*,4*S*,5*R*)-isomers.

The chlorophosphoramidates **3** and **4** underwent substitution reactions with a variety of nucleophiles, such as Grignard reagents, amines and alcohols, in a stereospecific manner to give the products **5-11** with retention of the configuration at the phosphorus centers. In many cases, the iso-

Dedicated to Professor Kung-Tsung Wang on the occasion of his 70th birthday.

lated yields were over 90% after chromatography. No C-2 epimers were formed as indicated by NMR and HPLC analyses. The C_2-symmetric *bis*-phosphoramidates **12-15** were derived from appropriate diamines and chlorophosphoramidates. The chiral phosphoramidate **16** was obtained by methylation of **15**. The C_3-symmetric *tris*-phosphoramidate **17** was prepared by the substitution reaction of **4** with *tris*-(2-aminoethyl)amine. The structures of **5-17** were determined by analyses of their spectral properties. Except for compound **10** with a bulky *t*-BuO group, each of the formed phosphorimidates exhibited the characteristic H-5 signal as a doublet due to the coupling with H-4. No apparent coupling with the ^{31}P atom was observed. The structures of **5, 8, 11, 13, 14, 15** and **17** were also verified by X-ray diffractions. Thus, the substitution reactions of **3** and **4** actually proceeded with an addition-elimination mechanism.[4a] The nucleophile attacked the chlorophosphoramidate (**3** or **4**) from the axial direction of the phosphorus center to form a bistrigonal pyramidal intermediate. A pseudorotation would place the P-Cl bond on the axial orientation for the subsequent cleavage to furnish the observed phosphoramidate products (**5-17**) with retention of the configuration of a phosphorus center.

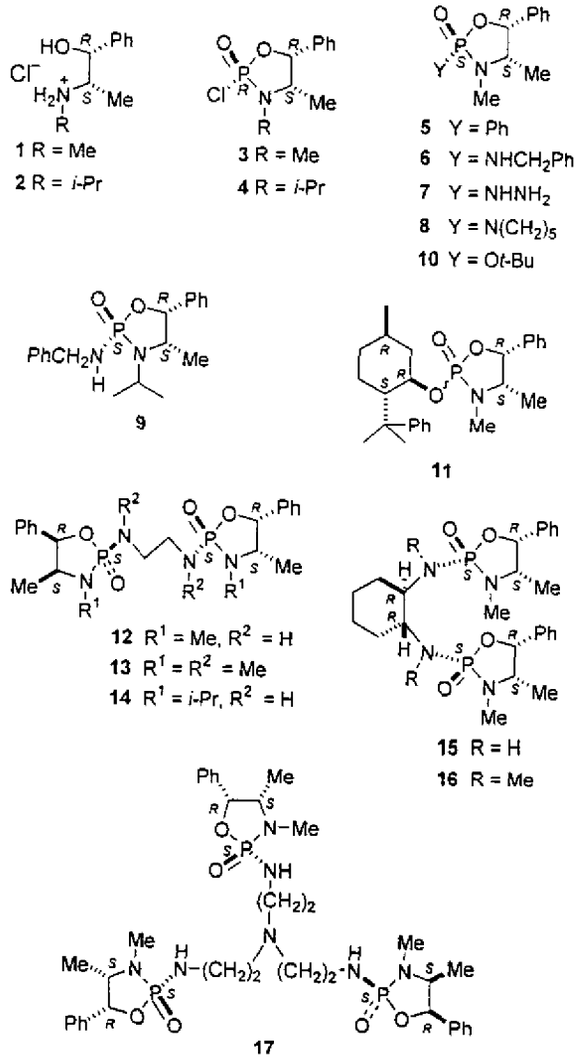


Fig. 1. The pentavalent phosphorus ligands used in this study.

Crystal data

Crystal and molecular structures of compounds **5, 8, 11, 12, 14, 15** and **17** were analyzed from X-ray diffraction data of single crystals. Essential crystal data of these compounds appear in Tables 1 and 2. Their molecular structures are displayed in Figs. 2-8. The structure of **12** has appeared as a supplementary material in one of our previous papers.[5a]

Asymmetric reactions (Fig. 9)

We have shown[5] that a combined use of $SmCl_3$ (1 mol %) and the *bis*-phosphoramidate ligand **12** (1 mol %) promotes the cyanosilylation of benzaldehyde at room temperature to give the corresponding cyanohydrin silyl ether with 72% ee in favor of the *R*-enantiomer. By using the *bis*-phosphoramidate **14** and the *tris*-phosphoramidate **17** instead of **12**, we also obtained the cyanosilylation product in 63% ee with predominance of the *R*-enantiomer and in 25% ee with predominance of the *S*-enantiomer, respectively, under similar reaction conditions.

We then studied the asymmetric reduction of acetophenone with borane ($Me_2S{\cdot}BH_3$) by using a phosphoramidate modifier **6** having a benzylamino substituent (Table 3). In order to procure a good enantioselectivity, one should carry out the reaction by adding acetophenone to the premixed solution of $Me_2S{\cdot}BH_3$ and the phosphoramidate **6**. The best asymmetric induction (63% ee in favor of the *R*-enantiomer of **18a**) among the examined examples was obtained by conducting the reaction at 0 °C in THF solution with a molar ratio of ketone/borane/phosphoramidate = 1:1:0.2 (entry 1). There was no significant change of enantioselectivity by lowering the reaction temperature to -20 °C (entry 2), but the enantioselectivity somewhat decreased at room temperature or refluxing temperature (entries 3 and 4). The reaction with less amount of phosphoramidate **6** (10 mol %) resulted in lower enantioselectivity (comparison of entries 1 and 5), but increase the amount of **6** to 30 mol % did not improve the enantioselectivity (comparison of entries 3 and 6). An alternative reaction procedure, i.e. by addition of $Me_2S{\cdot}BH_3$ to a premixed solution of **6** and PhCOMe (entry 7), did not show any enantioselectivity. Change of the amount of borane to 0.6 or 2 equiv gave the

Table 1. Crystal Data of Compounds **5**, **8**, **11** and **12**

Compound	**5**	**8**	**11**	**12**
Diffractometer	CAD-4	CCD	CAD-4	CAD-4
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	8.937(1)	6.399(2)	10.095(2)	30.901(9)
b (Å)	10.394(2)	11.153(3)	10.675(5)	10.157(4)
c (Å)	16.001(3)	22.546(7)	23.651(5)	5.296(1)
V (Å^3)	1486.3(5)	1609.2(8)	2548.9(1)	1662.2(9)
Z	4	4	4	2
D(calc), g.cm^{-3}	1.284	1.215	1.151	1.295
λ(Mo, K_α), Å	0.7107	0.7107	1.5418	0.7107
F(000)	609	632	956	678
Unit cell detn: #; 2θ range	25; 18–26	4427; 3–55	25; 37–55	25; 15–23
Scan type	θ/2 θ	ω scan	θ/2 θ	θ/2 θ
Scan width (deg.)	2(0.60 + 0.35 tanθ)	0.3/frame	2(0.60+0.15 tanθ)	2(0.60+0.35 tanθ)
2θ max, deg.	60.0	55.0	149.0	50.0
μ(Mo, K_α), cm^{-1}	1.792	1.740	11.348	3.179
Crystal size (mm)	0.50 × 0.50 × 0.60	0.08 × 0.08 × 0.12	0.20 × 0.30 × 0.50	0.05 × 0.15 × 0.50
Temperature (K)	298	296	298	298
No. of meas. reflns.	2465	12833	2975	1747
No. of unique reflns, R_{int}	2465	3424, 0.0613	2975	1747
No. of obs. reflns.(I>2(σ)I)	1569	2383	2481	799
No. of refined params.	254	182	281	174
R_F R_w	0.039, 0.037	0.065, 0.157*	0.054, 0.055	0.067, 0.063
GoF	1.62	1.047	1.67	2.38
Minimized function	$\Sigma w\lvert F_o - F_c\rvert^2$	$\Sigma w\lvert F_o^2 - F_c^2\rvert^2$	$\Sigma w\lvert F_o - F_c\rvert^2$	$\Sigma w\lvert F_o - F_c\rvert^2$
Weighing scheme	$1/\sigma^2(F_o)$	a = 0.1, b = 0#	unit	$1/\sigma^2(F_o)$
g(second ext. coeff.) × 10^4	1.35(3)	0.04(3)	2.63(4)	0.39(14)
$(\Delta/\sigma)_{mas}$	0.0075	0.0010	0.0000	0.0022
Residual in final D-map (e/Å^3)	−0.23, 0.27	−0.18, 0.18	−0.40, 0.28	−0.34, 0.26

$R_f = [\Sigma\lvert F_o - F_c\rvert/F_o]$; $R_w = [\Sigma w\lvert F_o - F_c\rvert^2/\Sigma w\lvert F_o\rvert^2]^{1/2}$
GoF = $[\Sigma w\lvert F_o - F_c\rvert^2$/No. of unique reflns. − No. of refined params.$]^{1/2}$
* wR2 = $[\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$
#w = $1/[\sigma^2(F_o^2) + (aP)^2 + bP]$; P = $(F_o^2 + 2F_c^2)/3$

alcohol product **18a** with lower ee values (entries 8-10). The enantioselectivity somewhat decreased in toluene or a mixed solvent of THF/Et_2O (entries 11 and 12), and dropped dramatically in CH_2Cl_2 (entry 13).

