Pergamon

Tetrahedron 54 (1998) 8827–8840

TETRAHEDRON

The Use of Phosphinamide N-Protecting Groups in the Diastereoselective Reduction of Ketones.

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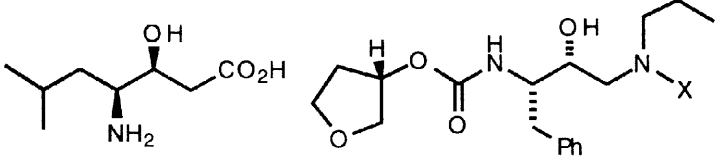
Received 15 April 1998; accepted 21 May 1998

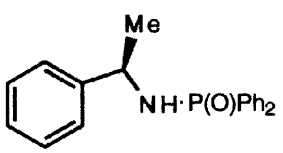
abstract; *The phosphinamide N-protecting group is demonstrated to be an effective directing group for diastereoselective reductions of proximal ketones. A range of methods for the preparation of the requisite α-amino ketones substrates are described.* © 1998 Elsevier Science Ltd. All rights reserved.

Diastereoselective reduction of α-amino ketones is an important chemical reaction which provides access to several classes of valuable target molecule. In particular peptide mimetics such as statine **1**,[1] the key component of the aspartic proteinase inhibitor pepstatin, and VX-478, **2**, a recently reported inhibitor of HIV-1 protease,[2] are potentially available by such methodology. An alternative approach to such target molecules involves the addition of nucleophiles to protected α-amino aldehydes.[3] In recent years a great deal of methodology has been developed for the stereoselective synthesis of such compounds and notable successes have been achieved. In all cases, however, the nature of the nitrogen protecting group is critical to the reaction; whilst not interfering adversely with the reaction, it must also be easily removable when required.[3] In this paper we report the use of phosphinamides as protecting groups for amines which also function as directing groups for the stereoselective reduction of proximal ketones.

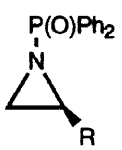


1

2 X=$SO_2(p\text{-}NH_2)C_6H_4$



3



4

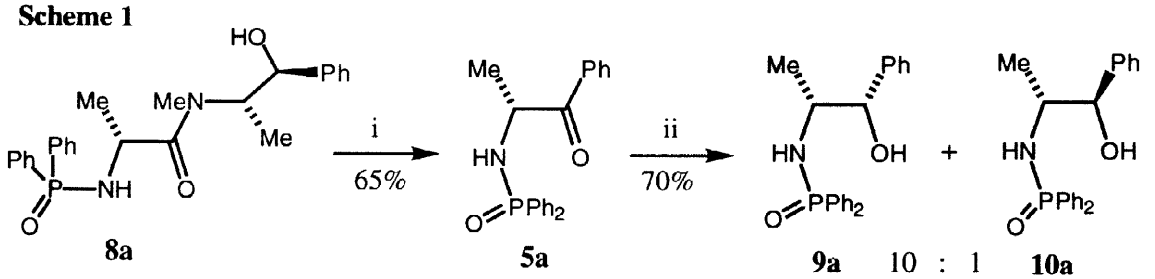
We have recently reported the preparation and use of phosphinamides such as **3** as catalysts for asymmetric reductions of ketones by borane.[4] However the use of phosphinamides as amine protecting groups, first reported by Ramage,[5] has been little exploited in synthetic chemistry. The very elegant recent work of Sweeney in the area of protected aziridines **4** provides a notable exception.[6] We wished to explore whether the phosphinamide group in protected α-amino ketones such as **5** could direct the stereochemical course of its reduction. However since we were mindful of the need to develop versatile methodology around this we also examined a number of methods for the efficient preparation of the requisite substrates.

PII: S0040-4020(98)00474-8

Using the method described by Myers,[7] we prepared a sample of the stereoselectively methylated derivative **7** of (1S,2S)-(+)-psuedoephedrine glycinamide **6** (73% yield). Phosphinylation of **7** was then carried out in 64% yield to give **8a** which was subsequently converted to the ketone **R-5** through the use of an excess of phenylmagnesium chloride (Scheme 1). Attempts to prepare the same ketones through Weinreb amides proved to be less successful in our hands. Myers[7a] had proved that, in the case of the analogous N-tBoc protected compounds, this method for ketone formation proceeds without racemisation. We anticipated, and will shortly demonstrate, that this is also the case for the sequence of key reactions described below.

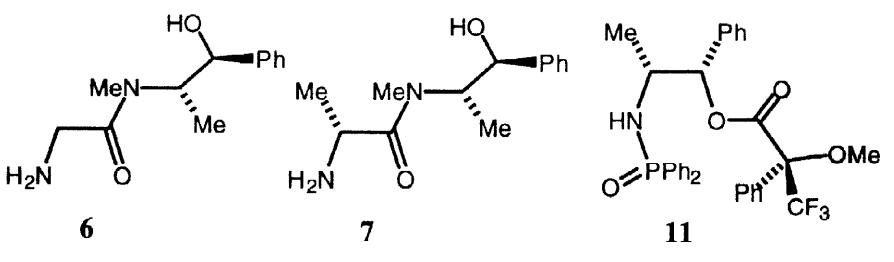
Reaction of R-**5a** with a stoichiometric quantity of borane-dimethylsulfide complex resulted in rapid and complete reduction to give alcohols **9a** and **10a** as a 10:1 ratio of diastereoisomers (Scheme 1). The assignment of the configurations of the chiral centres in the major isomer **9a** as 1S,2R was confirmed by the preparation of a sample of authenic material *via* direct N-phosphinylation of a sample of (1S,2R)-(+)-norephedrine (85%). The optical rotation values of the two samples of **9a** thus produced were essentially identical and this provided good evidence that no epimerisation had occured during the preparation of the ketone. However in order to confirm this each sample was independently converted to the corresponding Mosher ester derivative **11**, which were also exhibited identical spectroscopic and physical characteristics.[8]

Scheme 1



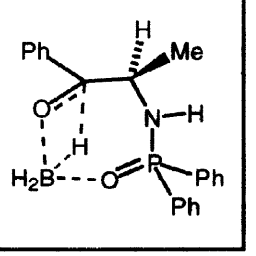
8a **5a** **9a** 10 : 1 **10a**

Reagents and conditions: i) 4 eq. PhMgCl, THF, 0°C to rt, 12 hrs. ii) 1.1 eq. $BH_3.SMe_2$, THF, 3 hrs.



