# A Novel Phosphinamide Catalyst for the Asymmetric Reduction of Ketones by Borane

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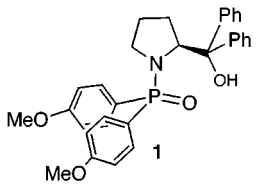
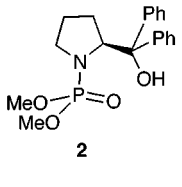
## Introduction

The reduction of ketones to enantiomerically enriched alcohols is a pivotal transformation in synthetic organic chemistry.[1] Many asymmetric catalysts have been developed for the reduction of ketones by borane, most significantly the oxazaborolidines, which have been extensively reviewed.[2] We have recently published the results of some of our ongoing studies of phosphinamide catalysts[3] that, in contrast to oxazaborolidines, exert a catalytic effect primarily through Lewis *base* interaction of the phosphinamide oxygen atom with the borane reducing agent.[4] While they are thus effective catalysts, asymmetric inductions have remained modest because there is no facility for the control of the conformation of the ketone during the reduction. In a recent paper, we reported an improvement to the reduction system through the incorporation of a proximal hydroxyl group in the catalyst.[3c] Other researchers have reported related catalysts that also give excellent results.[5] This hydroxyl group reacts with a molecule of borane to give a complex in which a boron-centered Lewis *acid* center is available to bind the ketone during the reduction process. In this paper, we describe an optimized catalyst **1** and procedure for its use in asymmetric carbonyl reductions.

The reaction of commercially available *S*-diphenylprolinol with dimethyl phosphite and triethylamine in the presence of carbon tetrachloride gave the *N*-(*O*,*O*-dimethylphosphoryl derivative **2** in 76% yield.[5,6] Treatment of **2** with an excess of *p*-anisylmagnesium bromide at 70 °C (oil bath temperature) for 2−3 h resulted in clean conversion to the target phosphinamide **1** in 70% yield. The application of **1** as a catalyst for the reduction of ketones was first tested using α-chloroacetophenone as substrate, since this has been demonstrated by ourselves[3c] and others[7e,8] to be a particularly good substrate in preliminary work (Scheme 1, Table 1).[3c] As has been demonstrated in previous studies, the best results were obtained at elevated temperature in toluene solution. Using 10 mol % of **1** at ca. 110 °C enantiomeric excesses of up to 94.4% were recorded, and yields were generally excellent.



**1**



**2**

Our optimized procedure for the reaction is summarized as follows: the catalyst and the borane were combined in toluene and heated to the required temperature, and then a solution of the ketone in toluene was added dropwise over 10−15 min. Analysis by TLC showed that the reaction was complete some 10−20 min after the addition of the ketone had been completed, at which point the reaction was cooled and worked up. The asymmetric induction remained high even at temperatures as low as 70 °C but dropped sharply thereafter. The catalyst did not appear to decompose under the reaction conditions and could be recovered and reused after the reaction without any apparant decrease in reactivity. Although routine precautions were taken to ensure dryness (i.e., azeotroping catalyst with toluene, the use of freshly distilled dry toluene, flame-dried glassware), the reaction could be performed without any of the above precautions with only a small drop in selectivity (90% ee for the chloroacetophenone reduction) and no change in the reaction time. This underlines the robustness and practicality that characterize phosphinamide reagents.

To confirm that the catalyst was not decomposing under the reaction conditions, to give, for example, an oxazaborolidine, we conducted a number of enlightening experiments. In the first, a solution of catalyst **1** and borane (10 equiv relative to **1**) were heated together for 20 min and then allowed to cool to room temperature. Dropwise addition of chloroacetophenone (10 equiv relative to **1**) resulted in reduction to give a product of 11.5% ee (21% yield). In contrast, the same reaction using an oxazaborolidine gave a product of 97% ee under these conditions.[7c]

We also carried out a number of NMR experiments. The in situ $^{11}B$ NMR spectra of a solution of **1** before and after treatment with a 10-fold excess of $BH_3{\cdot}SMe_2$ in

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(5) Hulst, R.; Heres, H.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1996**, *7*, 1373. Kellogg reports excellent results using compounds related to **2** as catalysts. In our hands, the use of 10 mol % of **2** in the reduction of chloroacetophenone gave a product of 38% ee. Compound **2** decomposed slowly under the reaction conditions.