We also investigated the reduction of acetophenone using different boranes and additives (Table 4). Our study

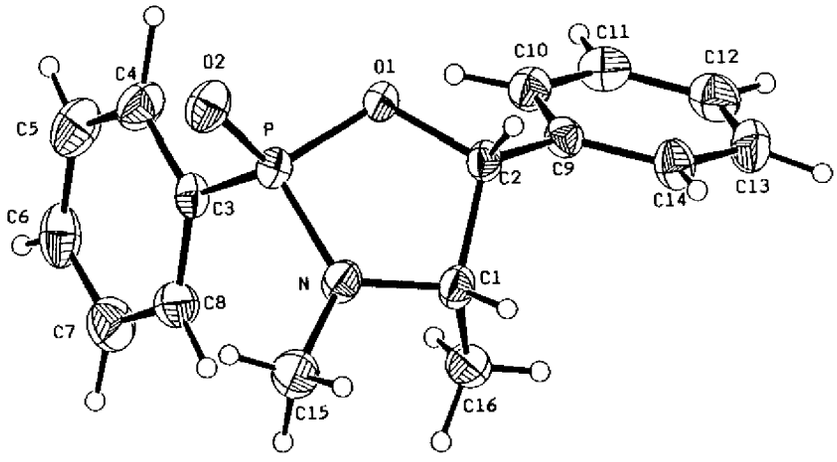


Fig. 2. ORTEP drawing of compound **5**.

Table 2. Crystal Data of Compounds **14**, **15** and **17**

Compound	**14**	**15**	**17**
Diffractometer	CAD-4	CCD	CAD-4
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
a (Å)	6.798(3)	6.649(1)	12.428(4)
b (Å)	29.629(8)	15.499(3)	21.713(1)
c (Å)	7.292(2)	26.639(1)	16.317(6)
β (deg.)			112.22(3)
V (Å^3)	1468.9(8)	2745.2(7)	4076.0(3)
Z	2	4	4
D(calc), g.cm^{-3}	1.204	1.289	1.261
λ(Mo, Kα), Å	1.5418	0.7107	0.7107
F(000)	571	1136	1650
Unit cell detn: #; 2θ range	25; 33–64	8192; 3–59	25; 17–21
Scan type	θ/2 θ	ω	θ/2 θ
Scan width (deg.)	2(0.70 +0.15 tanθ)	0.3/frame	2(0.65 +0.35 tanθ)
2θ max, deg.	150.0	59.1	50.0
μ(Mo, Kα), cm^{-1}	16.34	1.97	1.90
Crystal size (mm)	0.20 × 0.40 × 0.40	0.07 × 0.20 × 0.45	0.10 × 0.20 × 0.50
Temperature (K)	298	296	298
No. of meas. Reflns.	1795	19940	7383
No. of unique reflns., R_{int}	1795	7126, 0.0794	7377
No. of obs. reflns. (I>2(σ)I)	1424	4297	2733
No. of refined params.	164	326	937
R_f, R_w	0.074, 0.074	0.073, 0.108*	0.045, 0.039
GoF	3.51	1.06	1.26
Minimized function	$\Sigma w\|F_o - F_c\|^2$	$\Sigma w\|F_o^2 - F_c^2\|^2$	$\Sigma w\|F_o - F_c\|^2$
Weighing scheme	$1/\sigma^2(F_o)$	a = 0.03, b = 0.9#	$1/\sigma^2(F_o)$
g(second ext. coeff.) × 10^4	0.570(8)	0.045(5)	0.004(7)
$(\Delta/\sigma)_{max}$	0.0010	0.001	0.1025
Residual in final D-map (e/Å^3)	−0.76, 0.36	−0.31, 0.25	−0.35, 0.70

$R_f = [\Sigma|F_o - F_c|/F_o]$; $R_w = [\Sigma w|F_o - F_c|^2/\Sigma w|F_o|^2]^{1/2}$;
GoF = $[\Sigma w|F_o - F_c|^2$/No. of unique reflns. − No. of refined params.$]^{1/2}$
* wR2 = $[\Sigma w|F_o^2 - F_c^2|^2/\Sigma w|F_o^2|^2]^{1/2}$
#w = $1/[\sigma^2(F_o^2) + (aP)^2 + bP]$; P = $(F_o^2 + 2F_c^2)/3$

indicated that catechol borane, THF·BH_3, Me_3N·BH_3 or Me_2S·$BHCl_2$ were inferior to Me_2S·BH_3 in terms of efficiency and enantioselectivity in the reduction reactions. For the reductions using Me_2S·BH_3 and the phosphorimidate **6**, none of the additives (molecular sieves, LiCl and BuOH) could enhance the enantioselectivity.

Although the detailed reaction mechanism[7a] awaits further investigation, one can speculate that the phos-

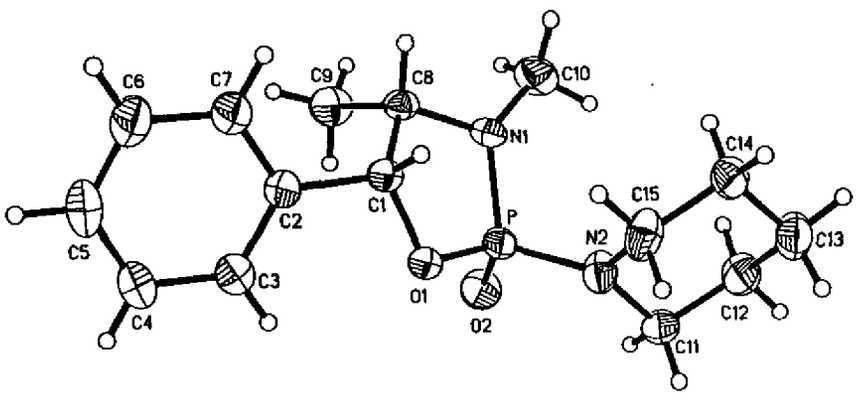


Fig. 3. ORTEP drawing of compound **8**.

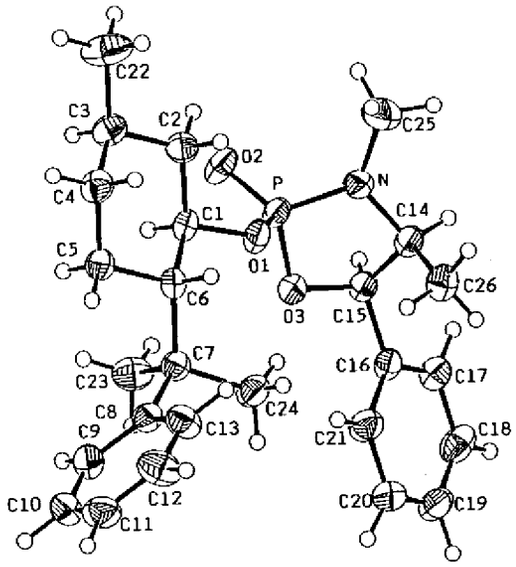


Fig. 4. ORTEP drawing of compound **11**.

phoramidate initially combined with borane to form a chiral zwitterionic reagent **A** (Scheme I). Acetophenone would approach the axial position of the phosphorus center from the less hindered face (top face) and the P-O-C5 side of **A**. The chair-like transition state **B** with the larger phenyl group (compared with the methyl group) on the equatorial position could account for the hydride transfer to the *si*-face of acetophenone. The alternative transition state with a disposition of the larger phenyl group on the axial direction is energetically disfavored because it would exert a steric effect against the C-5 proton. After ligand exchange from **C** to **D**, the phosphoramidate **6** could be released and subjected to initiate the next cycle of the reaction. The product (*R*)-1-phenylethanol was then obtained by hydrolysis of the borate intermediate **D** with MeOH or aqueous $NaHCO_3$ solution.

The effect of other phosphorus(V) modifiers in the asymmetric reduction of acetophenone with $Me_2S{\cdot}BH_3$ was examined (Table 5). The asymmetric reactions consistently

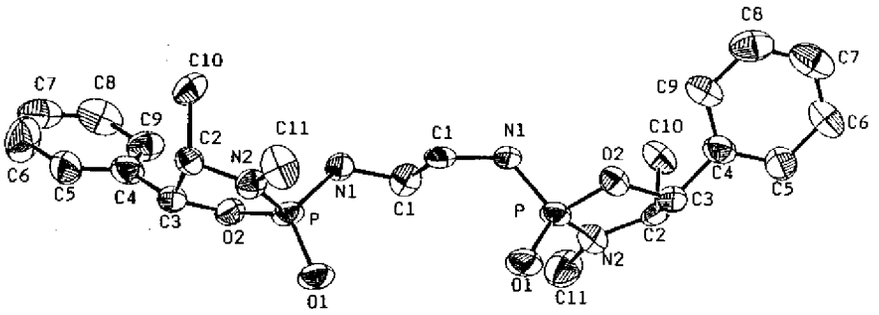


Fig. 5. ORTEP drawing of compound **12**.

