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Phosphinamides catalysts containing a stereogenic phosphorus atom for the asymmetric reduction of ketones by borane

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Abstract: The effect of the configuration of the phosphorus atom in phosphinamide reduction catalysts has been studied through the preparation and use of a series of catalysts containing stereogenic phosphorus atoms of known configuration. The conclusion of this work is that a stereogenic centre at phosphorus can improve the selectivity of reductions using this catalyst, but is not sufficient in itself to generate the higher levels of selectivity which have been achieved with related catalysts. The X-ray crystallographic structure of a key compound is also featured. © 1997, Elsevier Science Ltd. All rights reserved.

In a series of recent papers we have described the preparation and use of chiral phosphinamides typified by the structure **1** as catalysts for the asymmetric reduction of ketones by borane.[1] Catalysts of this type are generally easy to prepare, are robust and stable compounds and may be recovered and reused without appreciable decomposition or decrease in activity. Our studies have revealed that phosphinamides act as Lewis bases and activate borane by donation of electron density (Figure 1). Whilst this effectively accelerates the reductions, high enantiomeric excesses have been elusive with these compounds due to the conformational freedom allowed to the ketone in the transition state. The incorporation of a proximal hydroxyl group as illustrated in **2**, provides a catalyst which gives dramatically improved enantiomeric excesses (up to 92%).[2] It is believed that the hydroxyl group, upon reaction with borane, gives a complex with an electron-acceptor site for co-ordination of the ketone (Figure 2).[2] A closely related system has been reported by Buono.[3]

Although excellent results have been obtained using the new generation of catalysts based on **2**, we wished to examine whether the enantioselectivities induced by simple catalysts such as **1** could be improved through the incorporation of a stereogenic centre at the phosphorus atom. The results of a series of systematic investigations in this regard are reported herein. We first turned our attention to the diastereomerically pure phosphinamides **3** and **4**, the preparation and single crystal X-ray diffraction study of which has been reported by Jennings.[4]

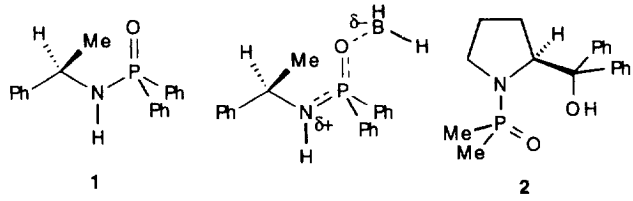

Figure 1.

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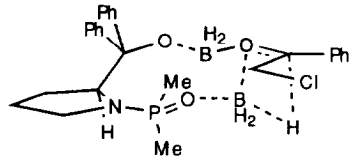
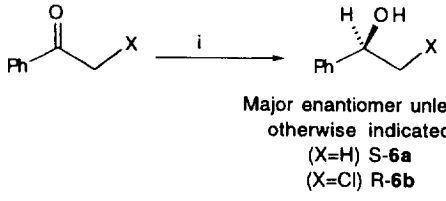


Figure 2.



X=H

Using 10 mol% **1**: <1 hr, 82% yield, 27% e.e.[1a]

Using 10 mol% **2**: <3 hr, 96% yield, 20% e.e.

Using 10 mol% **7**: <1 hr, 87% yield, 50% e.e

Using 10 mol% **8**: <1 hr, 89% yield, 5% e.e.(R)

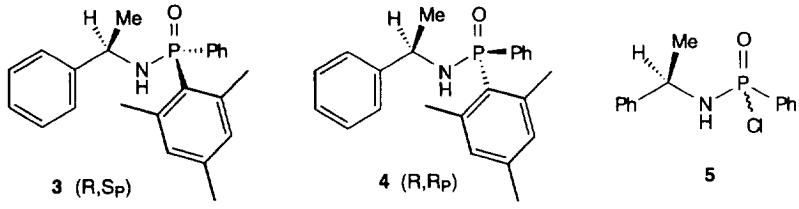
X=Cl

Using 10 mol% **7**: <1 hr, 97% yield, 42% e.e

Using 10 mol% **8**: <1 hr, 98% yield, 4% e.e.