6 **7** **11**

Figure 1

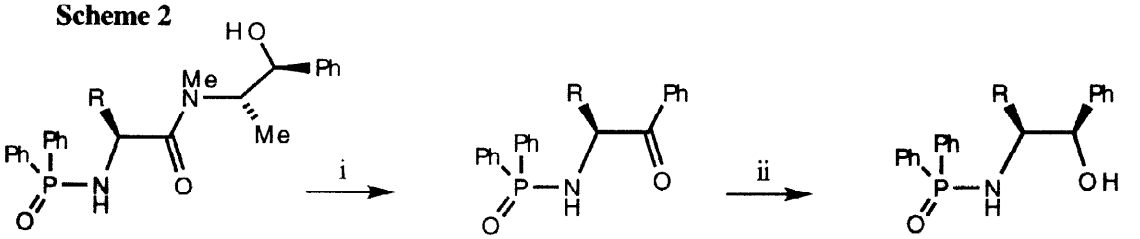


We have carried out a number of previous studies on phosphinamide catalysts[4] and it would be logical, in the light of our results, to assume that the phosphinamide promotes and directs the reduction *via* a donation of electron density from the oxygen atom to the borane[4] within a transition state similar to that shown in Figure 1. Evidence for such nucleophilic catalysis[4,9] was provided by the observation that sodium borohydride, which cannot benefit from electron donation from the phosphinamide, reduced **5** to give only a 2:1 mixture of diastereoisomeric products **9** and **10**. The reduction of the *t*-butoxycarbamate protected analogue of **5a**[10] proceeded with a selectivity of only 3.8:1 under the same conditions (70% yield), again emphasising the particular importance of the phospinamide directing group effect.

In order to demonstrate that amino acid derivatives may be employed as precursors we also prepared the α-amino ketones derived from valine and phenylalanine, **5b** and **5c** respectively. The former, **5b**, was

prepared by coupling of t-Boc protected valine with (1S,2S)-(+)-psudoephedrine[11] to give **12** followed by protecting group exchange and reaction with phenyllithium (31% yield from the protected valine). The latter ketone **5c** was obtained *via* the hydrolysis of the phosphinylated phenylalanine methyl ester **13** to acid **14**.[5] This product was then coupled to (1S,2S)-psuedoephedrine to give **8c** (71% yield) and subsequently converted to **5c**.[11] The reduction of both **5b** and **5c** (Scheme 2) proved to be even more selective than that of **5a** leading to products of high diastereoselectivity in high yield. In each case only one diastereoisomer of the reduction products, assigned the stereochemistry depicted in **9b** and **9c** respectively.

Scheme 2

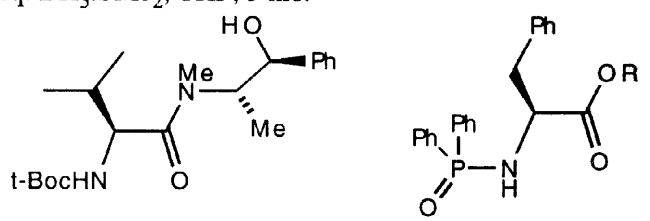


8b R=CH(Me)$_2$
8c R=CH$_2$Ph

5b R=CH(Me)$_2$, 33%
5c R=CH$_2$Ph, 79%

9b R=CH(Me)$_2$ 90%
9c R=CH$_2$Ph 89%

Reagents and conditions; i) 5 eq.PhLi, THF, -78-0°C, 6 hr (**8b**) or 5 eq. PhMgBr, THF, -78°C to rt, 12 hrs (**8c**). ii) 1.1 eq. BH$_3$.SMe$_2$, THF, 3 hrs.

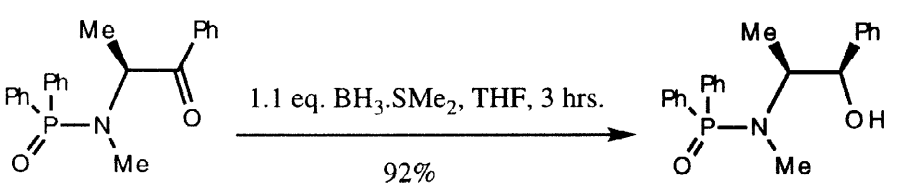


12

13, R=Me
14, R=H

A similarly high diastereoselectivity was observed in the analogous reaction of the N-methylated α-amino ketone **15** (Scheme 3). Upon treatment with borane in THF solvent a single diastereoisomer of product, **16**, was formed. The relative stereochemistry of **16** was confirmed by phosphinylation of a sample of (1R,2S)-(-)-ephedrine,[13] which gave a product with identical spectroscopic and physical characteristics.[14] The specific rotations of the two samples of **16** thus formed were essentially identical, confirming that no racemisation had taken place during the reduction sequence.

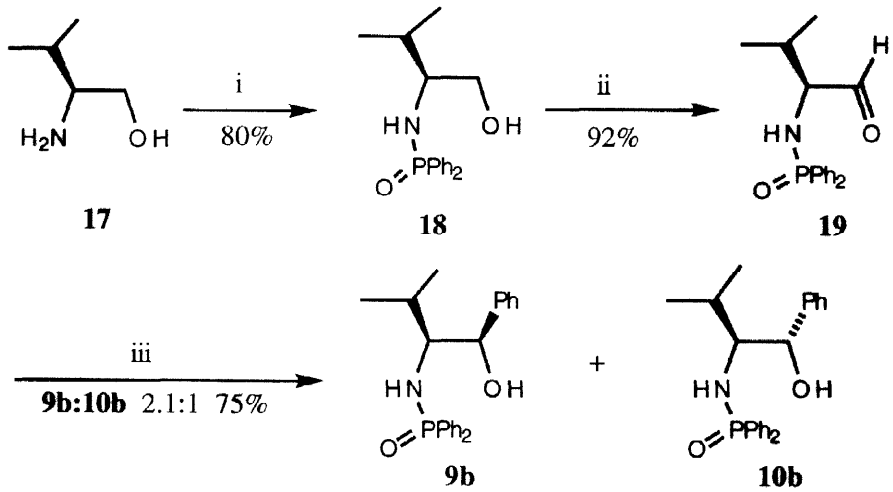
Scheme 3



15 **16**

In order to investigate the use of a phosphinamide to direct other reactions with adjacent carbonyl groups we prepared derivative **19** from L-valinol **17** and diphenylphosphinic chloride / triethylamine to give **18**, followed by oxidation. The oxidation step to the aldehyde was rather troublesome due to problems of overoxidation with most reagents (TPAP, Swern, PDC). After some experimentation, however, the Dess-Martin periodinane reagent[11] proved ideal for this reaction (Scheme 4).

Scheme 4



Reagents and conditions; i) $Ph_2P(O)Cl$, Et_3N, CH_2Cl_2, rt. ii) Dess-Martin periodinate, CH_2Cl_2, iii) PhMgBr, THF, -78°C to rt, o/n.