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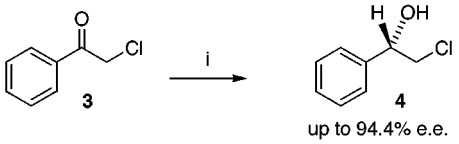
**Scheme 1**[a]




[a] Reagents and conditions: (i) 10 mol % of **1**, 1.05 equiv of $BH_3{\cdot}SMe_2$, toluene, 40−110 °C; see Table 1.

**Table 1. Reduction of α-Chloroacetophenone: Effect of Temperature**

| entry | *T*/°C | yield/% | % ee |
|---|---|---|---|
| 1 | 110 | 91 | 94.4 |
| 2 | 100 | 89 | 94.3 |
| 3 | 80−85 | 88 | 93.3 |
| 4 | 70−75 | 80 | 92.8 |
| 5 | 60−65 | 69 | 80.1 |
| 6 | 40−50 | 62 | 13.5 |

toluene-$d_8$ at room temperature and at elevated temperature (110 °C, 20 min) were compared with the corresponding spectra of a solution of diphenylprolinol treated under the same conditions. The $^{11}B$ NMR showed no peaks corresponding to the formation of an oxazaborolidine (these were seen in the control experiment).[7a,b,d] These observations are in agreement with those of Buono, who reported no cleavage of the N−P bond upon treatment of a cyclic oxazaphospholidine oxide with excess borane.[8a] No decomposition of **1** was observed by $^{31}P$ NMR after the above mixture had been cooled and quenched with deuterium oxide.

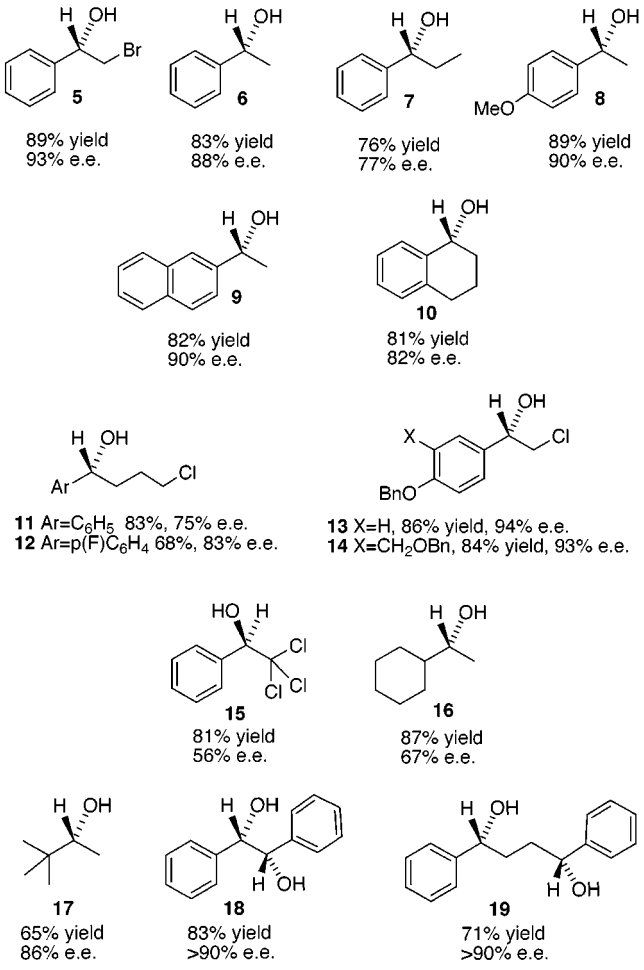



**Figure 1.** Reduction products obtained using catalyst **1**.

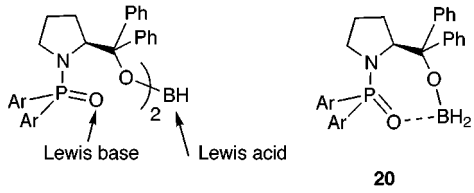



**Figure 2.**

The application of **1** to the synthesis of a range of alcohols in enantiomerically enriched form through the reduction of the corresponding ketones was investigated (Figure 1). While α-chloroacetophenone remained the optimal substrate, the results were generally good to excellent. Although the presence of an electron-withdrawing group at the α-position of the ketone was beneficial (**4**, **5**, **13**, and **14**), the electron density of the aromatic ring appeared to have no significant effect on selectivity (cf. **6** vs **8** and the **11** vs **14**). The products **13** and **14** may in principle be cyclized to the corresponding epoxides, which represent potential precursors to the drugs denopamine and salbutamol.