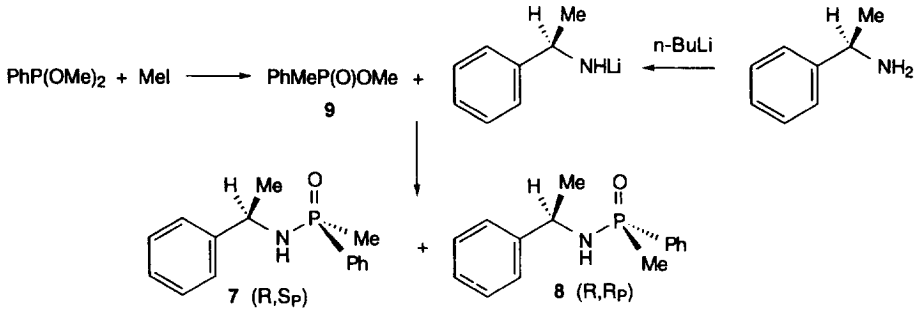
Reagents and conditions: (i) 10 mol% catalyst, 1.0 eq. $BH_3.SMe_2$ (10M), r.t., 2 hr.

Scheme 1.



Attempted preparation of these compounds *via* the route reported by Jennings, which involved a six-step sequence from dichlorophenylphosphine proved problematic in our hands. We therefore developed an alternative approach. We found that addition of (R)-(+)-α-methylbenzylamine to a very dilute solution of phenylphosphonic dichloride in DCM (1 equivalent of triethylamine, rt) gave the mono-chloride **5** as a viscous oil. Reaction of a crude solution of the chloride in diethyl ether with 2.5 equivalents of mesitylmagnesium bromide gave, after chromatography and crystallisation, a low yield of the pure (R,RP)-diastereoisomer **4** as a white crystalline solid. Assignment of the configuration at phosphorus was made by comparison of data with that reported by Jennings.[4] Use of 10 mol% of this compound under standard reduction conditions (Scheme 1) gave an acetophenone reduction product **6** of 20% e.e. (S-major, 96% yield) with reduction being complete in 2–3 hours at rt. The selectivity obtained with **4** appeared similar, and in the same sense, to that obtained with phosphinamide **1**; the increase in time required for complete reduction, we believed, reflecting the increase in steric crowding around the phosphorus atom (using **1**, the reaction is complete in under one hour). Unfortunately attempts to isolate the (R,SP)-diastereoisomer **3** were unsuccessful. However even if **4** represented the 'mismatched' diastereoisomer, the expected benefit from a 'matched' enantiomer was not expected to be significant. In view of this and the rate retardation we therefore moved on to an alternative system.

In order to avoid undue steric hindrance around the phosphorus atom we decided to prepare derivatives of **1** in which one of the attached phenyl groups was replaced by a methyl, i.e. **7** and **8** respectively. Our approach to the synthesis of these compounds is shown in Scheme 2. The reaction of lithiated (R)-(+)-phenethylamine with the racemic phosphinate **9** gave a 1:1 mixture of **7** and **8**



Scheme 2.

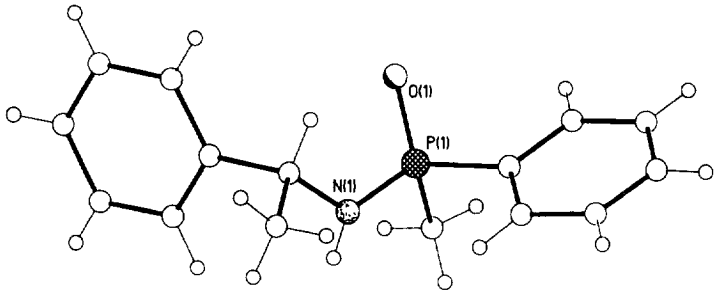


Figure 3. X-Ray crystallographic structure of **7**.

which could be easily separated by flash chromatography. In order to determine the configuration at phosphorus in these compounds we obtained an X-ray crystal structure of **7** (Figure 3). The absolute structure was identified from the known R configuration stereogenic centre at C(2).