Addition of phenylmagnesium bromide to **19** gave a mixture of **9b** and its diastereoisomer **10b** in good yield but poor poor selectivity. The lack of stereocontrol in this step was disappointing, and clearly indicates that the diphenylphosphinyl group is inferior to certain other groups, such as dibenzyl, for this application.[3b-d]

It is noteworthy that protected amino alcohols **9a/10a** and **10b/10b** could be oxidised to the corresponding ketones **5a** and **5b** in 73 and 93% yields respectively, thus providing another alternative sequence for preparation of reduction substrates. This latter sequence may prove useful when alternative starting materials are unavailable.

In conclusion we have demonstrated that the diphenylphosphinyl group may be employed both as a N-protecting group and as a directing and activating group for the stereoselective reduction of adjacent ketones by borane. A sequence of reactions has been developed which permits a range of diastereoisomerically pure β-amino alcohols to be prepared through alkylation of readily available glycine derivatives or directly from α-amino acids. In view of the known ease of removal of the diphenylphosphinyl group (dilute acid)[5] this represents a valuable new approach to the stereoselective synthesis of chiral amino alcohols. We are presently investigating applications of this new methodology to the synthesis of relevant target molecules, including **2**, which will be reported in detail in due course.

Experimental Section

Diethyl ether and tetrahydrofuran were freshly distilled from sodium benzophenone ketyl under nitrogen. Toluene was freshly distilled from sodium under nitrogen. Dichloromethane was freshly distilled from calcium hydride under nitrogen. Methanol was freshly distilled from magnesium sulfate under nitrogen. Dimethylformamide was distilled under reduced pressure (water aspirator) from magnesium sulfate and stored over activated 4Å molecular sieves under an atmosphere of nitrogen. Propan-2-ol (HPLC grade) was

degassed prior to use. All other solvents were used as supplied unless otherwise stated. Petroleum ether refers to that fraction which boils in the range 40-60 °C.

All reactions, unless otherwise stated, were run under an atmosphere of nitrogen in flame or oven dried glassware (Schlenk tubes or round bottomed flasks). Reactions were monitored by TLC using aluminium backed silica gel 60 (F_{254}) plates, visualised using UV_{254nm} and PMA, ninhydrin or permanganate dips as appropriate. Flash column chromatography[16] was carried out routinely using 60Å silica gel (Merck).

Reagents were used as received from commercial sources (Aldrich, Fluka or Lancaster) unless otherwise stated. Butyllithium reagents were titrated against 1,3-diphenylacetone *p*-tosylhydrazone in THF at 0 °C to obtain an accurate measure of molarity.[17]

NMR spectra were recorded on a Bruker AC-250 (250 MHz), Bruker ACF400 (400 MHz), Jeol GX270 (270 MHz) or Jeol EX400 (400 MHz) spectrometer. The spectra were for solutions in deuterated chloroform ($CDCl_3$) unless otherwise stated. ^{13}C spectra were routinely run proton-decoupled. DEPT (90 or 135) techniques were used to aid interpretation of ^{13}C spectra. IR spectra were recorded on a Perkin-Elmer 1310 FTIR instrument either as liquid films or nujol mulls between sodium chloride plates. Mass spectra (EI or CI) were recorded on a 7070E VG mass spectrometer. High resolution mass spectra (CI) were recorded by the EPSRC MS service at the university of Swansea. Melting points were recorded on a Stuart Scientific SMP1 instrument and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter (sodium D line) with a 1 cm rotation cell. $[\alpha]_D$ values are reported as 10^{-1} deg cm^2 g^{-1}. Microanalysis was carried out on a Carlo Erba 1106 elemental analyser.

(1S,2S)-(+)-pseudoephedrine N-diphenylphosphinyl-D-alaninamide (**8a**)

To a solution of **7**[7] (1.0 g, 1.0 eq, 4.24 mmol) in dichloromethane (60 ml) at 0 °C was added successively triethylamine (1.48 ml, 2.50 eq, 10.60 mmol) and diphenylphosphinic chloride (0.81 ml, 1.0 eq, 4.24 mmol). The mixture was warmed to room temperature and stirred for 16 hours. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate (50 ml)/water (50 ml). The separated aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed successively with water (100 ml) and brine (100 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **8a** as a white solid (1.18 g, 64%); mp 70-72 °C; $[\alpha]_D^{30}$ +41.0 (c 0.51, MeOH); ^1H-NMR (400 MHz, $CDCl_3$, 2.6:1 ratio of rotamers, * denotes minor rotamer): δ 7.90-7.71 (4H, m, aryl H), 7.50-7.11 (11H, m, aryl H), 4.66 (0.7H, br s, OH), 4.56 (0.8H, d, J 8.6, CH), 4.43* (0.3H, d, J 8.8, CH), 4.25 (0.3H, br s), 4.14-4.01 (2.5H, m), 3.62 (0.4H, m), 2.85* (0.8H, s, NCH_3), 2.72 (2.2H, s, NCH_3), 1.44* (0.8H, d, J 6.0, CH_3), 1.25 (2.2H, d, J 6.0, CH_3), 0.90 (2.2H, d, J 6.9, CH_3), 0.51* (0.8H, d, J 6.6, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.4 (C=O), 174.6* (C=O), 141.9, 141.8*, 132.9, 132.7, 132.5, 132.4, 132.3, 132.2, 132.1, 132.0, 131.9, 131.8, 131.6, 131.4, 131.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.7, 126.9, 75.5 (CH), 74.8* (CH), 58.1 (CH), 46.5 (CH), 46.3* (CH), 27.1 (NCH_3), 22.3* (CH_3), 20.8 (CH_3), 15.0* (CH_3), 14.5 (CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 25.2, 23.5*; HRMS: calc for $C_{25}H_{30}N_2O_3P$: 437.1994 ($[M+H]^+$). found 437.1994.

(R)-(+)-2-(N-diphenylphosphinyl)aminopropiophenone (**5a**)

To a solution of **8a** (145 mg, 0.33 mmol) in THF (1 ml) at 0 °C was added phenylmagnesium chloride (0.66 ml, 4.0 eq, 1.32 mmol, 2.0 M in THF) dropwise. The solution was warmed to room temperature and stirred for 5 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (1 ml). The aqueous layer was extracted with ethyl acetate (3 x 15 ml) and the combined organic extracts were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (80% v/v ethyl acetate/hexane) to afford **5a** as a white solid (72 mg, 65%); $[\alpha]_D^{26}$ +8.70 (c 0.23, MeOH). The identity of the product was confirmed by comparison of its spectroscopic data to that of a sample prepared by oxidation of **9a** (see below).