Aryl/alkyl ketones were the best substrates, although dialiphatic ketones could also be reduced in good yield and enantioselectivity (cf. **16** and **17**). The selectivity of reduction was reversed in the case of the reduction of the trichloromethyl substituted acetophenone adduct, in agreement with Corey's observations on the relative steric sizes of the groups bordering the ketone.[9]

Diols could be obtained in very high enantiopurity at the cost of diastereoselectivity due to the mathematical combination of two selective reactions upon the same molecule. Reduction of benzil proceeded in moderate diastereoselectivity (threo/erythro 86:14). The ee of the chiral (threo) isomer **18** was established by conversion to the diacetate followed by analysis with the shift reagent $Eu(hfc)_3$.[10a] Reduction of 1,2-dibenzoylethane proceeded to give the *R,R* enantiomer with moderate distereoselectivity (*R*/*S*/meso 84:16) but with an apparent ee of >90% as judged by the $^{19}F$ NMR analysis of the bis (*R*)-MTPA ester.[10b]

We have previously suggested that the actual catalytic species is a complex such as **20**, which is formed by the reaction of **1** with 1 equiv of borane.[3c] This may exist as the discrete species **20** or as a dialkoxyborane (Figure 2)[12] or perhaps even a more complex polymeric species. The system contains both a Lewis base and Lewis acid site, which interact with a molecule of borane and ketone, respectively. Thus, the reagents are effectively held within reactive distance and activated by the requisite electron-donating and -withdrawing properties of the groups involved, as shown in Figure 3. Following the hydride transfer step the alkoxyborane reduction product dissociates from the catalyst, and the latter then renters the catalytic cycle. The high temperature required for the best results in this process may be due to the acceleration of this dissociation process, which thus

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(12) DiMare, M. *J. Org. Chem.* **1996**, *61*, 8378 and references therein.

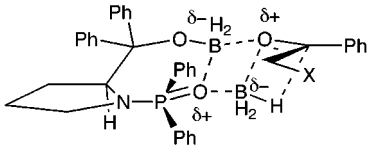

**Figure 3.** Stereochemical control in the asymmetric reduction.

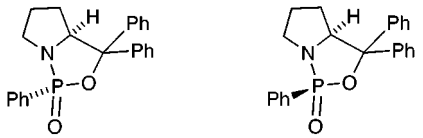


**Figure 4.** Oxazaphospholidine oxide catalysts.

ensures effective catalyst turnover.[13a,b] In the absence of an effective turnover the slower uncatalyzed pathway will dominate, resulting in lower overall yields and enantioselectivity. An alternative explanation is that an unproductive species, perhaps a dimer, predominates at lower temperature.[7]

Oxazaphospholidine oxides have been reported to be effective reagents for the asymmetric reduction of ketones by borane.[8] In view of the obvious similarity of these reagents to our own, we investigated the synthesis and reactivity of **21** and **22** (Figure 4).[8b] These were prepared in a 7:1 diastereoisomeric mixture from the reaction between diphenylprolinol and phenylphosphonic dichloride in 70% yield. The configuration of the phosphorus atom in the major diastereoisomer **21** was confirmed by single-crystal X-ray analysis.[13] Using the individual isomers **21** and **22**, we found that the former was a superior catalyst in terms of asymmetric induction, giving a product of 95% ee in the acetophenone reduction (10 mol % catalyst) compared to 75% ee for the latter. In contrast to **1** the best results for **21** and **22** were achieved at room temperature in THF solvent. Furthermore, the oxazaphospholidine oxides were not recoverable after the reaction. Buono has suggested that these compounds are ring-opened by cleavage of the P−O bond to give a catalytic species analogous to **20** (the P−N bond is retained), which is stable for the lifetime of the reaction but decomposes upon quenching and workup. It is therefore clear that the P−O bond cleavage must be streospecific and that the configuration at the phosphorus atom contributes to the asymmetric induction in some manner.[3e] We are presently investigating modified catalysts based on **1** that contain chiral phosphorus atoms and that may therefore give improved enantioselectivities.