With quantities of **7** and **8** in hand we investigated the catalysed reduction reactions. Both diastereoisomers proved to be ideal catalysts, affording complete reduction of acetophenone in less than one hour under the ambient temperature conditions (Scheme 1). The asymmetric inductions also indicated a dramatic 'matched/mismatched' relationship where **7** gave an e.e. twice that of the parent **1**. Conversely **8** gave a product of reversed selectivity, although of only 5% e.e. The pattern of results was repeated using α-chloroacetophenone (**1** gives (R)-product of 22% e.e.[1b]), a substrate which gives superior results over acetophenone using the hydroxy-bearing catalysts **2**.[2] Catalyst **2** also gives improved results at elevated temperatures, however no corresponding improvement was observed using either **7** or **8**. This suggests therefore that the improvement of asymmetric induction at elevated temperatures is a particular feature of the borate ester formed with the hydroxy group in **2**. The effect of replacing the diphenylphosphinyl group in **2** with a methylphenylphosphinyl group has been found to give an improved asymmetric induction although the 'matched/mismatched' effects have not been studied in detail.[2]

Literature evidence suggests that, in common with oxazaborolidines, there is an optimum temperature for asymmetric reductions using borane-co-ordinating catalysts.[2,5,6] This may be due to either the existence of a non-productive dimer[5] at low temperature or may be due to accelerated breakdown of the reduction complex at high temperature, thus allowing the catalytic cycle to be propagated rapidly.[6] We are currently investigating methods for the improvement of asymmetric inductions using these novel catalysts.

Experimental section

All reactions were carried out in flame-dried apparatus under nitrogen. Tetrahydrofuran was distilled from sodium and benzophenone; chloronated hydrocarbons, ethanol and methanol from calcium hydride; dimethylformamide was distilled from calcium hydride under reduced pressure and triethylamine from potassium hydroxide under reduced pressure. All reactions were monitered by TLC using commercially available aluminium backed plates, pre-coated with a 0.25 mL layer of silica containing a fluorescent indicator (Merck). All organic layers were dried with anhydrous sodium sulphate then the solvent removed using a Buchi rotary evaporator followed by drying on a static oil pump (2mmHg). Column chromatography was carried out on silica Merck 60 (40–63(m)). Optical rotations were recorded using a Perkin–Elmer spectrometer and a 10 cm cell, $[\alpha]D$ are given in 10^{-1} deg cm^2g^{-1}. Infra red spectra were recorded as thin films using a FT-IR Perkin–Elmer Paragon 1000 spectrometer. Peak intensities are specified as strong(s), medium(m) or weak(w). ^{1}H-NMR specta were recorded with a Bruker AC 250. Chemical shifts are recorded in ppm relative to tetramethylsilane in the sample to $CHCl_3$ (δ 7.25). Coupling constants (J) are given in Hz and multiplicity in singlet (s), doublet (d), triplet (t) quartet (q), multiplet (m) and double doublet (dd). ^{13}C-NMR spectra were recorded on Bruker AC 250 and ACF 400 spectrometers. Chemical shifts are recorded in ppm relative to tetramethylsilane in the sample to $CHCl_3$ (δ 77.0). Coupling constants (J) are given in Hz and multiplicity in singlet (s), doublet (d), multiplet (m) and double doublet (dd). DEPT spectra were obtained to aid spectral interpretation. ^{31}P-NMR spectra were recorded on a Bruker ACF 400. Chemical shifts are recorded in ppm relative to an internal reference. Mass spectra were recorded on a Kratos MS80RFAO and high resolution MS from the EPSRC service at Swansea. Chiral high preformance liquid chromatography was performed using a Walters 501 pump and 486 Absorbance detector.