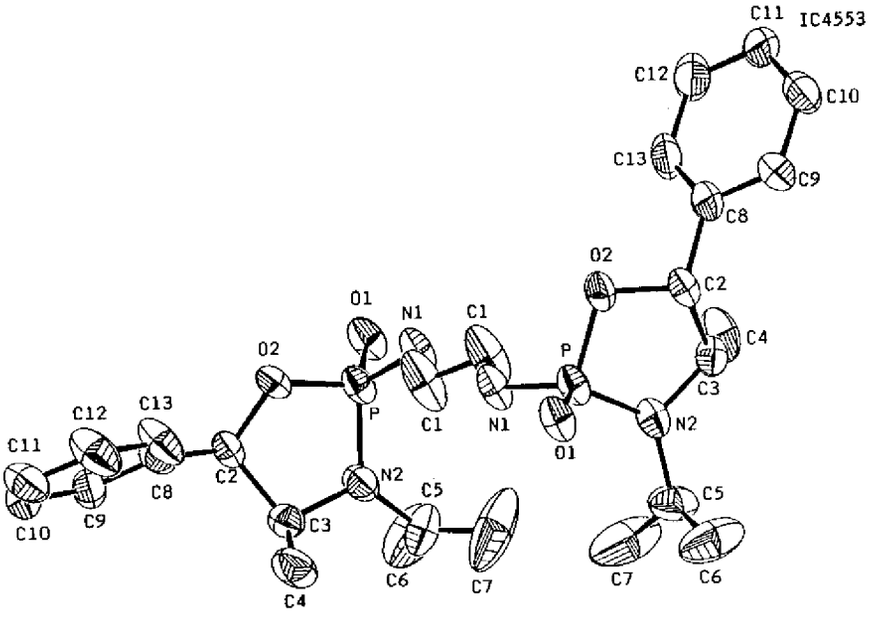
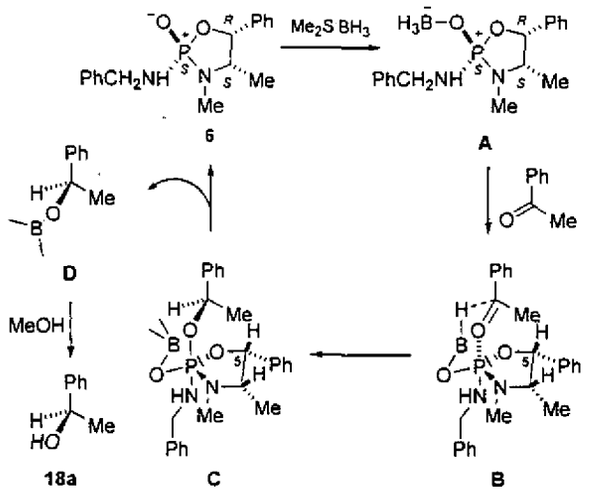


Fig. 6. ORTEP drawing of compound **14**.

Scheme I



gave the product **18a** with predominance of the *R*-enantiomer, except for the one using the *bis*-phosphoramidate **12** as the modifier (entry 8). The reason for this stereochemical discrepancy was unclear. The reduction of acetophenone in the presence of a C_2-symmetric modifier **16** appeared to afford the highest ee value (64%) of the product **18a** at room temperature (entry 12). The reactions using phosphorus(V) reagents **5**, **9** and **13**, possessing the substituents of phenyl, piperidyl and *N,N'-dimethyl-1,2-ethylenediamino groups*, also showed a slightly higher enantiomeric excesses than that using the modifier **6**.

The asymmetric reduction of other representative ketones were also carried out by using $Me_2S{\cdot}BH_3$ and phosphoramidate modifiers (Table 6). The ee values of the alcohol products were determined by HPLC analyses on a chiral column. The configuration of the major enantiomer was deduced by comparison of the optical rotation of the product with the reported value. The *ortho*- or *para*-substituted acetophenones (with methyl, methoxy, chloro or bromo substituents) were reduced to give **18b-h** with ee values close to that obtained from the reduction of acetophenone (entries 1-8). The reductions of 1'-acetonaphthone and α-tetralone also resulted in modest enantioselectivities. The reduction of α-chloroacetophenone, by using modifiers **5**, **6** or **11**, followed a similar stereochemical process to give the alcohol **21** in favor of the *S*-enantiomer (the notation is changed to *S* according to the priority of the chlorine atom in the sequence rule of nomenclature). However, the enantioselectivity (36-53%) was not as high as those values reported in related studies.[4e] The borane reductions of 2-acetothiophene, cyclopropyl phenyl ketone, cyclohexyl methyl ketone and 2-heptanone were also promoted by the modifier **6** to give the corresponding alcohols **22-25** with 16-44% ee.

In summary, we have prepared a variety of chiral pentavalent phosphorus reagents **5-17** and utilized them to complex with borane for the asymmetric reduction of representative methyl ketones. The P(V) modifiers **5-17** could be recovered from the reaction mixture and reused. High enantioselectivity of such reductions by catalysis of **5-17** is not yet realized. It will be worthwhile to investigate whether the enantioselectivity can be upgraded by using the P(V) re-

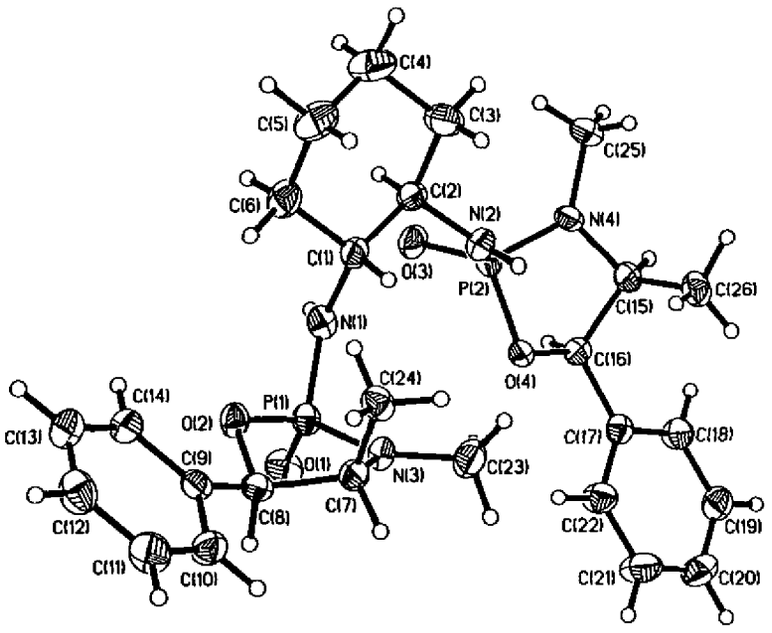


Fig. 7. ORTEP drawing of compound **15**.

agents with more rigid skeletons.

EXPERIMENTAL SECTION

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an atmosphere of nitrogen. Syringes and needles for the transfer of reagents were dried at 120 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; (chlorinated) hydrocarbons, and amines from CaH_2. Reactions were monitored by TLC using precoated with a 0.25 mm layer of silica gel containing a fluorescent indicator (Merck Art. 5544). Column chromatography was carried out on Kieselgel 60 (40-63 μm). Optical rotations were measured on a digital polarimeter with a cuvette of 1 cm length. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker AC-200 and AM-300 WB spectrometers. Chemical shifts are reported relative to $CHCl_3$ (δ_H 7.26), $CDCl_3$ [δ_C (central line of t) 77.0] or phosphoric acid (δ_P 0). Coupling constants (J) are given in Hz. Enantiomeric excess was determined by HPLC using a Chiralcel OB or Chiralcel OD column (0.46 cm ID × 25 cm).

(1*R*,2*S*)-2-Isopropylamino-1-phenyl-1-propanol (2)

The title compound was prepared by using a modified procedure of the known method.[9] A mixture of (1*R*,2*S*)-L-norephedrine (3.0 g, 20 mmol), 2,2-dimethoxypropane (3.9 mL, 30 mmol) and *p*-TsOH (20 mg) in acetone (30 mL) was heated under reflux for 12 h. The mixture was cooled, and filtered through a pad of Celite. The filtrate was concentrated, dissolved in anhydrous THF (5 mL), and added dropwise to a refluxing suspension of $LiAlH_4$ (1.0 g, 26.3 mmol) in THF (40 mL). The mixture was heated under reflux for 2 h, cooled, and to which was added successively water (1 mL), NaOH (10%, 2 mL) and water (1 mL). The mixture was heated under reflux for 1 h, cooled, and filtered through

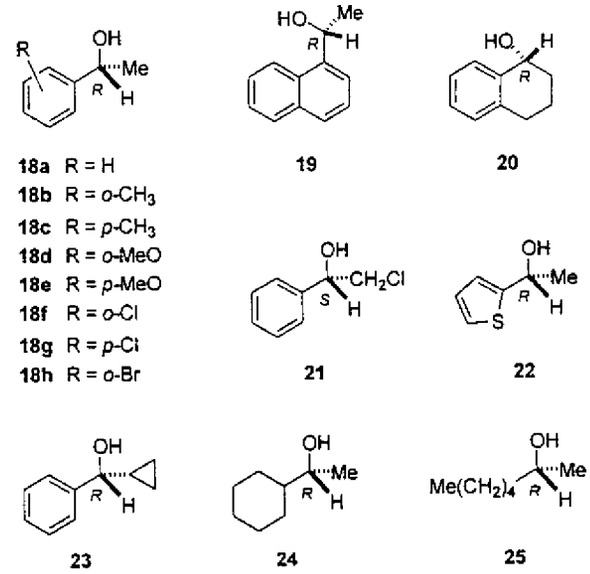


Fig. 9. The major enantiomers obtained by the asymmetric reductions in this study.