(R)-(+)-2-(N-diphenylphosphinyl)aminopropiophenone (**5a**) by reduction of **9a**

Tetrapropylammonium perruthenate (127 mg, 0.05 eq, 0.36 mmol) was added portionwise to a stirred mixture of **9a** (2.50 g, 1.0 eq, 7.11 mmol), N-methylmorpholine-N-oxide (1.25 g, 1.50 eq, 10.67 mmol) and powdered 4Å molecular sieves (3.50 g) in dichloromethane (14 ml) at room temperature. The mixture was stirred for 2 hours, then diluted with dichloromethane and suction filtered through celite. The filtrate was concentrated *in vacuo* and the crude product was purified by flash column chromatography (ethyl acetate) and recrystallised from dichloromethane/petrol to afford **5a** as a white solid (1.81 g, 73%); mp 124-127 °C; $[\alpha]_D^{26}$ +7.1 (c 0.35, MeOH); IR (nujol): υ 3174, 2360, 1686, 1593, 1298, 1222, 1179, 1124 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.97-7.79 (6H, m, aryl H), 7.61-7.40 (9H, m, aryl H), 4.95 (1H, m, C*H*(CH_3)), 4.31 (1H, br t, J 9.5, NH), 1.45 (3H, d, J 7.2, CH_3); ^{13}C-NMR (68 MHz, $CDCl_3$): δ 200.0 (C=O), 133.7, 133.6, 133.2, 132.0, 131.9, 131.8, 131.3, 128.7, 128.6, 128.5, 128.4, 128.3, 50.8 (*C*HCH_3), 23.0 (CH_3); ^{31}P-NMR (68 MHz, $CDCl_3$): δ 23.7; MS: *m/z* (CI) 350 ($[M+H]^+$, 100%), 244 (75%), 218 (50%), 201 (40%), 135 (22%),105 (21%); HRMS: calc for $C_{21}H_{21}NO2P$: 350.1310 ($[M+H]^+$). found 350.1321.

Reduction of **5a** by borane-DMS complex

To a stirred solution of **5a** (66 mg, 0.19 mmol) in THF (2 ml) at room temperature was added borane-dimethyl sulfide complex (0.019 ml, 1.0 eq, 0.19 mmol, ca. 10.0 M) dropwise. The reaction was stirred for one hour and quenched by the addition of saturated aqueous ammonium chloride solution (2 ml). The separated aqueous layer was extracted with ether (3 x 5 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (60% v/v ethyl acetate/petrol) to afford a white solid (44 mg, 70%) as a 10:1 diastereomeric mixture (major product is **9a**). The identity of **9a** was confirmed by comparison to an authentic sample prepared by the phosphinylation of (1S,2R)-(+)-norephedrine (see below).

(1S,2R)-(-)-(N-diphenylphosphinyl)norephedrine (**9a**)

To a stirred solution of (1S,2R)-(+)-norephedrine (2.00 g, 13.23 mmol) in dichloromethane (100 ml) at 0 °C was added successively triethylamine (7.38 ml, 4.0 eq, 52.92 mmol) and diphenylphosphinic chloride (2.78 ml, 1.10 eq, 14.55 mmol) dropwise. The mixture was slowly warmed to room temperature and stirred for 20 hours. Saturated aqueous ammonium chloride solution (100 ml) was added to the solution and the separated aqueous layer extracted with dichloromethane (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (20->70% v/v ethyl acetate/petrol) to afford **9a** as a white solid (3.97 g, 85%); mp 155-158 °C; analysis ($C_{21}H_{22}NO_2P$): calc. C 71.78, H 6.31, N 3.99. found C 71.90, H 6.30, N 3.98; $[\alpha]_D^{26}$ -34.5 (c 1.0, MeOH); IR (nujol): υ 3207, 2671, 1603, 1170, 1099, 1013, 970 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.99-7.78 (4H, m, aryl H), 7.56-7.23 (11H, m, aryl H), 5.76 (1H, d, J 9.0, OH), 4.74 (1H, d, J 8.7, C*H*OH), 3.61-3.45 (1H, m, C*H*(CH_3)), 2.87-2.80 (1H, m, NH), 1.09 (3H, d, J 7.0, CH_3); ^{13}C-NMR (68 MHz, $CDCl_3$): δ 141.1, 132.5, 132.4, 131.9, 131.6, 131.5, 128.7, 128.5, 128.3, 127.8, 126.9, 126.8, 76.8, 53.8, 17.9; ^{31}P-NMR (109 MHz, $CDCl_3$): δ 26.5; MS: *m/z* (CI) 352 ($[M+H]^+$, 52%), 334 (39%), 272 (33%), 244 (87%), 201 (100%), 178 (68%), 134 (58%), 107 (77%), 91 (60%), 79 (71%).

(1S,2S)-(+)-pseudoephedrine N-diphenylphosphinyl-L-valinamide (**8b**)

To a solution of N-(*tert*-butoxycarbonyl)-L-valine (2.00 g, 1.0 eq, 9.22 mmol) in dichloromethane (35 ml) at 0 °C was added successively triethylamine (1.54 ml, 1.20 eq, 11.06 mmol) and pivaloyl chloride (1.14 ml, 1.0 eq, 9.22 mmol). The mixture was stirred at 0 °C for 30 minutes and then triethylamine (1.54 ml, 1.20 eq, 11.06 mmol) and (1S,2S)-(+)-pseudoephedrine (1.52 g, 1.0 eq, 9.22 mmol) were added at the same temperature. The mixture was stirred at 0 °C for one hour and then concentrated *in vacuo* to give crude **12**. The residue was dissolved in methanol (30 ml)/water (30 ml) and cooled to 0 °C. To the solution was added concentrated hydrochloric acid (20 ml) and mixture was stirred at 0 °C for 4 hours. The solvent was removed *in vacuo* and the residue basified to pH 14 at 0 °C by the addition of 50% w/v aqueous sodium hydroxide solution. The aqueous solution was extracted with chloroform (4 x 100 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a clear oil, which was then dissolved in dichloromethane (50 ml) and cooled to 0 °C. To this solution was added successively triethylamine (5.0 ml, 4.0 eq (based on crude yield of N-Boc-deprotected product), 36.0 mmol) and diphenylphosphinic chloride (1.90 ml, 1.10 eq, 9.90 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The solution was then concentrated *in vacuo* and the residue dissolved in ethyl acetate (100 ml) and water (100 ml). The separated aqueous layer was extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford **8b** as a white solid (1.31 g, 31% overall yield from protected valine); mp 79-82 °C; $[\alpha]_D^{30}$ +35.8 (c 1.0, MeOH); IR (nujol): υ 3262, 1624, 1192, 1123 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$, 1.3:1 ratio of rotamers, * denotes minor rotamer): δ 8.12-7.75 (4H, m, aryl H), 7.57-7.26 (11H, m, aryl), 6.05 (0.5H, br s), 4.94 (0.5H, br s), 4.44 (0.5H, d, J 8.0), 4.09-3.85 (3H, m), 3.59 (0.5H, m), 3.03 (1.7H, s, NCH_3), 2.84* (1.3H, s, NCH_3), 1.94 (0.55H, m, C*H*(CH_3)$_2$), 1.83* (0.45H, m,

