Stereocontrolled route to some optically active β-hydroxy phosphine oxides using the stereoselective addition of metallated phosphine oxides to proline-derived keto aminals

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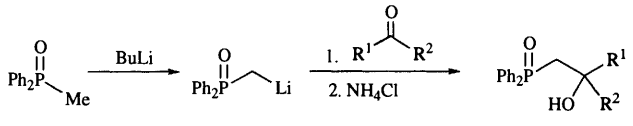
An asymmetric Horner–Wittig addition reaction with a chiral auxiliary attached to the electrophile is described. The key step is the addition of metallated phosphine oxides to Mukaiyama's proline-derived keto aminals (for which improved syntheses are described) and a detailed study of the factors affecting the stereoselectivity of these reactions is presented. In particular, by suitable choice of metallation conditions, complementary stereoselectivities are observed: reactions in THF with no additives are *syn* selective (Felkin non-chelation control) whereas reactions in toluene with added lithium bromide are *anti* selective (Cram chelation control).

Currently, we are involved in a programme of research aimed at establishing new synthetic routes to optically active β-hydroxy phosphine oxides. Previous results from our laboratory have revealed the synthetic potential of such compounds—for example, they have been transformed into enantiomerically enriched unsaturated α-amino acids[1] and alkenyl oxazolidinones[2] as well as allylic alcohols and sulfides.[3,4] In these synthetic sequences, optically active β-hydroxy phosphine oxides were obtained either directly using a chiral auxiliary approach[3] or indirectly by regioselective ring opening of optically active diphenylphosphinoyl epoxy alcohols themselves generated using a reagent based strategy[5] (Sharpless asymmetric epoxidation).[6] More recently,[7] we have synthesised optically active β-hydroxy phosphine oxides using another reagent based approach, the Sharpless asymmetric dihydroxylation reaction.[8]

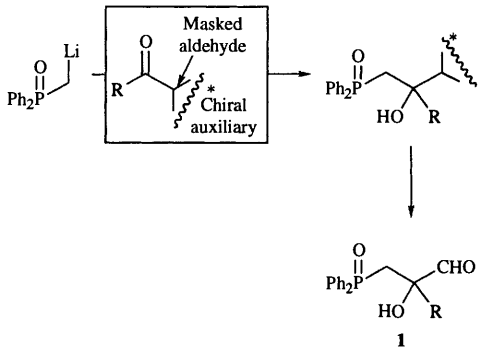
The simplest and most direct way of synthesising β-hydroxy phosphine oxides is the combination of lithiated phosphine oxides and carbonyl compounds—the Horner–Wittig addition reaction[9,10] (Scheme 1). An asymmetric version of this reaction



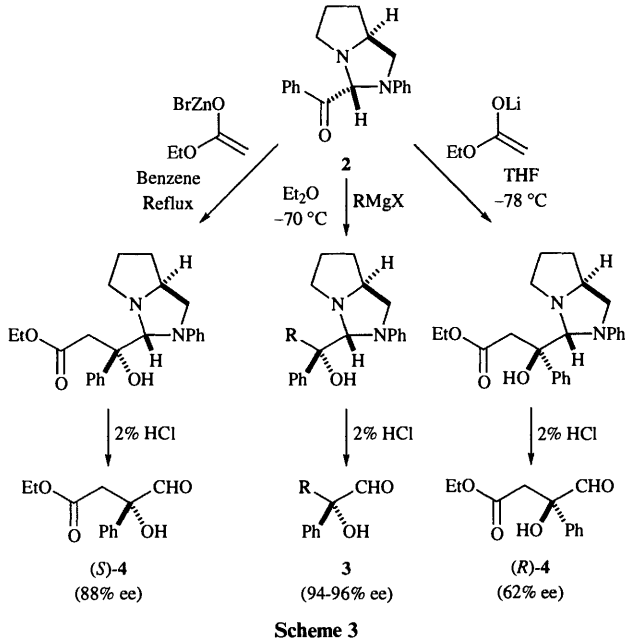
Scheme 1

appeared to us to be an attractive way of making optically active β-hydroxy phosphine oxides. Previously, we had found that the use of a chiral auxiliary attached to the nucleophile in such addition reactions was only moderately successful.[3] Instead, then, we have investigated the use of a chiral auxiliary attached to the carbonyl compound *i.e.* the electrophile (Scheme 2). We imposed an additional design feature on our chiral auxiliary: an aldehyde functionality would remain when we finally removed the chiral auxiliary as this should allow us to manipulate further the β-hydroxy phosphine oxide products **1** obtained from such a reaction sequence.