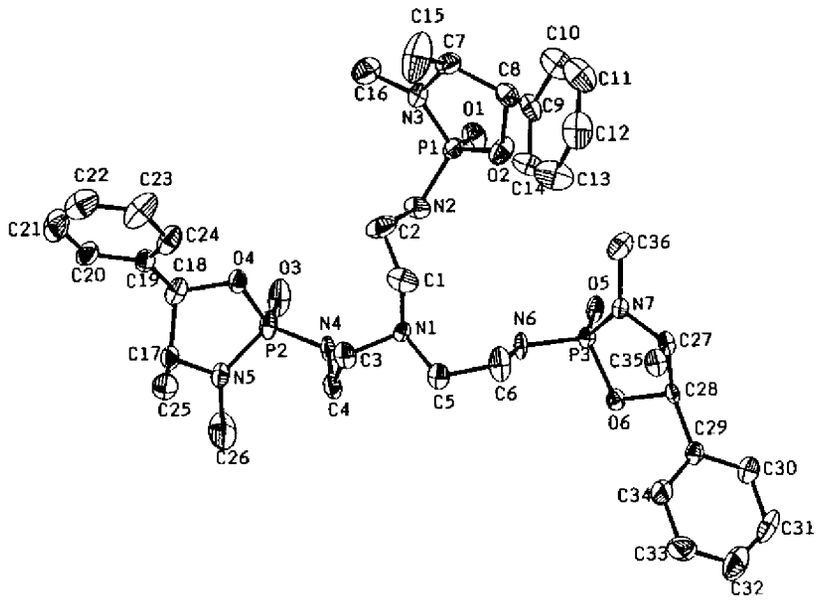


Fig. 8. ORTEP drawing of compound **17**.

Table 3. The Effects of Solvents, Reaction Temperature and the Ratio of Substrates in the Reduction of Acetophenone with Borane ($Me_2S{\cdot}BH_3$) and a Phosphoramidate Modifier **6**, Giving Alcohol **18a** with Predominance of the *R*-Enantiomer[a]

Entry	PhCOMe/Borane/**6**	Solvent	Reaction Temp./°C	Product **18a** Yield/%	Ee/%[b]
1	1/1/0.2	THF	0	>95	63
2	1/1/0.2	THF	−20	91	61
3	1/1/0.2	THF	27	79	51
4	1/1/0.2	THF	68	>95	52
5	1/1/0.1	THF	0	95	53
6	1/1/0.3	THF	27	93	51
7[c]	1/1/0.1	THF	0	>95	0
8	1/2/0.2	THF	27	>95	49
9	1/0.6/0.1	THF	0	80	28
10	1/0.6/1	THF	0	78	46
11	1/1/0.2	THF/Et_2O (1:1)	0	>95	47
12	1/1/0.2	$PhCH_3$	0	83	41
13	1/1/0.2	CH_2Cl_2	0	69	7

[a] The reaction was conducted by addition of acetophenone to a premixed solution of **6**/$Me_2S{\cdot}BH_3$. [b] The ee value was determined by comparison of optical rotation with the reported value, and/or by HPLC analysis on a chiral column. [c] The reaction was conducted by addition of $Me_2S{\cdot}BH_3$ to a premixed solution of **6**/PhCOMe.

Table 4. The Effects of Different Boranes and Additives in the Reduction of Acetophenone Promoted by the Phosphoramidate Modifier **6**, Giving Alcohol **18a** with Predominance of the *R*-Enantiomer[a]

Entry	Borane	PhCOMe/ Borane/**6**	Additive	Reaction Temp./°C	Product **18a** Yield/%	Ee/%
1	$Me_2S{\cdot}BH_3$	1/1/0.2	sieves (1 g)	27	45	3
2	$Me_2S{\cdot}BH_3$	1/1/0.2	LiCl (0.25 equiv)	27	80	39
3	$Me_2S{\cdot}BH_3$	1/1/0.2	BuOH (2 equiv)	27	>95	43
4	$THF{\cdot}BH_3$	1/1/0.2		0	>95	36
5	$Me_3N{\cdot}BH_3$	1/1/0.2		0	0	
6	$Me_2S{\cdot}BHCl_2$	1/1/0.2		0	90	3
7	catechol borane	1/1/0.2		0	4	2

[a] The reaction was conducted by addition of acetophenone to a premixed THF solution of **6**/borane.

Table 5. Asymmetric Reduction of Acetophenone by Using $Me_2S{\cdot}BH_3$ and Various Pentavalent Phosphorus Modifiers[a]

Entry	Modifier	PhCOMe /Borane/Modifier	Products Yield/%	Ee/%	Config.[b]
1	**5**	1/1/0.2	>95	58	*R*
2	**6**	1/1/0.2	>95	49	*R*
3[c]	**7**	1/1/0.2	>95	31	*R*
4[c]	**8**	1/1/0.2	>95	53	*R*
5[c]	**9**	1/1/0.2	>95	8	*R*
6	**10**	1/0.6/0.1	80	38	*R*
7	**11**	1/1/0.2	87	37	*R*
8[d]	**12**	1/1/0.2	66	23	*S*
9	**13**	1/1/0.2	>95	58	*R*
10	**15**	1/1/0.2	>95	43	*R*
11[d]	**16**	1/0.6/0.1	83	42	*R*
12[e]	**16**	1/1/0.2	>95	64	*R*

[a] *The reaction was generally conducted by addition of acetophenone (1 mmol, 0.1 M) to a premixed THF solution of* borane/P(V)-modifier at room temperature, except for those noted in *c–e*. [b] The configuration of major enantiomer. [c] The reaction was conducted in 0.2 M THF solution. [d] The reaction was conducted at 0 °C. [e] The reaction was conducted in CH_2Cl_2 solution.

Table 6. The Asymmetric Reduction of Various Ketones with $Me_2S{\cdot}BH_3$ and Phosphoramidate Modifiers[a]

Entry	Substrate	Modifier	Products (Yield/%)	Ee/%[b]	Config.[c]
1	Acetophenone	**6**	**16a** (>95)	63	*R*
2	2'-methylacetophenone	**6**	**16b** (>95)	51	*R*
3	4'-methylacetophenone	**6**	**16c** (>95)	67	*R*
4	2'-methoxyacetophenone	**6**	**16d** (87)	57	*R*
5	4'-methoxyacetophenone	**6**	**16e** (82)	65	*R*
6	2'-chloroacetophenone	**6**	**16f** (95)	45	*R*
7	4'-chloroacetophenone	**6**	**16g** (79)	55	*R*
8	2'-bromoacetophenone	**6**	**16h** (>95)	37	*R*
9	1'-acetonaphthone	**6**	**17** (79)	54	*R*
10[d]	α-tetralone	**6**	**18** (>95)	54	*R*
11[d]	α-tetralone	**16**	**18** (>95)	47	*R*
12[d]	α-chloroacetophenone	**5**	**19** (>95)	53	*S*
13[d]	α-chloroacetophenone	**6**	**19** (>95)	46	*S*
14[d]	α-chloroacetophenone	**11**	**19** (>95)	36	*S*
15	2-acetylthiophene	**6**	**20** (82)	44	*R*
16	cyclopropyl phenyl ketone	**6**	**21** (94)	29	*R*
17	cyclohexyl methyl ketone	**6**	**22** (>95)	16	*R*
18[c]	2-heptanone	**6**	**23** (69)	24	*R*

[a] The reaction was generally conducted by addition of ketone (1 mmol, 0.1 M) to a premixed THF solution of $Me_2S{\cdot}BH_3$ (1 mmol)/P(V)-modifier (0.2 mmol) at 0 °C, except for those noted. [b] The ee value was determined by comparison of optical rotation with the reported value, and/or by HPLC analysis on a chiral column. [c] The configuration of major enantiomer. [d] The reaction was conducted in 0.2 M THF solution at room temperature.

a pad of Celite. The filtrate was concentrated and chromatographed on a silica gel column by elution with $MeOH/CH_2Cl_2$ (2:98) to give compound **2** (3.3 g, 86%) as solids, mp 97-98 °C (lit.[9e] 102-103 °C), $[\alpha]_D^{19}$ -7.8 (c = 1.5, $CHCl_3$) (lit.[9e] $[\alpha]_D^{20}$ -2.64 (c = 1.48, EtOH).

(2*R*,4*S*,5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (3) and the (2*S*,4*S*,5*R*)-Isomer

Compounds **3** and the (2*S*,4*S*,5*R*)-isomer were prepared in 85% and 8% yields from (1*R*,2*S*)-(-)-ephedrine hydrochloric salt and $POCl_3$ according to the reported procedure.[8a]

(2*R*,4*S*,5*R*)-2-Chloro-3-isopropyl-4-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (4) and the (2*S*,4*S*,5*R*)-Isomer

A benzene solution (100 mL) of **2** (1.96 g, 10 mmol) and Et_3N (5.0 mL, 36 mmol) was cooled in an ice bath. $POCl_3$ (1.0 mL, 10 mmol) was added dropwise, and the mixture was stirred for 4 h. The resulting precipitates were filtered, and the filtrate was concentrated and subjected to chromatography (silica gel, EtOAc/hexane (1:1)) to give **4** (2.34 g, 86%) and the (2*S*,4*S*,5*R*)-isomer (0.12 g, 4%).