In conclusion, we have demonstrated that phosphinamide **1** is a readily available, robust, versatile, and recoverable reagent for the asymmetric catalysis of the reduction of ketones by borane.

## Experimental Section

General reagents and conditions have been described in a previous paper.[14]

***N*-(*O*,*O*-Dimethylphosphoryl)-(*S*)-α,α-diphenyl-2-pyrrolidinemethanol (2).** Carbon tetrachloride (2.04 mL, 3.25 g, 21.1 mmol) was added dropwise to an ice-cold stirred solution of (*S*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol (2.14 g, 8.45 mmol), dimethyl phosphite (930 mL, 1.12 g, 10.1 mmol), and triethylamine (1.41 mL, 1.03 g, 10.1 mmol) in anhydrous $CH_2Cl_2$ (20 mL). The resulting solution was allowed to slowly warm to room temperature and then stirred for a further 10 h. After this period, the reaction was quenched with water and the organic layer separated. The aqueous layer was extracted with $CH_2Cl_2$, the combined organic layers were washed with saturated $NH_4Cl$, water, and then brine and dried ($MgSO_4$), and the solvent was removed in vacuo. The resulting solid was recrystallized from *n*-hexane−$CH_2Cl_2$ (4:1) to give **2** (2.13 g, 76%) as a white solid: mp 118−120 °C (from *n*-hexane−$CH_2Cl_2$); $[\alpha]_D$ −61.6 (*c* 0.5, $CH_2Cl_2$); $\upsilon_{max}/cm^{-1}$ 3405 (OH), 1233 (P=O); $^1H$ NMR (250 MHz; $CDCl_3$) $\delta$ 1.02−1.17 (1H, m), 1.46−1.63 (1H, m), 2.58−2.70 (1H, m), 3.06−3.18 (1H, m), 3.58 (3H, d, $J$ = 11.0 Hz), 3.66 (3H, d, $J$ = 11.0 Hz), 4.72 (1H, dt, $J$ = 5.2, 8.4 Hz), 5.69 (1H, bs, exchangeable), 7.20−7.33 (6H, m), 7.40−7.51 (4H, m); $^{13}C$ NMR (62.9 MHz; $CDCl_3$) $\delta$ 24.9 (d, $J$ = 5.9 Hz), 30.8 (d, $J$ = 7.9 Hz), 53.1 (d, $J$ = 5.9 Hz), 67.6 (d, $J$ = 4.9 Hz), 80.5, 126.8, 126.9, 127.2, 127.4, 127.7, 128.1, 143.7, 146.1; *m*/*z* (CI) 344 ($M^+$ − OH, 100), 183 (98); $^{31}P$ NMR (162 MHz; $CDCl_3$) $\delta$ 15.2. Anal. Calcd for $C_{19}H_{24}NO_4P$: C, 63.15; H, 6.69; N, 3.88. Found: C, 63.1; H, 6.7; N, 3.9.