C*H*(CH_3)$_2$), 1.10 (1.6H, d, J 7.0, CH_3), 1.03* (1.4H, d, J 7.0, CH_3), 0.95 (3.6H, d, J 4.7, CH(C*H*$_3$)$_2$), 0.85* (2.4H, d, J 6.7, CH(C*H*$_3$)$_2$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.7 (C=O), 174.3* (C=O), 142.7, 142.5, 133.0, 132.2, 132.1, 132.0, 131.4, 131.3, 128.7, 128.6, 128.5, 128.4, 128.3, 127.7, 127.5, 127.3, 126.8, 76.0 (CH), 75.0* (CH), 58.8 (CH), 56.3* (CH), 55.5 (CH), 33.2 (CH), 32.2* (CH), 27.2 (NCH_3), 19.4 (CH_3), 18.1* (CH_3), 16.0 (CH_3), 14.4 (CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 27.4, 24.4*; MS: *m/z* (CI) 465 ([M+H]$^+$, 91%), 331 (32%), 272 (100%), 218 (65%), 148 (35%), 100 (74%), 78 (71%), 58 (65%), 44 (60%); HRMS: calc for $C_{27}H_{34}N_2O_3P$: 465.2307 ([M+H]$^+$). found 465.2307.

(S)-(-)-(N-diphenylphosphinyl)phenylalanine methyl ester **13**[5b]

To a stirred mixture of L-phenylalanine methyl ester hydrochloride (1.13 g, 5.24 mmol) in dichloromethane (50 ml) at 0 °C was added triethylamine (1.83 ml, 2.5 eq, 13.1 mmol) and diphenylphosphinic chloride (1.00 ml, 1.0 eq, 5.24 mmol). The mixture was slowly warmed to room temperature and stirred for 18 hours. The solvent was removed *in vacuo* to leave a crude solid which was partitioned between ethyl acetate (80 ml) and water (50 ml). The separated aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution (50 ml), 5% w/v aqueous citric acid solution (50 ml), water (50 ml), saturated aqueous sodium bicarbonate solution (50 ml), water (50 ml) and brine (50 ml). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (70% v/v ethyl acetate/petrol) to afford **13** was a white solid (1.70 g, 86%); $[\alpha]_D^{28}$ -51.6 (c 1.0, MeOH) (lit[5b] $[\alpha]_D^{25}$ -49.7 (c 1.0, MeOH)); ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.87-7.13 (15H, m, aryl H), 4.08 (1H, m, C*H*Bn), 3.59 (3H, s, OCH_3), 3.50 (1H, m, NH), 3.10 (2H, d, J 6.1, C*H*$_2$Ph).

(S)-(-)-(N-diphenylphosphinyl)phenylalanine **14**[5b]

To a stirred solution of **13** (2.00 g, 5.28 mmol) in THF (12 ml) at room temperature was added aqueous sodium hydroxide solution (2.90 ml, 1.10 eq, 5.81 mmol, 2.0 M). The mixture was stirred for 30 minutes at room temperature and then the solvent was removed *in vacuo*. The residual solution was acidified to pH 3-4 by the addition of saturated aqueous citric acid solution. The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic extracts were washed successively with water (5 ml) and brine (5 ml). The organic solution was dried ($MgSO_4$) and concentrated *in vacuo* to afford **14** white solid (1.93 g, quant); $[\alpha]_D^{26}$ -34.6 (c 1.0, MeOH) (lit[19] $[\alpha]_D^{25}$ -40.1 (c 1.0, MeOH)); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.50-8.50 (1H, br s, CO_2H), 7.83-7.15 (15H, m, aryl H), 3.91-3.63 (2H, m, NH and C*H*Bn), 3.15 (1H, m, C*H*H), 2.85 (1H, dd, J 13.0 and 8.0, CH*H*).

(1S,2S)-(+)-pseudoephedrine N-diphenylphosphinyl-L-phenylalaninamide (**8c**)

This compound was prepared according to the procedure employed for **8b** using **14** (800 mg, 1.0 eq, 2.19 mmol), pivaloyl chloride (0.27 ml, 1.0 eq, 2.19 mmol), triethylamine (2 x 0.37 ml, 1.20 eq, 2.63 mmol) and (1S,2S)-(+)-pseudoephedrine (362 mg, 1.0 eq, 2.19 mmol) in dichloromethane (5 ml) at 16 hours at room temperature. The product **8c** was isolated as a white solid (793 mg, 71%); mp 80-82 °C; $[\alpha]_D^{28}$ +23.3 (c

1.0, MeOH); IR (nujol): υ 3245, 1626, 1188, 1124, 1110, 1078 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, 3:1 ratio of rotamers, * denotes minor rotamer): δ 7.98-6.98 (20H, m, aryl H), 6.02 (0.75H, br s), 4.94 (0.25H, br d, J 8.0), 4.42-4.00 (3H, m), 3.79-3.72 (1H, m), 3.16* (0.75H, dd, J 12.7 and 9.2, CHH), 3.03-2.95 (1.25H, m, CHH), 2.87 (2.25H, s, NCH_3), 2.51* (0.75H, s, NCH_3), 1.02* (0.75H, d, J 7.0, CH_3), 0.19 (2.25H, d, J 6.7, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.1* (C=O), 173.8 (C=O), 142.8, 142.2*, 136.8, 136.7*, 132.9, 132.8, 132.3, 132.2, 132.1, 131.9, 131.8, 131.4, 131.3, 131.1, 130.8, 129.7, 129.4, 128.9, 128.7, 128.6, 128.4, 128.3, 127.6, 127.3, 127.1, 126.9, 75.9 (CH), 74.7* (CH), 59.0 (CH), 52.8* (CH), 51.7 (CH), 42.7 (CH_2), 41.6* (CH_2), 27.0 (NCH_3), 22.7* (NCH_3), 15.0 (CH_3), 14.3* (CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 27.0*, 24.7; MS: *m/z* (CI) 513 ($[M+H]^+$, 37%), 379 (32%), 320 (100%), 278 (79%), 254 (54%); HRMS: calc for $C_{31}H_{34}N_2O_3P$: 513.2307 ($[M+H]^+$). found 513.2307.