4: Solid; mp 87-88 °C; $[\alpha]_D^{29}$ -67.9 (c = 2.45, $CHCl_3$); R_f = 0.42 (EtOAc/hexane (1:1)); δ_H (300 MHz, $CDCl_3$) 0.84 (3H, d, J = 6.7 Hz), 1.31 (3H, d, J = 6.5 Hz), 1.47 (3H, d, J = 6.7 Hz), 3.60 (1H, septet, J = 6.6 Hz), 3.92 (1H, doublet of quintets, J = 25.6 Hz, 6.6 Hz, H-4), 5.71 (1H, d, J = 6.0 Hz, H-5), 7.23-7.40 (5H, m); δ_P (121 MHz, $CDCl_3$) 20.2; δ_C NMR (75 MHz, $CDCl_3$) 13.7, 21.6 ($J_{P\text{-}C}$ = 3.0 Hz), 22.7 ($J_{P\text{-}C}$ = 4.1 Hz), 46.6 ($J_{P\text{-}C}$ = 5.2 Hz), 56.9 ($J_{P\text{-}C}$ = 14.5 Hz), 82.7, 125.4, 128.5, 128.6, 134.8 ($J_{P\text{-}C}$ = 9.8 Hz). FAB *m/z* 274.0 (M^+ + 1) (Found: M^+, 273.0686. $C_{12}H_{17}PO_2NCl$ requires *M*, 273.0685).

(2*S*,4*S*,5*R*)-Isomer **4'**: R_f = 0.57 (EtOAc/hexane (1:1)); δ_H (200 MHz, $CDCl_3$) 0.84 (3H, d, J = 6.5 Hz), 1.33 (3H, d, J = 6.6 Hz), 1.46 (3H, d, J = 6.7 Hz), 3.55 (1H, doublet of quintets, J = 18.0 Hz, 6.6 Hz), 3.84 (1H, septet, J = 6.3 Hz), 5.57 (1H, dd, J = 2.8 Hz, 8.9 Hz), 7.28-7.41 (5H, m); δ_P (121 MHz, $CDCl_3$) 20.9; δ_C NMR (50 MHz, $CDCl_3$) 16.5 ($J_{P\text{-}C}$ = 3.2 Hz), 21.3, 21.8, 46.3 ($J_{P\text{-}C}$ = 5.2 Hz), 56.0 ($J_{P\text{-}C}$ = 13.0 Hz), 80.8, 125.8, 128.6, 128.7, 134.5 ($J_{P\text{-}C}$ = 10.0 Hz).

(2*S*,4*S*,5*R*)-3,4-Dimethyl-2,5-diphenyl-1,3,2-oxazaphospholidin-2-one (5)

Under an atmosphere of argon, a THF solution (10 mL) of phenylmagesium bromide (20 mmol) was prepared from bromobenzene (2.3 mL, 22 mmol) and magnesium (0.48 g, 20 mmol). The freshly prepared Grignard reagent was added dropwise via syringe to an ice-cooled THF solution (20 mL) of **3** (5.0 g, 20 mmol). The mixture was stirred at room temperature (27 °C) for 2 h, and quenched by addition of saturated NH_4Cl solution. The mixture was concentrated, and partitioned between brine (10 mL) and EtOAc

(10 mL). The aqueous layer was separated, and extracted with EtOAc (10 mL). The organic phase was combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated, and the residue was chromatographed on a silica gel column by elution with EtOAc/hexane (4:1) to give compound **5** (4.0 g, 70%) as a single isomer.

5: Solid; mp 140-141 °C; $[\alpha]_D^{26}$ -31.6 (c = 2.1, CH_2Cl_2); R_f = 0.30 (EtOAc/hexane (80:20)); δ_H (200 MHz, $CDCl_3$) 0.80 (3H, d, J = 6.6 Hz), 2.74 (3H, d, J = 9.4 Hz), 3.77-3.89 (1H, m), 5.94 (1H, d, J = 6.2 Hz), 7.26-7.38 (5H, m), 7.46-7.53 (3H, m), 7.83-7.92 (2H, m); δ_P (121 MHz, $CDCl_3$) 32.2; δ_C NMR (50 MHz, $CDCl_3$) 14.4, 29.4 (J = 6.8 Hz), 60.8 (J = 8.8 Hz), 80.3, 125.7, 128.1, 128.4, 128.7, 132.2 (J = 3.0 Hz), 132.4, 132.6, 136.1 (J = 10.0 Hz); m/z 287 (M^+) (Found: M^+, 287.1086. $C_{16}H_{18}NO_2P$ requires M, 287.1076).

(2*S*,4*S*,5*R*)-(2-Benzylamino-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (6)

Under an atmosphere of argon, a solution of chlorophosphoramidate **3** (2.45 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of benzylamine (1.10 g, 10 mmol) and Et_3N (2 mL) in CH_2Cl_2 (20 mL). The mixture was stirred for 24 h, washed with brine (10 mL × 2), dried (Na_2SO_4), concentrated and chromatographed on a silica gel column by elution with MeOH/CH_2Cl_2 (1:49) to give **6** (3.29 g, 95%) as a single isomer.

6: Solid; mp 143-144 °C; $[\alpha]_D^{26}$ -85.4 (c = 2, CH_2Cl_2); R_f = 0.12 (MeOH/CH_2Cl_2 (1:49)); δ_H (200 MHz, $CDCl_3$) 0.67 (3H, d, J = 6.4 Hz), 2.65 (3H, d, J = 9.4 Hz), 3.50-3.64 (1H, m), 3.64-3.78 (1H, m), 4.13 (2H, dd, J = 11.7, 7.0 Hz), 5.64 (1H, d, J = 6.5 Hz), 7.03-7.37 (10H, m); δ_P (121 MHz, $CDCl_3$) 24.8; δ_C (50 MHz, $CDCl_3$) 14.8, 28.9 (J = 6.6 Hz), 45.0, 59.1 (J = 12.3 Hz), 78.0, 125.4, 126.9, 127.0, 127.7, 128.1, 128.4, 136.2 (J = 10.5 Hz), 139.8 (J = 5 Hz); m/z 316 (M^+); (Found: M^+, 316.1347. $C_{17}H_{21}O_2N_2P$ requires M, 316.1340) (Found: C, 64.67; H, 6.66; N, 8.94%. $C_{17}H_{21}O_2N_2P$ requires C, 64.55; H, 6.69; N, 8.86).

(2*R*,4*S*,5*R*)-(3,4-Dimethyl-2-hydrazino-5-phenyl-1,3,2-oxazaphospholidin-2-one (7)

The title compound was prepared in 90% yield from a CH_2Cl_2 solution of chlorophosphoramidate **3** (2.45 g, 10 mmol) and hydrazine hydrochloric salt (1.05 g, 10 mmol) in the presence of Et_3N (2 mL) by a procedure similar to that for compound **6**.

7: Solid; mp 166-167 °C; $[\alpha]_D^{26}$ -88.0 (c = 2.3, CH_2Cl_2); R_f = 0.25 (CH_2Cl_2/MeOH (19:1)); δ_H (200 MHz, $CDCl_3$) 0.80 (3H, d, J = 6.6 Hz), 2.70 (3H, d, J = 9.4 Hz), 2.95-3.40 (1H, br s), 3.59-3.72 (1H, m), 4.75 (1H, d, J = 32 Hz), 5.67 (1H, d, J = 4.5 Hz), 7.26-7.34 (5H, m); δ_P (121 MHz, $CDCl_3$) 26.1; δ_C (75 MHz, $CDCl_3$) 14.4, 28.8 (J = 6.0 Hz), 59.5 (J = 11.6 Hz), 78.8, 125.7, 128.0, 128.3, 136.4 (J = 10.1 Hz); m/z 241 (M^+); (Found: M^+, 241.0982. $C_{10}H_{16}O_2N_3P$ requires M, 241.0980).

(2*S*,4*S*,5*R*)-(3,4-Dimethyl-5-phenyl-2-piperidyl-1,3,2-oxazaphospholidin-2-one (8)

The title compound was prepared in 90% yield from a CH_2Cl_2 solution of chlorophosphoramidate **3** (2.45 g, 10 mmol) and piperidine hydrochloric salt (1.21 g, 10 mmol) in the presence of Et_3N (2 mL) by a procedure similar to that for compound **6**.