Preparation of (1R)-N-(1-phenethyl)-(Rp)-P-phenyl-P-(2,4,6- trimethylphenyl) phosphinamide ***4***

To a stirred solution of phenylphosphonic dichloride (1.1 cm^3, 7.76 mmol) in DCM (15 cm^3) at −78°C was added a solution of (R)-(+)-α-methylbenzylamine (1.0 cm^3, 7.76 mmol) and triethylamine (1.08 cm^3, 7.76 mmol) in DCM (6 cm^3) dropwise over 10 minutes. The resulting solution was allowed to warm slowly to room temperature and stirred for 10 hours. The mixture was then concentrated *in vacuo* and the residue extracted with anhydrous diethyl ether. The combined extracts were filtered to remove hydrochloride salts and again concentrated *in vacuo* to give chloride **5** as a viscous pale yellow oil. This was then redissolved in anhydrous ether (20 cm^3) and the solution cooled to 0°C. 2,4,6-trimethylphenylmagnesium bromide (2 M diethyl ether solution, 2.5 equivalents, 9.7 cm^3, 19.4 mmol) was added dropwise over 10 minutes and the cloudy mixture stirred at 0°C for 1 hour. It was then warmed to room temperature and stirred for a further 3 hours (or until all chloride was consumed by TLC). The mixture was then poured into an equal volume of saturated aqueous ammonium chloride solution and extracted with DCM (3×7 cm^3). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo*. The residue was purified on silica eluting with a gradient of 0→50% v/v ethyl acetate–petrol. This afforded phosphinamide **4** as a white solid which was further purified by recrystallisation from toluene (253 mg, 9%). The configuration at phosphorus assigned by comparison with literature data; isolated as a single diastereoisomer,[4] $[\alpha]_D^{19}=-10.8$ (*c* 0.01, chloroform) (lit., [4] −10.5 *c*0.01, chloroform); δ_H (270 MHz, $CDCl_3$) 1.63 (3 H, d, *J* 6.8, $CHCH_3$), 2.27 (3 H, s, 4-Me), 2.35 (6 H, s, 2-Me and 4-Me), 3.16 (1 H, br t, *J* 9, NH), 4.51 (1 H, m, $CHCH_3$), 6.82 (2 H, d, *J* 3.7, aryl H), 7.23 (5 H, s, aryl H), 7.4–7.43 (3 H, m, aryl H), 7.64–7.69 (2 H, m, aryl H); δ_C (68 MHz, $CDCl_3$) 21.0 (q), 23.7 (q), 25.6 (q), 51.1 (d), 126.1, 127.0, 128.3, 128.4, 128.5, 130.4, 130.6, 130.8, 131.0, 141.3, 143.4 (d, J_{PC} 10), 145.1 (d, J_{PC} 5.5); *m/z* (CI) 364 (M^++1, 100%), 290 (68), 274 (7), 245 (9), 120 (100), 105 (32), 91 (15), 79 (32).

Preparation of methyl(phenylmethylphosphinate) ***9***

Methanol (2.25 mL, 57 mmol) was added dropwise to a solution of dichlorophenylphosphine (5.0 g, 28 mmol) and pyridine (4.74 mL, 58 mmol) in hexane (18 mL) at 0°C. The reaction was stirred

for 2 hours at room temperature. Pyridine hydrochloride was removed by filtration under nitrogen and the filtrate concentrated by the use of a vacuum pump. A small amount of methyl iodide was added to the residue and the reaction was heated to about 60°C, a violent exothermic reaction then occurred and the further methyl iodide added at a rate to maintain the temperature at 100°C. After all the methyl iodide had been added (2.78 mL, 45 mmol) the reaction was stirred for 16 hours to yield methyl(phenylmethylphosphinate) **9** (3.6 g, 76%) Rf 0.35 (5% methanol/dichloromethane); υ_{max} 2844 w, 1438 m, 1221 s, 1038 s cm^{-1}; ^1H (250MHz, $CDCl_3$) δ 1.68 (3H, d, *J* 14.5, PCH_3), 3.61 (3H, d, *J* 11.0, OCH_3), 7.49–7.79 (3H, m, Ar), 7.80–7.83 (2H, m, Ar); ^{13}C (62.5MHz, $CDCl_3$) 15.3 (d, *J* 102.4, PCH_3), 50.7 (d, *J* 5.9 OCH3), 128.4, 128.6, 129.8, 131.0, 163.2, 131.8, 132.1, 132.2; ^{31}P-NMR (162MHz, $CDCl_3$) δ 44.6; *m/z* (CI) 188 (M^++NH_4^+, 18%), 171 (MH+, 100%), 155 (24%), 140 (14%), 124 (7%), 108(6%), 94(17%).