(S)-(+)-2-(N-diphenylphosphinyl)amino-3-methylbutyrophenone (**5b**)

This compound was prepared according to the procedure employed for **5a** using **8b** (200 mg, 0.43 mmol) and PhLi (1.31 ml, 5.0 eq, 2.16 mmol, 1.64 M in cyclohexane/ether) in THF (2.5 ml) for 4 hours at 0 °C. The product **5b** was a white solid (52 mg, 33% (44% based on recovered **8b**)); $[\alpha]_D^{24}$ +35.0 (c 0.50, MeOH). The identity of **5b** was confirmed by comparison to a sample prepared by oxidation of a mixture of **9b/10b** (see below).

(S)-(+)-2-(N-diphenylphosphinyl)amino-3-methylbutyrophenone (**5b**) *via* oxidation of a mixture of **9b/10b** formed in the Grignard addition reaction in Scheme 4.

Tetrapropylammonium perruthenate (6 mg, 0.05 eq, 0.017 mmol) was added to a stirred mixture of **9b/10b** (127 mg, 0.34 mmol), NMO (59 mg, 1.50 eq, 0.50 mmol) and powdered 4Å molecular sieves (170 mg) in dichloromethane (2 ml) at room temperature. The mixture was stirred for 2 hours at room temperature and then directly eluted through a short silica gel column with ethyl acetate to afford **5b** as a white solid which was recrystallised from dichloromethane/petrol (117 mg, 93%); mp 169-170 °C; $[\alpha]_D^{26}$ +46.5 (c 0.60, MeOH); IR (nujol): υ 3273, 1688, 1192, 1126 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.95-7.72 (6H, m, aryl H), 7.58-7.31 (9H, m, aryl H), 4.69 (1H, dt, J 10.6 and 3.7, C*H*^{i}Pr), 4.05 (1H, t, J 10.6, NH), 2.10-2.01 (1H, m, C*H*$(CH_3)_2$), 1.07 (3H, d, J 6.8, CH_3), 0.79 (3H, d, J 6.8, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.0 (C=O), 135.4, 133.8, 133.6, 132.9, 132.5, 132.3, 132.2, 132.0, 131.9, 131.8, 131.7, 128.8, 128.6, 128.5, 128.3, 59.9, 32.1, 20.2, 16.4; ^{31}P-NMR (109 MHz, $CDCl_3$): δ 24.4; MS: *m/z* (CI) 378 ($[M+H]^+$, 100%), 272 (62%), 218 (89%), 201 (27%), 163 (69%), 145 (20%), 83 (27%), 69 (43%); HRMS: calc for $C_{23}H_{25}NO_2P$: 378.1623 ($[M+H]^+$). found 378.1623.

(S)-(+)-2-(N-diphenylphosphinyl)amino-3-phenylpropiophenone (**5c**)

This compound was prepared according to the procedure employed for **5a** using **8c** (400 mg, 0.78 mmol) and PhMgCl (1.95 ml, 5.0 eq, 3.91 mmol, 2.0 M in THF) in THF (3 ml) for 12 hours at room temperature. The

product **5c** was a white solid (263 mg, 79%); mp 85-86 °C; $[\alpha]_D^{26}$ +28.6 (c 0.56, MeOH); IR (nujol): υ 1682, 1181, 1080 cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 7.84-7.68 (6H, m, aryl H), 7.59-7.34 (9H, m, aryl H), 7.26-7.16 (3H, m, aryl H), 7.05-7.02 (2H, m, aryl H), 5.16-5.03 (1H, m, C*H*Bn), 4.00 (1H, br t, J 9.0, NH), 3.24 (1H, dd, J 13.7 and 6.1, C*H*H), 3.05 (1H, dd, J 13.7 and 5.5, CH*H*); ^{13}C-NMR (63 MHz, $CDCl_3$): δ 199.3 (C=O), 135.6, 134.7, 133.6, 133.1, 132.1, 132.0, 131.8, 131.7, 131.4, 129.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 126.8, 55.8 (*C*HBn), 41.7 (CH_2); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 24.3; MS: *m/z* (CI) 426 ([M+H]$^+$, 100%), 320 (40%), 218 (29%); HRMS: calc for $C_{27}H_{25}NO_2P$: 426.1623 ([M+H]$^+$). found 426.1623.

Reduction of **5b** with borane-DMS complex

This was performed according to the procedure employed for **5a** using **5b** (58 mg, 0.15 mmol) and $BH_3.SMe_2$ (0.017 ml, 1.10 eq, 0.165 mmol, ca. 10.0 M) in THF (1.5 ml) for 8 hours at room temperature. Product was a white solid (52 mg, 90%) as a >25:<1 diastereomeric mixture (major product is *cis*-**9b**); mp 180-182 °C; $[\alpha]_D^{26}$ +11.4 (c 0.35, MeOH); IR (nujol): υ 3284, 1167, 1124, 1065 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 8.00-7.88 (4H, m, aryl H), 7.56-7.41 (8H, m, aryl H), 7.34-7.20 (3H, m, aryl H), 6.44 (1H, br d, J 10.7, OH), 4.98 (1H, br d, J 8.9, C*H*OH), 3.00-2.93 (1H, m, C*H*^{i}Pr), 2.59 (1H, dd, J 7.1 and 5.1, NH), 1.52-1.44 (1H, m, C*H*$(CH_3)_2$), 1.06 (3H, d, J 6.6, CH_3), 0.93 (3H, d, J 6.6, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 140.5, 133.1, 132.3, 132.1, 131.7, 130.7, 129.3, 128.7, 128.4, 128.0, 127.4, 127.2, 73.6, 64.6, 30.5, 21.3, 20.2; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 26.1; MS: *m/z* (CI) 380 ([M+H]$^+$, 100%), 362 (34%), 272 (77%), 201 (30%), 162 (20%), 107 (59%), 69 (72%); HRMS: calc for $C_{23}H_{27}NO_2P$: 380.1779 ([M+H]$^+$). found 380.1779.

Reduction of **5c** with borane-DMS complex

This was performed according to the procedure employed for **5a** using **5c** (35 mg, 0.08 mmol) and $BH_3.SMe_2$ (0.04 ml, 1.10 eq, 0.09 mmol, 2.0 M in toluene) in THF (1.0 ml) for 12 hours at room temperature. Product was a white solid (31 mg, 89%) as a >25:1 diastereomeric mixture (major product is *cis*-**9c**); mp 150-154 °C; $[\alpha]_D^{28}$ -11.0 (c 0.40, MeOH); IR (nujol): υ 3201, 1191, 1123, 1084 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.73-7.63 (2H, m, aryl H), 7.48-7.14 (16 H, m, aryl H), 7.06-7.02 (2H, m, aryl H), 6.34 (1H, d, J 9.6, OH), 4.94 (1H, m, C*H*OH), 3.55-3.43 (1H, m, C*H*Bn), 2.92-2.83 (2H, m, CH_2), 2.44-2.33 (1H, m, NH); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 140.6, 138.8, 132.8, 132.6, 132.0, 131.6, 131.5, 130.4, 128.6, 128.2, 127.1, 126.4, 76.5, 60.9, 38.8; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 26.9; MS: *m/z* (CI) 428 ([M+H]$^+$, 21%), 366 (100%), 258 (33%), 210 (41%), 148 (22%), 58 (31%); HRMS: calc for $C_{27}H_{27}NO_2P$: 428.1779 ([M+H]$^+$). found 428.1779.