At the outset of this project, a number of chiral auxiliaries which fulfilled our design criteria had been reported: Eliel's keto oxathianes[11] and keto oxazines,[12] Fujisawa's prolinol-derived oxazolidines[13] and Alexakis's hydrazones synthesised from C_2 symmetric diamines[14] all appeared to be suitable. However, we decided to investigate reactions with Mukaiyama's proline-derived keto aminals[15] and it is the full details of the addition of Grignard reagents, organolithiums and metallated phosphine



Scheme 2



(*S*)-4 (88% ee) **3** (94-96% ee) (*R*)-4 (62% ee)

Scheme 3

oxides to these keto aminals that we report in this paper.[16] Whilst our work was in progress, Hoppe,[17] Scolastico,[18] Agami[19] and Colombo[20] all independently reported the addition of Grignard reagents (and in some cases organolithiums) to keto oxazolidines, a new class of chiral auxiliary.

Mukaiyama has used his bicyclic aminal methodology to synthesise a wide range of α-hydroxy aldehydes[21] and some examples are depicted in Scheme 3. Addition of Grignard

reagents[22,23] or a zinc enolate[24] to phenyl ketone **2** followed by aminal hydrolysis generated α-hydroxy aldehydes **3** and **4** respectively with high enantiomeric excesses and the same sense of asymmetric induction. This was rationalised using the Cram[25] chelated intermediate depicted in Fig. 1 (M = MgBr). Here, the metal is coordinated to the alkyl nitrogen lone pair (presumably the aniline lone pair is less available for coordination) and the carbonyl oxygen: nucleophilic attack then occurs alongside the carbon–hydrogen bond in this chelated form. In contrast, reaction of a lithium enolate with phenyl ketone **2** generated the other enantiomer of α-hydroxy aldehyde **4** with moderate selectivity.[24] Presumably, with lithium as the counterion and THF as the solvent, Felkin[26] non-chelation control predominates: further related examples from our own work are described in detail later.

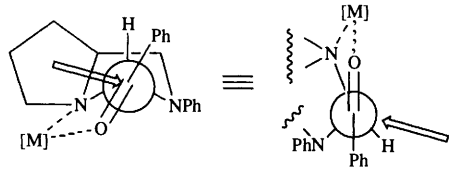


Fig. 1 Cram chelated intermediate responsible for stereoselective addition to phenyl ketone **2**

Using Mukaiyama's enolate results as a guide, we imagined synthesising both enantiomers of β-hydroxy phosphine oxides **1** *via* the addition of differently metallated phosphine oxides to keto aminals. Herein, we describe the results obtained from a detailed study into the factors affecting the stereoselectivity of addition of metallated phosphine oxides to proline-derived keto aminals, our improved syntheses of two of Mukaiyama's keto aminals and a reinvestigation of some of Mukaiyama's work including the previously unreported addition of methyllithium to phenyl ketone **2**.

Improved synthesis of keto aminals

Phenyl and methyl ketones **2** and **11** can be synthesised from diamine (*S*)-**8** which is commercially available.[27] However, we chose to synthesise significant quantities of diamine (*S*)-**8** using a published synthetic route (Scheme 4).[28] This simple four step synthesis was carried out on a 25 g scale with a 60% overall yield from (*S*)-proline.

For conversion into methyl ketone **11**, we proceeded by way of methyl ester **10** which Mukaiyama had previously synthesised from diamine (*S*)-**8** and methyl hydroxymethoxyacetate.[23] We found that condensation of methyl glyoxylate **9** (prepared according to the method of Hook)[29] with diamine (*S*)-**8** in toluene for 15 min at room temperature afforded an essentially quantitative yield of methyl ester **10** as a single diastereoisomer (Scheme 4). That we had obtained the expected thermodynamically favoured *exo* diastereoisomer was confirmed by 500 MHz NOESY analysis (see Experimental section).