8: Solid; mp 129-130 °C; $[\alpha]_D^{26}$ -88.4 (c = 2.1, CH_2Cl_2); R_f = 0.27 (EtOAc); δ_H (300 MHz, $CDCl_3$) 0.65 (3H, d, J = 6.6 Hz), 1.50-1.62 (6H, m), 2.62 (3H, d, J = 9.4 Hz), 3.17-3.22 (4H, m), 3.56-3.63 (1H, m), 5.66 (1H, d, J = 6.9 Hz), 7.20-7.34 (5H, m); δ_P (121 MHz, $CDCl_3$) 24.7; δ_C (75 MHz, $CDCl_3$) 14.6, 24.6, 26.5 (J = 3.9 Hz), 29.0 (J = 6.7 Hz), 45.5 (J = 2.9 Hz), 58.7 (J = 11.6 Hz), 77.3, 125.5, 127.8, 128.2, 136.6 (J = 10.1 Hz); FAB m/z 294 (M^+) (Found: M^+, 294.1496. $C_{15}H_{23}O_2N_2P$ requires M, 294.1497).

(2*S*,4*S*,5*R*)-(2-Benzylamino-3-isopropyl-4-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (9)

The title compound was prepared in 92% yield from a CH_2Cl_2 solution of chlorophosphoramidate **4** (0.7 g, 2.5 mmol) and benzylamine (0.3 g, 2.5 mmol) in the presence of Et_3N (0.5 mL) by a procedure similar to that for compound **6**.

9: Solid; mp 118-119 °C; $[\alpha]_D^{26}$ -98.1 (c = 2.0, CH_2Cl_2); R_f = 0.23 (EtOAc/hexane (4:1)); δ_H (300 MHz, $CDCl_3$) 0.68 (3H, d, J = 6.4 Hz), 1.24 (3H, d, J = 6.6 Hz), 1.39 (3H, d, J = 6.7 Hz), 3.44-3.53 (1H, m), 3.69-3.77 (1H, m), 4.16 (2H, dd, J = 12.0, 7.0 Hz), 5.57 (1H, d, J = 6.1 Hz), 7.04-7.40 (10H, m); δ_P (121 MHz, $CDCl_3$) 23.7; δ_C (75 MHz, $CDCl_3$) 17.3, 21.5, 22.8 (J = 3.8 Hz), 45.1, 45.8, 54.9 (J = 11.5 Hz), 78.5 (J = 4.4 Hz), 125.3, 126.9, 127.6, 128.1, 128.4, 136.3 (J = 4.1 Hz), 139.8 (J = 5.6 Hz); m/z 316 (M^+) (Found: M^+, 344.1656. $C_{19}H_{25}O_2N_2P$ requires M, 344.1653).

(2*R*,4*S*,5*R*)-2-*tert*-Butoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (10)

The title compound was prepared in 90% yield from a THF solution (50 mL) of chlorophosphoramidate **3** (2.45 g, 10 mmol) and *t*-BuOK (1.12 g, 10 mmol) by a procedure similar to that for compound **6**.

10: Oil; R_f = 0.23 (EtOAc/hexane (1:1)); $[\alpha]_D^{25}$ -104 (c = 1, $CHCl_3$); ν_{max} neat/cm^{-1} 3059, 2973, 2930, 1636, 1602, 1493, 1367, 1263 (P=O); δ_H (200 MHz, $CDCl_3$) 0.73 (3H, d, J = 6.6 Hz), 1.57 (9H, s), 2.67 (3H, d, J = 10.3 Hz), 3.63 (1H,

ddq, J = 18.5, 6.6, 6.4 Hz), 5.59 (1H, dd, J = 6.4, 2.7 Hz), 7.27-7.38 (5H, m); δ_C (75 MHz, $CDCl_3$) 12.7, 29.0 (J = 4.2 Hz), 30.0 (J = 4.7 Hz), 59.3 (J = 12.5 Hz), 80.5, 81.7 (J = 7.9 Hz), 125.8, 127.9, 128.2, 136.6 (J = 7.0 Hz); δ_P (121 MHz, $CDCl_3$) 16.8; *m/z* 283 (M^+, 5%), 227 (100) (Found: M^+, 283.1346. $C_{14}H_{22}NO_3P$ requires M, 283.1337).

(2*S*,4*S*,5*R*)-2-[(1*R*,2*S*,5*R*)-8-Phenylmenthoxy]-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (11)

Under an atmosphere of argon, a THF solution (15 mL) of (1*R*,2*S*,5*R*)-8-phenylmenthol (0.70 g, 3 mmol) was treated with methylmagesium chloride (3 mmol, 1 mL of 3 M THF solution), and then added dropwise to a THF solution (15 mL) of chlorophosphoramidate **3** (0.75 g, 3 mmol) at 0 °C. The mixture was stirred at 0 °C for 12 h, and worked up as usual to give **11** (1.03 g, 78%).

11: Solid; mp 158-160 °C; $[\alpha]_D^{25}$ -66.4 (c = 2.1, CH_2Cl_2); R_f = 0.44 (EtOAc); δ_H (300 MHz, $CDCl_3$) 0.76 (3H, d, J = 6.6 Hz), 0.86 (3H, d, J = 6.6 Hz), 0.70-0.87 (4H, m), 1.10-1.25 (2H, m), 1.44 (3H, s), 1.60 (3H, s), 1.78-1.86 (1H, m), 2.21-2.24 (1H, m), 2.71 (3H, d, J = 10.3 Hz), 3.56-3.66 (1H, m), 4.43-4.47 (1H, m), 5.67 (1H, d, J = 5.7 Hz), 7.11-7.35 (5H, m); δ_C (75 MHz, $CDCl_3$) 12.9, 21.7, 22.2, 27.4, 29.1, 29.2, 31.5 (J = 5.0 Hz), 34.3, 40.6, 44.9, 52.1 (J = 7.6 Hz), 60.2 (J = 12.2 Hz), 80.0 (J = 7.3 Hz), 80.5 (J = 2.3 Hz), 125.2, 125.5, 125.7, 127.9, 127.95, 128.3, 136.0 (J = 9.2 Hz), 150.8; δ_P (121 MHz, $CDCl_3$) 18.7; *m/z* 441 (M^+, 4%), 119 (100) (Found: M^+, 441.2434. $C_{26}H_{36}NO_3P$ requires M, 441.2433).

(2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Bis(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl)ethane-1,2-diamine (12)

The title compound[5a] was prepared in 85% yield from a THF solution of chlorophosphoramidate **3** (5.0 g, 20 mmol) and ethane-1,2-diamine (0.63 g, 10 mmol) in the presence of Et_3N according to reported procedures. **12**: Solid, mp 199-201 °C; $[\alpha]_D^{19}$ -115.9 (c = 4, $CHCl_3$).

(2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Bis(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl)ethane-1,2-dimethyl-1,2-diamine (13)

The title compound was prepared in 91% yield from a CH_2Cl_2 solution of chlorophosphoramidate **3** (2.45 g, 10 mmol) and *N*,*N*′-dimethylethane-1,2-diamine (0.44 g, 5 mmol) in the presence of Et_3N by a procedure similar to that for **6**.

13: Oil; R_f = 0.44 (MeOH/CH_2Cl_2 (1:9)); $[\alpha]_D^{19}$ -114.2 (c = 4.0, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.55 (6H, d, J = 6.5 Hz), 2.51 (6H, dd, J = 9.5, 1.9 Hz), 2.67 (6H, dd, J = 10.3, 1.8 Hz), 3.15-3.29 (4H, m), 3.44-3.54 (2H, m), 5.54 (2H, d, J = 6.7 Hz), 7.07-7.17 (10H, m); δ_P (121 MHz, $CDCl_3$) 26.3; δ_C (75 MHz, $CDCl_3$) 14.5, 28.9 (J = 6.2 Hz), 34.0 (J = 4.4 Hz), 48.0, 59.0 (J = 11.8 Hz), 77.4, 125.3, 127.7, 128.1, 136.2 (J = 10.9 Hz); FAB *m/z* 506 (M^+) (Found: M^+, 506.2216. $C_{24}H_{36}O_4N_4P_2$ requires M, 506.2211).

(2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Bis(3-isopropyl-4-methyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl)ethane-1,2-diamine (14)

Solid; mp 247-249 °C; $[\alpha]_D^{17}$ -122.5 (c = 1, $CHCl_3$); R_f = 0.63 (MeOH/CH_2Cl_2 = 1:5); δ_H (300 MHz, $CDCl_3$) 0.71 (6H, d, J = 6.5 Hz), 1.26 (6H, t, J = 6.5 Hz), 3.17 (4H, br s), 3.46 (2H, sept, J = 6.6 Hz), 3.68-3.72 (2H, m, H-4), 5.55 (2H, d, J = 5.9 Hz, H-5), 7.19-7.29 (10H, m); δ_P (121 MHz, $CDCl_3$) 23.9; δ_C (75 MHz, $CDCl_3$) 17.2, 21.7 ($J_{p\text{-}c}$ = 1.9 Hz), 23.0 ($J_{p\text{-}c}$ = 3.5 Hz), 43.2 ($J_{p\text{-}c}$ = 6.6 Hz), 45.9 ($J_{p\text{-}c}$ = 5.5 Hz), 55.4 ($J_{p\text{-}c}$ = 11.3 Hz), 78.7 ($J_{p\text{-}c}$ = 4.4 Hz), 125.5, 127.8, 128.0, 136.5 ($J_{p\text{-}c}$ = 12.1 Hz); *m/z* 534 (M^+, 7%), 460 (100); (Found: M^+, 534.2544. $C_{25}H_{40}N_4O_4P_2$ requires M, 534.2525).