Preparation of phosphinamides 7 and 8

n-Butyllithium (28 mmol) was added to a solution of (R)-(+)-α-methylbenzylamine (3.63 mL, 28 mmol) in tetrahydrofuran (100 mL) at −78°C and stirred for 15 minutes. The reaction mixture was then added to a solution of methyl(phenylmethylphosphinate) **9** (2.4 g, 14 mmol) in tetrahydrofuran (30 mL) was slowly warmed to room temperature. After 20 hours, saturated ammonium chloride solution (50 mL) was added to the reaction mixture, which was stirred for 10 minutes then the solvent removed in vacuo. Dichloromethane (3×100 mL) was used to extract the organics from the aqueous phase. The phases were separated and the organic layer dried, filtered and the solvent removed in vacuo to give a brown oil. The oil was purified by flash chromatography on silica eluting with 5% methanol/dichloromethane to give both diastereomers as white solids, these were then crystallised from petroleum ether 40:60 and dichloromethane to yield phosphinamide **7** (401 mg, 11%), Rf 0.36 (5% methanol/dichloromethane); mp 115–116°C. $[\alpha]_D^{19}$= +46.2 (c 0.58, chloroform); υ_{max} (CD_2Cl_2) 3200s, 3055w, 2969w, 1265 s cm^{-1}; ^1H-NMR (250MHz, $CDCl_3$) δ 1.41 (3H, d, *J* 7.0, $CHCH_3$), 1.50 (3H, d, *J* 14.0, PCH_3), 3.43 (1H, dd, *J* 7.6, NH), 4.42 (1H, m, CH), 7.20–7.51 (8H, m, Ar), 7.79–7.90 (2H, m, Ar); ^{13}C-NMR (62.5MHz, $CDCl_3$) δ 16.1 (d, *J* 94.3, PCH_3), 25.2 (d, *J* 5.1, CH_3), 49.9 (s, CH) 125.7, 126.7, 128.0, 128.1, 128.2, 131.0, 131.1, 131.3, 131.4, 133.6 (d, *J* 123.7), 145.1 (d, *J* 4.0); ^{31}P-NMR (162MHz, $CDCl_3$) δ 30.0; *m/z* (CI) 260 (MH^+, 100%), 244 (39%), 182 (2%), 156 (13%), 139 (19%), 120 (72%); HRMS, found 260.1204, $C_{15}H_{19}PNO^+$ requires 260.1204. Phosphinamide **8** (706mg, 19%), Rf 0.25 (5% methanol/dichloromethane), mp 130–131°C. $[\alpha]_D^{19}$=+44.9 (c 0.65, chloroform); υ_{max} (CD_2Cl_2) 3200w, 3052w, 2979w, 1265s cm^{-1}; ^1H-NMR (250MHz, $CDCl_3$) δ 1.54 (3H, d, *J* 6.7, $CHCH_3$), 1.62 (3H, d, *J* 14.0, PCH_3), 3.43 (1H, dd, *J* 8.2, NH), 4.22 (1H, m, CH), 7.50–7.14 (8H, m, Ar), 7.68–7.76 (2H, m, Ar); ^{13}C-NMR (62.5MHz, $CDCl_3$) δ 16.6 (d, *J* 92.7, PCH_3), 25.7 (d, *J* 3.4, CH_3), 50.6, 125.7, 126.6, 127.9, 128.0, 128.1, 131.2, 131.3, 131.3, 131.4, 132.7 (d, *J* 125.2), 144.9 (d *J* 4.0); ^{31}P-NMR (162MHz, $CDCl_3$) δ 30.8 (s); *m/z* (CI) 260 (MH+, 100%), 244 (64%), 182 (4%), 156 (31%), 139 (27%), 120 (79%), HRMS; found 260.1204, $C_{15}H_{19}PNO^+$ requires 260.1204.