***N*-(Di-*p*-Anisylphosphoryl)-(S)-α,α-diphenyl-2-pyrrolidinemethanol (1).** *p*-Anisylmagnesium bromide 2 M in THF (12.8 mL, 25.6 mmol) was added dropwise to a stirred solution of *N*-(*O*,*O*-dimethylphosphoryl)-(*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**2**) (2.10 g, 5.81 mmol) in anhydrous THF (50 mL) at −78 °C under a nitrogen atmosphere. The resulting mixture was allowed to slowly warm to room temperature over a 3 h period and then heated at 60 °C for a further 90 min whereupon the reaction was complete as assayed by thin-layer chromatography. The solution was allowed to cool to room temperature and diluted with water and the THF removed in vacuo. The residue was acidified with saturated $NH_4Cl$ and the aqueous phase extracted with EtOAc. The combined organic layers were washed with water and brine and dried ($MgSO_4$), and the solvent removed in vacuo. The residue was purified by column chromatography using EtOAc−$CH_2Cl_2$−$NEt_3$ (2:98:0.1) and then EtOAc−$CH_2Cl_2$−$NEt_3$ (5:95:0.1) as the eluants. This gave **1** (2.09 g, 70%) as a white solid that was further purified by recrystallization from *n*-hexane−$CH_2Cl_2$ (4:1). This gave the pure product as white solid: mp 169−172 °C (from *n*-hexane−$CH_2Cl_2$); $[\alpha]_D$ −66.6 (*c* 0.5, $CH_2Cl_2$); $\upsilon_{max}/cm^{-1}$ 3230 (OH), 1255 (P=O); $^1H$ NMR (250 MHz; $CDCl_3$) $\delta$ 1.06−1.18 (1H, m), 1.25−1.42 (1H, m), 1.69 (1H, bs, exchangeable), 2.00−2.11 (2H, m), 2.33 (1H, ddd, $J$ = 7.5, 10.3, 15.6 Hz), 2.64−2.94 (1H, m), 3.84 (3H, s), 3.88 (3H, s), 4.73 (1H, dt, $J$ = 5.5, 8.3 Hz), 6.87−7.02 (4H, m), 7.21−7.70 (14H, m); $^{13}C$ NMR (62.9 MHz; $CDCl_3$) $\delta$ 24.8 (d, $J$ = 4.9 Hz), 31.0 (d, $J$ = 4.9 Hz) 49.8 (d, $J$ = 4.9 Hz), 55.2, 67.2, 80.0, 113.8 (d, $J$ = 13.8 Hz), 114.1, 120.9, 121.9, 122.9, 124.0, 126.6, 126.8, 127.0, 127.7, 127.9, 128.7, 133.8 (d, $J$ = 10.8 Hz) 144.4, 146.1, 162.4 (d, $J$ = 2.0 Hz); *m*/*z* (CI) 514 ($M + H^+$, 2), 236 (100); $^{31}P$ NMR (162 MHz; $CDCl_3$) $\delta$ 34.4. Anal. Calcd for $C_{31}H_{32}NO_4P$: C, 72.5; H, 6.28; N, 2.73. Found: C, 72.7; H, 6.3; N, 3.0.

**Standard Optimized Procedure for the Catalytic Asymmetric Reduction of Prochiral Ketones with *N*-(Di-*p*-anisylphosphoryl)-(*S*)-α,α-diphenyl-2-pyrrolidinemethanol (1).** *N*-(Di-*p*-anisylphosphoryl)-(*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**1**) (359 mg, 0.70 mmol) was azetroped in situ under a nitrogen atmosphere with anhydrous toluene (3 × 4 mL). The catalyst was then dissolved in anhydrous toluene (14 mL) to which was added borane−methyl sulfide (2 M in toluene, 3.67 mL, 7.34 mmol), and the mixture was heated to 110 °C. At approximately 80 °C, a white precipitate forms, which does not affect the reduction. Once the temperature had stabilized at 110 °C, chloroacetophenone (1.08 g, 6.99 mmol) in anhydrous toluene (14 mL) was added dropwise via a syringe pump at a flow rate of 0.5 mL/min. Once all the ketone had been added, stirring was continued for a further 20 min, whereupon the reaction was complete as assayed by thin-layer chromatography. The mixture was allowed to cool to room temperature and quenched with water. This was acidified with saturated $NH_4$-

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(14) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226.

Cl and the organic layer separated. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with water and brine and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography using light-petroleum−EtOAc−$Et_3N$ (89:10:1) as the eluant. This gave (*S*)-(+)-2-chloro-1-phenylethanol (971 mg, 89%) in 94.4% ee (see below for determination). The catalyst could be recovered from the reaction by eluting the column with EtOAc−$CH_2Cl_2$−$Et_3N$ (2:97:1) and then EtOAc−$CH_2Cl_2$−$Et_3N$ (5:94:1) as the eluants. ***(S)*−(+)-2-Chloro-1-phenylethanol (4):** 94.4% ee (*S*) by HPLC (Chiralcel OD, ethanol/*n*-hexane/diethylamine = 5:95:0.01:0.5 mL/min) (*S* isomer 18.8 min, *R* isomer 22.3 min); $[\alpha]_D$ +47.0 (*c* 1, cyclohexane) [lit.[15a] $[\alpha]_D$ +49.6 (*c* 2.8, cyclohexane), (*S*)]; $^1$H NMR (250 MHz; $CDCl_3$) $\delta$ 2.72 (1H, bs, exchangeable), 3.64 (1H, dd, $J$ = 8.7, 11.2 Hz), 3.75 (1H, dd, $J$ = 3.5, 11.2 Hz), 4.90 (1H, dd, $J$ = 3.5, 8.7 Hz), 7.31−7.35 (5H, m).