(2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Bis(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl) (1*R*,2*R*)-cyclohexane-1,2-diamine (15)

The title compound was prepared in a quantitative yield from a CH_2Cl_2 solution of chlorophosphoramidate **3** (2.45 g, 10 mmol) and (1*R*,2*R*)-cyclohexane-1,2-diamine (0.6 g, 5 mmol) in the presence of Et_3N by a procedure similar to that for **6**.

15: Solid; mp 260-261 °C; R_f = 0.25 (MeOH/CH_2Cl_2 (5:95)); $[\alpha]_D^{19}$ -102.4 (c = 0.53, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.68 (6H, d, J = 6.5 Hz), 1.29-1.33 (4H, m), 1.72 (2H, m), 2.18-2.21 (2H, m), 2.69 (6H, d, J = 9.8 Hz), 2.92 (2H, m), 3.56-3.64 (2H, m), 5.63 (2H, d, J = 6.2 Hz), 7.15-7.21 (10H, m); δ_P NMR (121 MHz, $CDCl_3$) 24.7; δ_C (75 MHz, $CDCl_3$) 14.3, 25.0, 29.1 (J = 5.7 Hz), 36.0, 56.9 (J = 5.6 Hz), 59.5 (J = 12.0 Hz), 78.7 (J = 10.8 Hz), 125.6, 127.7, 128.2, 136.2 (J = 9.9 Hz); FAB *m/z* 532 (M^+) (Found: M^+, 532.2363. $C_{26}H_{38}O_4N_4P_2$ requires M, 532.2369).

(2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl) (1*R*,2*R*)-cyclohexane-1,2-diamine (16)

Under an atmosphere of argon, a THF solution (20 mL) of **15** (270 mg, 0.5 mmol) was treated with NaH (0.12 g, mmol) for 30 min at 0 °C. Iodomethane (1 mL, 16.0 mmol) was added, and the mixture was stirred until it became a clear solution. The reaction was quenched by addition of water (10 mL). Volatiles were removed, and the residue was extracted with EtOAc (10 mL × 2). The organic

phase was dried (Na_2SO_4), concentrated and chromatographed on a silica gel column by elution with MeOH/CH_2Cl_2 (5:95) to give **16** (0.19 g, 68%).

16: Solid; mp 228-230 °C; R_f = 0.18 (MeOH/CH_2Cl_2 (5:95)); $[\alpha]_D^{19}$ -90.2 (c = 2.1, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 0.70 (6H, d, J = 6.6 Hz), 1.33-1.37 (2H, m), 1.70-1.73 (4H, m), 1.85-1.88 (2H, m), 2.62 (3H, s), 2.65 (3H, s), 2.67 (3H, s), 2.71 (3H, s), 3.57-3.66 (2H, m), 3.82 (2H, m), 5.69 (2H, d, J = 6.8 Hz), 7.22-7.36 (10H, m); δ_P (121 MHz, $CDCl_3$) 27.5; δ_C (75 MHz, $CDCl_3$) 14.7, 25.3, 27.4, 29.4 (J = 5.7 Hz), 30.9, 55.4 (J = 4.7 Hz), 59.1 (J = 11.8 Hz), 77.4, 125.6, 127.9, 128.3, 136.5 (J = 10.4 Hz); FAB m/z 560 (M^+) (Found: M^+, 560.2686. $C_{28}H_{42}O_4N_4P_2$ requires M, 560.2681).

(2*S*,2′*S*,2″*S*,4*S*,4′*S*,4″*S*,5*R*,5′*R*,5″*R*)-*N*,*N*′,*N*″-Tris[2-(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl)aminoethyl]amine (17)

Solid; mp 127-130 °C; $[\alpha]_D^{19}$ -91.5 (c = 1, $CHCl_3$); R_f = 0.43 (MeOH/CH_2Cl_2 = 1:4); δ_H (300 MHz, $CDCl_3$) 0.66 (9H, d, J = 6.5 Hz), 2.66 (15H, d, J = 9.6 Hz), 3.03-3.09 (6H, m), 3.55-3.63 (3H, m, H-4), 5.67 (3H, d, J = 6.4 Hz, H-5), 7.20-7.32 (15H, m); δ_P (81 MHz, $CDCl_3$) 25.1; δ_C (50 MHz, $CDCl_3$) 14.7, 29.0 ($J_{p\text{-}c}$ = 6.0 Hz), 39.4, 56.0, 59.2 ($J_{p\text{-}c}$ = 12.2 Hz), 78.3, 125.5, 127.9, 128.3, 136.4 ($J_{p\text{-}c}$ = 9.9 Hz); FAB m/z 774.6 (M^+ + 1).

General Procedure for Asymmetric Reduction of Ketones

Under an atmosphere of nitrogen, $Me_2S{\cdot}BH_3$ (1 mmol, 0.5 mL of 2 *M* THF solution) was added to a THF solution (10 mL) of chiral phosphorus(V) reagent (0.2 mmol) at 0 °C. After stirring for 15 min, a THF solution (10 mL) of ketone (1 mmol) was added dropwise. The reaction was complete in 3-6 h as monitored by TLC analysis. The reaction was quenched by addition of MeOH or aqueous $NaHCO_3$. The mixture was concentrated by rotary evaporation, and extracted twice with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was purified on a silica gel column by elution with EtOAc/hexane (15:85).

1-Phenylethanol (18a)

$[\alpha]_D^{25}$ +31.6 (c = 1.0, CH_2Cl_2) (63% ee favoring the *R*-isomer), lit.[10] $[\alpha]_D$ = +51 (c = 1.35, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (1:19), 0.8 mL/min) t_R 10.0 min (*S*-isomer), 14.5 min (*R*-isomer).

1-(2-Methylphenyl)ethanol (18b)

$[\alpha]_D^{25}$ +35.2 (c = 1.2, CH_2Cl_2) (51% ee favoring the *R*-isomer), lit.[11] $[\alpha]_D^{22}$ +70 (c = 0.34, EtOH); HPLC (Chiralcel OB, 2-propanol/hexane (1:9), 1.0 mL/min) t_R 5.3 min (*S*-isomer), 7.5 min (*R*-isomer).

1-(4-Methylphenyl)ethanol (18c)

$[\alpha]_D^{25}$ +38.6 (67% ee favoring the *R*-isomer), lit.[11] $[\alpha]_D$ +57.7 (c = 0.36, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (1:9), 1.0 mL/min) t_R 6.8 min (*S*-isomer), 7.6 min (*R*-isomer).

1-(2-Methoxyphenyl)ethanol (18d)

$[\alpha]_D^{25}$ +15.2 (c = 4.5, CH_2Cl_2) (57% ee favoring the *R*-isomer), lit.[12] $[\alpha]_D$ +26.0 (c = 5, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (1:9), 1.2 mL/min) t_R 5.7 min (*S*-isomer), 9.7 min (*R*-isomer).

1-(4-Methoxyphenyl)ethanol (18e)

$[\alpha]_D$ +21.0 (c = 1.4, $CHCl_3$) (65% ee favoring the *R*-isomer), lit.[13] $[\alpha]_D$ +32.3 (c = 2.00, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (3:97), 0.6 mL/min) t_R 14.1 min (*S*-isomer), 16.7 min (*R*-isomer).

1-(2-Chlorophenyl)ethanol (18f)

$[\alpha]_D$ +29.6 (c = 2.6, $CHCl_3$) (45% ee favoring the *R*-isomer), lit.[11] $[\alpha]_D$ +65.7 (c = 0.625, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (1:9), 1.0 mL/min) t_R 4.8 min (*S*-isomer), 6.4 min (*R*-isomer).

1-(4-Chlorophenyl)ethanol (18g)

$[\alpha]_D^{25}$ +28.8 (c = 5.3, CH_2Cl_2) (55% ee favoring the *R*-isomer), lit.[11] $[\alpha]_D$ +51.3 (c = 0.595, Et_2O); HPLC (Chiralcel OB, 2-propanol/hexane (3:97), 0.6 mL/min) t_R 17.8 min (*S*-isomer), 19.4 min (*R*-isomer).

1-(2-Bromophenyl)ethanol (18h)

$[\alpha]_D$ +21.8 (c = 1.8, CH_2Cl_2) (37% ee favoring the *R*-isomer), lit.[14] $[\alpha]_D$ +58.8 (c = 0.57, CH_2Cl_2); HPLC (Chiralcel OB, 2-propanol/hexane (3:97), 1.0 mL/min) t_R 8.0 min (*S*-isomer), 11.8 min (*R*-isomer).

1-(1-Naphthyl)ethanol (19)

$[\alpha]_D^{25}$ +36.7 (c = 4.3, CH_2Cl_2) (54% ee favoring the *R*-isomer), lit.[15] $[\alpha]_D$ +67.3 (c = 0.4, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (1:9), 1.0 mL/min) t_R 8.4 min (*S*-isomer), 10.7 min (*R*-isomer).

1,2,3,4-Tetrahydro-1-naphthol (20)

$[\alpha]_D^{25}$ -17.0 (c = 3.4, CH_2Cl_2) (54% ee favoring the *R*-isomer), lit.[16] $[\alpha]_D^{25}$ -31.6 (c = 2.50, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (8:92), 0.4 mL/min) t_R 40.4 min (*S*-isomer), 40.6 min (*R*-isomer).