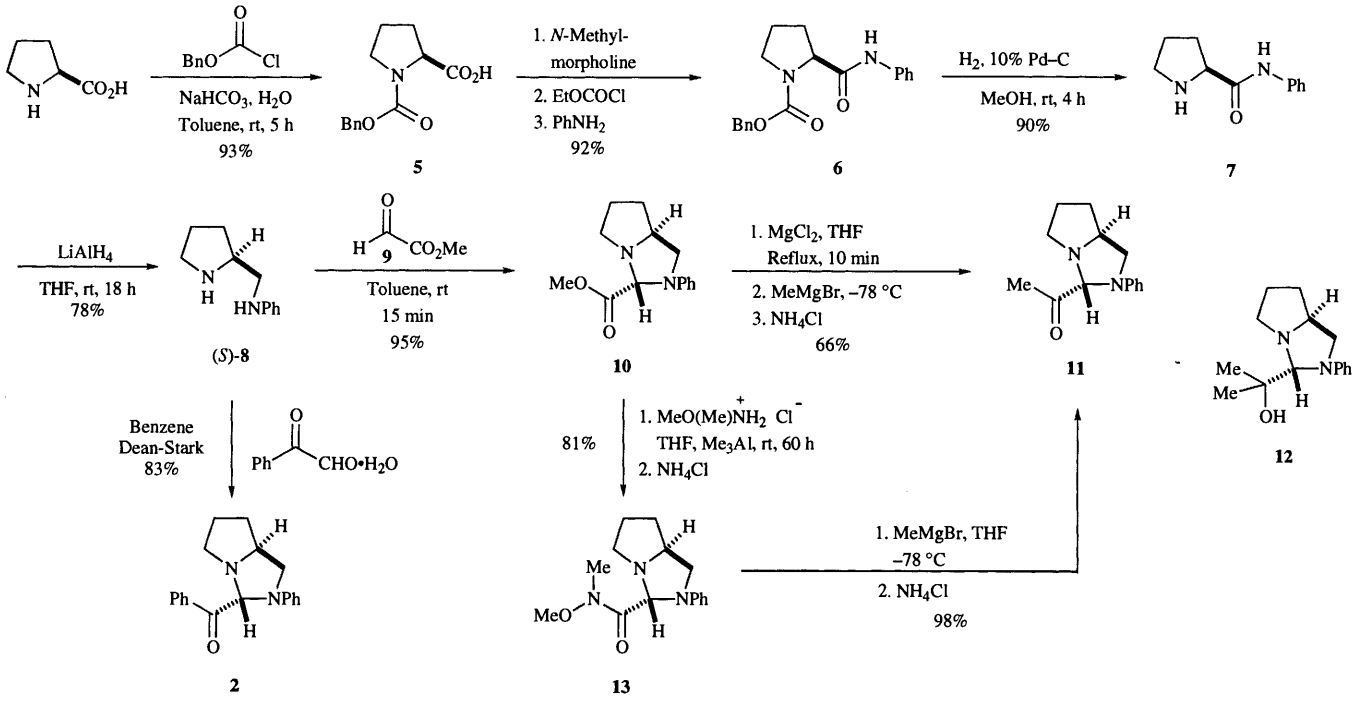
Initially, we repeated Mukaiyama's procedure[23] for the conversion of methyl ester **10** into methyl ketone **11** and obtained a 66% yield of the ketone along with a 12% yield of alcohol **12**. In order to avoid formation of the unwanted alcohol side product, we developed an alternative synthesis of methyl ketone **11** making use of the Weinreb amide **13**.[30,31] This two step synthetic route is higher yielding (79% overall) and it allows easier purification of methyl ketone **11**.

In contrast to methyl ketone **11**, phenyl ketone **2** can be synthesised by direct condensation of diamine (*S*)-**8** with phenylglyoxal monohydrate in refluxing benzene (as reported by Mukaiyama)[22] or in toluene with azeotropic removal of water. For most of the addition reactions described in this paper, we used the crude unpurified phenyl ketone **2** prepared immediately before use.