X-ray crystal stucture details for 7

A crystal of approximate dimensions 0.8 × 0.8 × 0.16 mm was used for data collection. *Crystal data:* $C_{15}H_{18}NOP$, *M*=259.27 monoclinic, *a*=5.318(2), *b*=15.834(3), *c*=8.639(4) Å, β=102.82(2)°, *U*=709.3(4) $Å^3$, space group $P2_1$, Z=2, D_c=1.214 Mg m^{-3}, λ(Mo-K_α)=0.71073 Å, μ=0.18 mm^{-1} *F*(000)=276. Data were measured at 230K[7] on a Siemens SMART area detector system in the range 2.42≤θ≤23.27°. 1474 reflections were collected of which 1429 were unique. Data were corrrected for Lorentz and polarisation effects but not for absorption. Structure solution was by direct methods and refinement used full-matrix least-squares on F^2.[8] Hydrogen atoms were included at calculated positions. Final residuals were *R*=0.0369, wR_2=0.1011 for a weighting scheme of $w=1[\sigma^2(Fo^2)+0.0796P^2+0.11P]$ where P=max($(Fo^2,0)$+2Fc^3)/3. The max. and min. residual densities were 0.24 and −0.27 e$Å^{-3}$ respectively. The absolute configuration of the molecule was assigned on

the basis of the stereogenic centre at C2, which was known to be R configuration. Full details have been deposited at the Cambridge Crystallographic Data Centre.

Typical reduction procedure and e.e. measurement

The phosphinamide (0.066 mmol) was dried by azeotroping with toluene (2×1 mL) then dissolved in toluene (2.5 mL). Acetophenone (79 mg, 0.66 mmol) was added to the reaction mixture, which has then heated to 110°C prior to the dropwise addition of borane–dimethyl sulphide complex (0.69 mmol) and left for 90 minutes. The reaction mixture was allowed to cool to room temperature, saturated ammonium chloride solution (5 mL) added and stirred for 5 minutes. Ethyl acetate (5 mL) was added, the phases separated and the aqueous phase extracted with ethyl acetate (2×5 mL). The organic layers were combined, washed with saturated ammonium chloride solution (5 mL), dried, filtered and the solvent removed in vacuo to give an oil. The oil was purified by flash chromatography on silica eluting with 10% ethyl acetate/petroleum ether 40:60 to yield the benzyl alcohol (62 mg, 80%). The enantiomeric excess of the alcohol was determined by chiral HPLC (see HPLC experimental). Rf=0.38 (20% ethyl acetate/petroleum ether 40:60), ^{1}H-NMR (250MHz, $CDCl_3$) δ 1.45 (2H, d, *J* 7.0, CH_3), 2.34 (1H, s, OH), 4.83 (1H, q, *J* 7.0, CH), 7.22–7.34 (5H, m, Ar). When tetahydrofuran was used instead as a solvent the experimental was as above except the reaction was carried out at room temperature. For the reduction of chloroacetophenone the procedure is the same as above. Data for the chlorobenzyl alcohol; Rf=0.52 (20% ethyl acetate/petroleum ether 40:60): ^{1}H-NMR (250MHz, $CDCl_3$) δ 2.76 (1H, bs, OH), 3.64 (1H, dd, *J* 8.7, 11.2, C*H*H), 3.75 (1H, dd, *J* 3.5, 11.2, CH*H*), 4.90 (1H, dd, *J* 3.5, 8.7, CH), 7.31–7.40 (5H, m, Ar).

Determination of enantiomeric excess of the alcohols

Chiral high performance liquid chromatography was used for the determination of all enantiomeric excesses. A 22.5 cm Chiralcel-OD column was used with a 0.1% diethylamine/5% ethanol/hexane mobile phase and a flow rate of 0.5cm per minute. The alcohols were detected by uv (λ=254nm). The retention times are: chlorobenzyl alcohol 14.2 min. for the (S) enantiomer and 16.1 min. for the (R) enantiomer; 2-phenethanol 11.6 min. for the R enantiomer and 13.0 min. for the S enantiomer. Base line resolution was achieved for each enantiomer. The absolute configurations of the products were established by comparison of the signs of their specific rotation with known literature values.[1,2a]

Acknowledgements

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