2-Chloro-1-phenylethanol (21)

$[\alpha]_D^{25}$ +26.7 (c = 4.3, CH_2Cl_2) (57% ee favoring the *R*-isomer), lit.[17] $[\alpha]_D^{20}$ +47 (c = 1.84, cyclohexane).

1-(2-Thienyl)ethanol (22)

$[\alpha]_D^{25}$ +10.8 (c = 2.8, CH_2Cl_2) (44% ee favoring the *R*-isomer), lit.[18] $[\alpha]_D$ +24.2 (c = 5, $CHCl_3$); HPLC (Chiralcel OB, 2-propanol/hexane (1:9), 0.8 mL/min) t_R 10.8 min (*S*-isomer), 12.7 min (*R*-isomer).

1-Cyclopropyl-1-phenylmethanol (23)

$[\alpha]_D^{25}$ +8.4 (c = 5.0, CH_2Cl_2) (29% ee favoring the *R*-isomer), lit.[19] $[\alpha]_D^{25}$ +27.99 (c = 1.072, $CHCl_3$, 92% ee favoring the *R*-isomer); HPLC (Chiralcel OD, 2-propanol/hexane (1:9), 0.8 mL/min) t_R 8.2 min (*S*-isomer), 9.1 min (*R*-isomer).

1-Cyclohexylethanol (24)

$[\alpha]_D^{25}$ -1.3 (c = 3.6, CH_2Cl_2) (16% ee favoring the *R*-isomer), lit.[11] $[\alpha]_D^{26}$ -8.1 (c = 0.48, Et_2O); HPLC (Chiralcel OB, 2-propanol/hexane (6:94), 0.4 mL/min) t_R 40.7 min (*S*-isomer), 40.9 min (*R*-isomer).

2-Heptanol (25)

$[\alpha]_D^{25}$ -2.7 (c = 2.0, CH_2Cl_2) (24% ee favoring the *R*-isomer), lit.[20] $[\alpha]_D^{30}$ -11.3 (c = 1, CH_3CN).

ACKNOWLEDGEMENT

We thank the National Science Council for financial support.

Received May 5, 1999.

Key Words

Phosphorus(V) reagents; Borane; Ketones; Ephedrine; Enantioselective; Reduction.

REFERENCES

1. (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Chang, C.-J.; Fang, J.-M.; Liao, L.-F. *J. Org. Chem.* **1993**, *58*, 1754 and the references cited therein.
2. Chiral P(V)-reagents as resolving agents: (a) Jacques, J.; Fouquey, C.; Vitero, R. *Tetrahedron Lett.* **1971**, 4617. (b) Mikes, F.; Boshart, G. *J. Chem. Soc., Chem. Commun.* **1978**, 173. (c) Arnold, W.; Daly, J. J.; Imhof, R.; Kyburz, E. *Tetrahedron Lett.* **1983**, *24*, 343. (d) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304. (e) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (f) Alexakis, A.; Mutti, S.; Normant, J. F.; Mangeney, P. *Tetrahedron Asymmetry* **1990**, *1*, 437.
3. Representative examples of chiral P(V)-auxiliaries: (a) Hua, D. H.; King, R. C.-Y.; McKie, J. A.; Myer, L. *J. Am. Chem. Soc.* **1987**, *109*, 5026. (b) Sting, M.; Steglich, W. *Synthesis* **1990**, 132. (c) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1992**, *114*, 10674. (d) Narasaka, K.; Hidai, E.; Hayashi, Y.; Gras, J.-L. *J. Chem. Soc., Chem. Commun.* **1993**, 102. (f) Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393. (g) Schrader, T. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 917.
4. For reviews: (a) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *21*, 2059. (b) Katti, K. V.; Reddy, V. S.; Singh, P. R. *Chem. Soc. Rev.* **1995**, 97. Representative examples for using chiral P(V)-reagents as ligands: (c) Soai, K.; Hirose, Y.; Ohno, Y. *Tetrahedron Asymmetry* **1993**, *4*, 1473. (d) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron Asymmetry* **1996**, *7*, 2755. Representative examples for using chiral P(V)-reagents as Lewis bases: (e) Chiodi, O.; Fotiadu, F.; Sylvestre, M.; Buono, G. *Tetrahedron Lett.* **1996**, *37*, 39. (f) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (g) Burns, B.; Gamble, M. P.; Simm, A. R. C.; Studley, J. R.; Alcock, N. W.; Wills, M. *Tetrahedron Asymmetry* **1997**, *8*, 73.
5. (a) Yang, W.-B.; Fang, J.-M. *J. Org. Chem.* **1998**. (b) For a chiral bis-azaphosphole: Brenchley, G.; Fedouloff, M.; Merifield, E.; Wills, M. *Tetrahedron Asymmetry* **1996**, *7*, 2809.
6. For reviews on asymmetric reduction of ketones: (a) Nishizawa, M.; Noyori, R. in Comprehensive Organic Synthesis, Trost, B. M.; Fleming, I. Eds.; Pergamon Press, Oxford, 1991, Vol. 8, 159-182. (b) Singh, V. K. *Synthesis* **1992**, 605. Examples of asymmetric reductions with boranes: (c) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (d) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (e) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.
7. (a) Burns, B.; King, N. P.; Studley, J. R.; Tye, H.; Wills, M. *Tetrahedron Asymmetry* **1994**, *5*, 801. (b) Gamble, M. P.; Studley, J. R.; Wills, M. *Tetrahedron Asymmetry* **1996**, *7*, 3071. (c) Gamble, M. P.; Studley, J. R.; Wills, M. *Tetrahedron Lett.* **1996**, *37*, 2853. For the use of phospholidine-borane complex: (d) Brunel, J.-M.;

Pardigon, O.; Faure, B.; Buono, G. *J. Chem. Soc., Chem. Commun.* **1992**, 287. (e) Brunel, J.-M.; Buono, G. *Synlett* **1996**, 177.

8. Examples of ephedrine-derived P(V)-reagents: (a) Cooper, D. F.; Hall, C. R.; Harrison, J. M.; Inch, T. D. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1969. (b) Welch, S. C.; Levine, J. A.; Bernal, I.; Cetrullo, J. *J. Org. Chem.* **1990**, *55*, 5991. (c) Sum, V.; Davies, A. J.; Kee, T. P. *J. Chem. Soc, Chem. Commun.* **1992**, 1771. (d) Jommi, G.; Miglierini, G.; Pagliarin, R.; Sello, G.; Sisti, M. *Tetrahedron* **1992**, *48*, 7275. (e) Neidlein, R.; Keller, H.; Boese, R. *Heterocycles* **1993**, *35*, 1185. (f) Sheehan, S. K.; Jiang, M.; McKinstry, L.; Livinghouse, T.; Garton, D. *Tetrahedron* **1994**, *50*, 6155.
9. (a) Narasaka, K.; Miwa, T.; Hayashi, H.; Ohta, M. *Chem. Lett.* **1984**, 1399. (b) Piva, O.; Mortezaei, R.; Henin, F.; Muzart, J.; Pete, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 9263. (c) Chaloner, P. A.; Langadianou, E.; Perera, S. A. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2731. (d) Cain, M. J.; Baird, C. A.; Kee, T. P. *Tetrahedron Lett.* **1994**, *35*, 8671. (e) Effenberger, F.; Gutterer, B.; Jaeger, J. *Tetrahedron Asymmetry* **1997**, *8*, 459.
10. (a) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393. (b) Takemura, T,; Saito, K.; Nakazawa, S.; Mori, N. *Tetrahedron Lett.* **1992**, *33*, 6335.
11. Nakamura, K.; Kawasaki, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1079.
12. Kaufman, T. S. *Tetrahedron Lett.* **1996**, *37*, 5329.
13. Brown, S. M.; Davis, S. G.; de Sousa, J. A. A. *Tetrahedron Asymmetry* **1993**, *4*, 813.
14. Resnick, S. M.; Torok, D. S.; Gibson, D. T. *J. Org. Chem.* **1995**, *60*, 3546.
15. Ziffer, H.; Kawai, K.; Kasai, M.; Imuta, M.; Forussios, C. *J. Org. Chem.* **1983**, *48*, 3017.
16. (a) Hashiguchi, S.; Fujii, A. *Angew. Chem.* **1997**, *109*, 300. (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D. *J. Org. Chem.* **1993**, *58*, 2880. (c) Corley, E. G.; Grabowski, E. J. J.; Kabuto, K.; Imuta, M.; Kempner, E. S.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 2357.
17. Wilken, J.; Martens, J. *Synth. Commun.* **1996**, *26*, 4477.
18. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Poli, S.; Gardini, F. *Tetrahedron Asymmetry* **1993**, *4*, 1607. (b) Bradshaw, C. W.; Hummel, W.; Wong, C.-H. *J. Org. Chem.* **1992**, *57*, 1532.
19. Bradshaw, C. W.; Fu, H.; Shen, G.-J.; Wong, C.-H. *J. Org. Chem.* **1992**, *57*, 1526.
20. Craine, L. E.; Bicknell, L. K.; Mailloux, R. C.; Mark, J. P.; Mitchell, S. A.; Vicente, S. R.; Jasinski, J. P.; Woudenberg, R. C. *J. Org. Chem.* **1993**, *58*, 1251.