(1R,2S)-(+)-(N-diphenylphosphinyl)ephedrine (**16**) (authentic sample).

This compound was prepared according to the procedure employed for **9a** using (1R,2S)-(-)-ephedrine (0.50 g, 3.03 mmol), $Ph_2P(O)Cl$ (0.58 ml, 1.0 eq, 3.03 mmol) and Et_3N (1.70 ml, 4.0 eq, 12.12 mmol) in CH_2Cl_2 (20 ml) for 18 hours at room temperature. Product **16** was a white solid (283 mg, 25%); mp 199-202 °C; analysis ($C_{22}H_{24}NO_2P$): calc. C 72.31, H 6.62, N 3.83. found C 72.30, H 6.50, N 3.79; $[\alpha]_D^{24}$ +64.6 (c 1.0, MeOH); IR (nujol): υ 3234, 2692, 1590, 1045, 1003 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.61-7.38 (15H, m, aryl H), 4.85 (1H, d, J 4.2, C*H*OH), 4.60 (1H, br s, OH), 3.72-3.64 (1H, m, C*H*CH_3), 2.44 (3H, d, J 10.8, NCH_3), 1.25 (3H, d, J 7.0, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.6, 132.4, 132.3, 132.2, 132.0, 131.8, 131.1, 130.7, 128.6, 128.5, 128.4, 128.0, 127.2, 126.5, 76.7, 58.0, 30.9, 13.6; ^{31}P-NMR (109 MHz, $CDCl_3$): δ 34.4; MS: *m/z* (CI) 366 ([M+H]$^+$, 70%), 348 (24%), 258 (64%), 201 (26%), 107 (37%), 79 (46%), 69 (100%).

(1R,2S)-(+)-(N-diphenylphosphinyl)ephedrine (**16**) by ring-opening process

To a solution of the prerequisite *cis*-oxazaphospholidine oxide[18] (100 mg, 0.35 mmol) in THF (1.5 ml) at -30 °C was added phenylmagnesium chloride (0.44 ml, 2.50 eq, 0.88 mmol, 2.0 M in THF). The solution was warmed to room temperature and stirred for 22 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (0.5 ml). The aqueous layer was extracted with ether (3 x 10 ml) and the combined organic extracts were washed with brine (10 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (5% v/v MeOH/dichloromethane) to afford **16** as a white solid (80 mg, 63%).

(S)-(-)-2-(N-diphenylphosphinyl-N-methyl)aminopropiophenone (**15**)

This compound was prepared according to the procedure employed for **5a** using **16** (69 mg, 1.0 eq, 0.19 mmol), TPAP (3.3 mg, 0.05 eq, 0.0095 mmol), NMO (33 mg, 1.50 eq, 0.29 mmol) and powdered 4Å molecular sieves (95 mg) in CH_2Cl_2 (1.8 ml) for 30 minutes at room temperature. Product **15** was a clear gum (59 mg, 86%); $[\alpha]_D^{28}$ -5.3 (c 0.08, MeOH); IR (nujol): υ 3434, 1688, 1596, 1198, 1121 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.98 (2H, d, J 7.3, aryl H), 7.82-7.77 (2H, m, aryl H), 7.56-7.40 (9H, m, aryl H), 7.32 (2H, dt, J 7.6 and 3.1, aryl H), 5.48 (1H, m, C*H*CH_3), 2.51 (3H, d, J 10.8, NCH_3), 1.37 (3H, d, J 7.0, CH_3); ^{13}C-NMR (68 MHz, $CDCl_3$): δ 200.1 (C=O), 135.7, 133.0, 132.2, 132.1, 132.0, 131.9, 131.8, 131.0, 130.5, 128.7, 128.5, 128.4, 52.9 (*C*HCH_3), 29.6 (NCH_3), 14.2 (CH_3); ^{31}P-NMR (162 MHz, $CDCl_3$): δ 32.4; MS: *m/z* (CI) 364 ([M+H]$^+$, 100%), 258 (48%), 232 (55%), 171 (70%), 133 (66%), 105 (33%); HRMS: calc for $C_{22}H_{23}NO_2P$: 364.1466 ([M+H]$^+$). found 364.1466.

Reduction of **15** using borane-DMS complex This was performed according to the procedure employed for **5a** using **15** (82 mg, 0.23 mmol) and $BH_3.SMe_2$ (0.023 ml, 1.0 eq, 0.23 mmol, ca. 10.0 M) in THF (3 ml) for 6 hours at room temperature. The product was a white solid (78 mg, 77%) apprantly as a single diastereosiomer **16**.

(S)-(-)-(N-diphenylphosphinyl)valinol (**18**)

This compound was prepared according to the procedure employed for **9a** using L-valinol **17** (1.16 g, 11.22 mmol), $Ph_2P(O)Cl$ (2.14 ml, 1.0 eq, 11.22 mmol) and Et_3N (6.26 ml, 4.0 eq, 44.90 mmol) in CH_2Cl_2 (75 ml) for 16 hours at room temperature. Product **18** was a white solid (2.72 mg, 80%); mp 135-136 °C; analysis ($C_{17}H_{22}NO_2P$): calc. C 67.31, H 7.31, N 4.62. found C 67.20, H 7.22, N 4.57; $[\alpha]_D^{26}$ -40.8 (c 1.0, MeOH); IR (nujol): υ 3361, 3236, 1436, 1157, 1103, 1022 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 7.98-7.88 (4H, m, aryl H), 7.54-7.40 (6H, m, aryl H), 5.20 (1H, d, J 7.5, OH), 3.66 (1H, m, C*H*H), 3.53 (1H, m, CH*H*), 3.06 (1H, dd, J 11.3 and 3.3, NH), 2.86-2.79 (1H, m, C*H*^{i}Pr), 1.81 (1H, septet, J 6.6, C*H*$(CH_3)_2$), 0.95 (6H, t, J 6.6, CH$(CH_3)_2$); ^{13}C-NMR (68 MHz, $CDCl_3$): δ 133.3, 132.8, 132.7, 132.1, 131.9, 131.8, 131.7, 131.5, 129.9, 128.7, 128.5, 128.3, 66.0, 60.6, 31.1, 19.7, 18.4; ^{31}P-NMR (162 MHz, $CDCl_3$): δ 26.2; MS: *m/z* (CI) 304 ($[M+H]^+$, 100%), 286 (26%), 272 (22%), 203 (58%), 91 (35%), 79 (69%), 69 (94%).