Details of the characterization and enantiomeric excess determination of reduction products **5**−**19** are given in the Supporting Information.

**(2*S*$_p$,5*S*)-2,4,4-Triphenyl-3-oxa-1-azaphosphorylbicyclo-[3.3.0]octane (21 and 22).** Phenylphosphonic dichloride (2.01 g, 1.46 mL, 10.3 mmol) was added dropwise to an ice-cold stirred solution of (*S*)-(−)-α,α-diphenylpyrrolidinemethanol (2.38 g, 9.39 mmol) and triethylamine (2.09 g, 2.88 mL, 20.7 mmol) in anhydrous $CH_2Cl_2$ (20 mL). The reaction was allowed to slowly warm to room temperature and was stirred at this temperature for a further 12 h. The mixture was filtered and the solvent removed in vacuo. The crude $^1$H NMR showed a 7:1 mixture of diastereomers, which was purified by column chromatography using $CH_2Cl_2$−$NEt_3$ (99.9:0.1) and then EtOAc−$CH_2Cl_2$−$NEt_3$ (10:90:0.1) as the eluants. This gave **21** and **22** (**21**: 2.48 g, 70%, **22**: 320 mg, 9%) as white powders. These were further purified by recrystallization from *n*-hexane−$CH_2Cl_2$ (4:1). Major isomer **21**: mp 158−161 °C; $[\alpha]_D$ −236.4 (*c* 0.55, $CHCl_3$) [lit.[8b] $[\alpha]_D$ −235.6 (*c* 1.15, $CHCl_3$)]; $\upsilon_{max}$/cm$^{-1}$ 1447, 1241; $^1$H NMR (270 MHz; $CDCl_3$) $\delta$ 1.56−1.84 (4H, m), 2.95−3.03 (1H, m), 3.67−3.79 (1H, m), 4.70 (1H, qu, $J$ = 6.4 Hz), 7.24−7.61 (15H, m); $^{13}$C NMR (67.8 MHz; $CDCl_3$) $\delta$ 26.3, 30.2, 44.8, 71.3, 88.7, 126.5, 126.7, 127.4, 128.0, 128.2, 128.3, 129.9, 131.6, 131.7, 132.5, 141.2, 143.6 (d, $J$ = 4.4 Hz); *m*/*z* (CI) 376 (M + H$^+$, 100%); $^{31}$P NMR (162 MHz; $CDCl_3$) $\delta$ 36.09. Characterization for the minor diastereomer **22**: mp 157−160 °C; $[\alpha]_D$ −64.4 (*c* 0.28, $CH_2Cl_2$); $^1$H NMR (250 MHz; $CDCl_3$) $\delta$ 1.20−1.40 (1H, m), 1.53−2.00 (3H, m), 2.99−3.24 (2H, m), 4.76 (1H, ddd, $J$ = 5.2, 11.0, 16.5 Hz), 7.24−7.87 (15H, m); $^{13}$C NMR (62.9 MHz; $CDCl_3$) $\delta$ 24.6, 30.6 (d, $J$ = 27.6 Hz), 44.4 (d, $J$ = 3.9 Hz), 72.6 (d, $J$ = 8.9 Hz), 89.7, 125.3, 126.3, 126.5, 127.3, 128.0, 128.1, 128.4, 128.6, 129.1, 132.4, 133.1 (d, $J$ = 10.8 Hz), 142.0 and 144.7; *m*/*z* (CI) 376 (M + H$^+$, 55), 236 (100); $^{31}$P NMR (162 MHz; $CDCl_3$) $\delta$ 34.5. Anal. Calcd for $C_{23}H_{22}NO_2P$: C, 73.58; H, 5.91; N, 3.73. Found: C, 73.4; H, 5.8; N, 3.7.

The catalytic asymmetric reduction of acetophenone with **21** and **22** was carried out following the procedure described by Martens.[16]

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**Supporting Information Available:** Experimental data for the synthesis of all compounds related to the novel compounds **13** and **14**, characterization and ee determination data for compounds **5**−**19**, $^1$H NMR spectra of **13**, **14**, and related synthetic intermediates, X-ray crystallographic data on **21**, and $^{11}$B and $^{31}$P NMR data from the borane stability study of **1** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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