(S)-(-)-2-(N-diphenylphosphinyl)amino-3-methylbutanal (**19**)

To a stirred solution of Dess-Martin periodinane[15] (700 mg, 2.0 eq, 1.66 mmol) in dichloromethane (7 ml) at room temperature was added a solution of **18** (250 mg, 1.0 eq, 0.83 mmol) in dichloromethane (4 ml) *via* cannula. The mixture was stirred for 2 hours at room temperature after which time it was diluted with ether (5 ml) and a 4:1 mixture (2.5 ml) of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium bicarbonate solution. After five minutes stirring the organic layer became clear and the separated aqueous layer was then extracted with ether (3 x 10 ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution (15 ml), water (15 ml) and brine (15 ml) before being dried ($MgSO_4$). The solvent was removed *in vacuo* and the product purified by flash column chromatography (ethyl acetate) to afford **19b** as a white solid (227 mg, 92%); mp 133-137 °C; analysis ($C_{17}H_{20}NO_2P$): calc. C 67.76, H 6.69, N 4.65. found C 67.50, H 6.67, N 4.59; $[\alpha]_D^{26}$ -36.3 (c 0.60, MeOH); IR (nujol): υ 3186, 2712, 2360, 1729, 1176, 1128, 1109, 1083 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$): δ 9.72 (1H, s, CHO), 7.93-7.79 (4H, m, aryl H), 7.55-7.40 (6H, m, aryl H), 3.88-3.72 (2H, m, C*H*^{i}Pr and NH), 2.27-2.21 (1H, m, C*H*$(CH_3)_2$), 1.03 (3H, d, J 7.0, CH_3), 0.97 (3H, d, J 7.0, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.0 (CHO), 133.2, 132.5, 132.2, 132.1, 132.0, 131.9, 131.8, 131.6, 131.3, 128.6, 128.5, 128.4, 64.7, 30.2, 18.7, 17.5; ^{31}P-NMR (109 MHz, $CDCl_3$): δ 24.5; MS: *m/z* (CI) 302 ($[M+H]^+$, 100%), 286 (10%), 272 (40%), 218 (23%0, 201 (33%), 72 (32%).

1-phenyl-2-(N-diphenylphosphinyl)amino-3-methylbutanol (**9b/10b**)

To a stirred solution of **19** (475 mg, 1.0 eq, 1.58 mmol) in THF (8 ml) at -78 °C was added dropwise freshly prepared phenylmagnesium bromide (9.50 ml, 2.0 eq, 3.15 mmol, ca. 0.3 M in ether). The mixture was stirred for one and a half hours at -78 °C after which time a further one equivalent of Grignard reagent was

added. Following stirring for an hour at -78 °C, two extra equivalents of Grignard reagent were added and the reaction was slowly warmed to room temperature. After a total of 5 hours the reaction was quenched by the dropwise addition of saturated aqueous ammonium chloride solution (8 ml). The aqueous layer was extracted with ether (3 x 20 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (70% v/v ethyl acetate/petrol) to afford a white solid **9b** and **10b** (476 mg, 75%) as an inseparable 2.1:1 *trans:cis* diastereomeric mixture.

major diastereomer (**9b**): ^{1}H-NMR (270 MHz, $CDCl_3$): δ 8.00-7.89 (4H, m, aryl H), 7.57-7.43 (7H, m, aryl H), 7.36-7.24 (4H, m, aryl H), 5.76 (1H, br s, OH), 4.52 (1H, d, J 5.3, C*H*OH), 3.01-2.96 (2H, NH and C*H*^{i}Pr), 1.53-1.40 (1H, m, C*H*$(CH_3)_2$), 0.86 (3H, d, J 6.8, CH_3), 0.80 (3H, d, J 6.8, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.2, 140.4, 133.1, 133.0, 132.9, 132.8, 132.6, 132.3, 132.0, 131.7, 131.6, 131.3, 131.2, 129.8, 128.8, 128.7, 128.5, 128.4, 128.0, 127.6, 127.4, 127.3, 126.9 (two diastereomers), 76.8, 64.4, 29.1, 21.1, 15.4; ^{31}P-NMR (109 MHz, $CDCl_3$): δ 27.5.

minor diastereomer (**10b**): ^{1}H-NMR (270 MHz, $CDCl_3$): δ 8.00-7.89 (4H, m, aryl H), 7.57-7.43 (7H, m, aryl H), 7.36-7.24 (4H, m, aryl H), 6.43 (1H, d, J 11.4, OH), 4.97 (1H, br d, J 8.0, C*H*OH), 3.01-2.96 (1H, m, C*H*^{i}Pr), 2.57-2.50 (1H, m, NH), 1.53-1.40 (1H, m, C*H*$(CH_3)_2$), 1.08 (3H, d, J 6.6, CH_3), 0.92 (3H, d, J 6.6, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.2, 140.4, 133.1, 133.0, 132.9, 132.8, 132.6, 132.3, 132.0, 131.7, 131.6, 131.3, 131.2, 129.8, 128.8, 128.7, 128.5, 128.4, 128.0, 127.6, 127.4, 127.3, 126.9 (two diastereomers), 73.6, 64.7, 30.5, 21.3, 20.3; ^{31}P-NMR (109 MHz, $CDCl_3$): δ 27.0.

Acknowledgment

We thank the EPSRC and SmithKline Beecham (Tonbridge) for generous funding of this project and Dr J. Ballantine (EPSRC Mass Spectrometry Service) for HRMS analyses on certain compounds.

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8. During an attempt to prepare **8a** *via* the N-diphenylphosphinyl derivative of S-methylalanamide we found that racemisation occured when the ester was coupled to (S,S)-(+)-psuedoephedrine using n-butyllithium as a base. Although this rendered this approach unsuitable for the required application, its conversion to **9a** provided a convenient method for the preparation of enantiomeric standards for the Mosher ester analysis.
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10. Preparation of the t-Boc compound was achieved *via* oxidation of protected (1R,2S)-norephedrine using TPAP/NMO[12] in 70% yield.
11. We found that this was best achieved *via* the formation of the mixed anhydride derived from pivaloyl chloride.[7b] In our hands **8c** was formed in 71% yield from the corresponding acid and **8b** was formed in 31% overall yield from the t-Boc protected valine (4 processes in two pots, as described in the text).
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