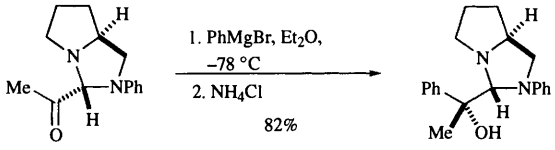
Reinvestigation of Mukaiyama's work

Initially, we repeated Mukaiyama's addition[22,23] of simple Grignard reagents to the phenyl and methyl ketones **2** and **11** (Scheme 5 and entry 1 in Table 1) but preferred to isolate alcohols **14** rather than converting them into α-hydroxy aldehydes. In both cases, we obtained single and different diastereoisomers of alcohols **14**† as judged by ^{1}H NMR spectroscopy of the crude product mixtures. The stereo-

† In alcohols such as **14**, *syn* and *anti* are used to describe the relative stereochemistry between the aminal hydrogen (H^2) and the hydroxy group as drawn. The stereoselectivity of these and subsequent addition reactions was most easily determined by observing the singlet due to the aminal hydrogen (H^2) which appeared in the 4.5–6.0 ppm region of the ^{1}H NMR spectrum of the crude product mixtures.



Scheme 4



Scheme 5

chemistry was assigned by comparison with Mukaiyama's results.

We anticipated studying the addition of lithiated phosphine oxides to keto aminals by investigating the addition of methyllithium to phenyl ketone **2**. Table 1 compares the results obtained from the addition of methyllithium to phenyl ketone **2** in Et_2O and THF (entries 2 and 3) with the Grignard addition result (entry 1). Clearly, the use of lithium or magnesium as the counterion in Et_2O ensures high levels of stereoselectivity, the sense of which can be explained using the Cram chelated intermediate depicted in Fig. 1 (M = MgBr or Li). However, addition of methyllithium in THF is unselective (entry 3)—presumably the more coordinating solvent interferes with efficient formation of a chelated intermediate and Felkin non-chelation control becomes the significant controlling factor.

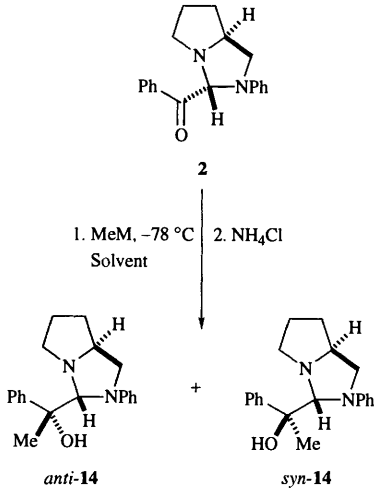


Table 1 Stereoselectivity of addition of MeM (M = Li and MgBr) to phenyl ketone **2** in different solvents

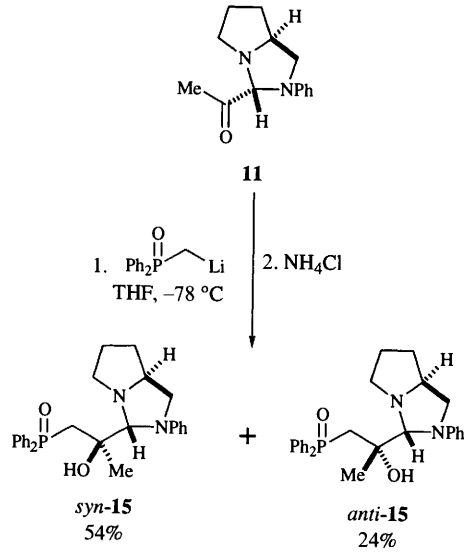
Entry	M	Solvent	*syn*:*anti*
1	MgBr	Et_2O	>97:3[a]
2	Li	Et_2O	95:5
3	Li	THF	39:61

[a] 50% isolated yield of hydroxy aminal *syn*-**14**.

Additions of metallated phosphine oxides to keto aminals

Usually, Horner–Wittig addition reactions are carried out by reacting a lithiated phosphine oxide with the desired carbonyl compound in THF at −78 °C. Thus, as a starting point in our investigation, methyldiphenylphosphine oxide was lithiated with butyllithium and allowed to react with methyl ketone **11** using these normal reaction conditions. Analysis of the crude product mixture by ^1H NMR spectroscopy showed it to contain some remaining starting material and a 64:36 mixture of alcohols **15** (Scheme 6).

By careful flash column chromatography, we isolated a 24% yield of alcohols **15** enriched in the minor diastereoisomeric product. Subsequent recrystallisation from 2:1 EtOAc–MeOH afforded a single diastereoisomer from which suitable crystals were grown for X-ray crystal structure analysis[32] (Fig. 2). This



Scheme 6

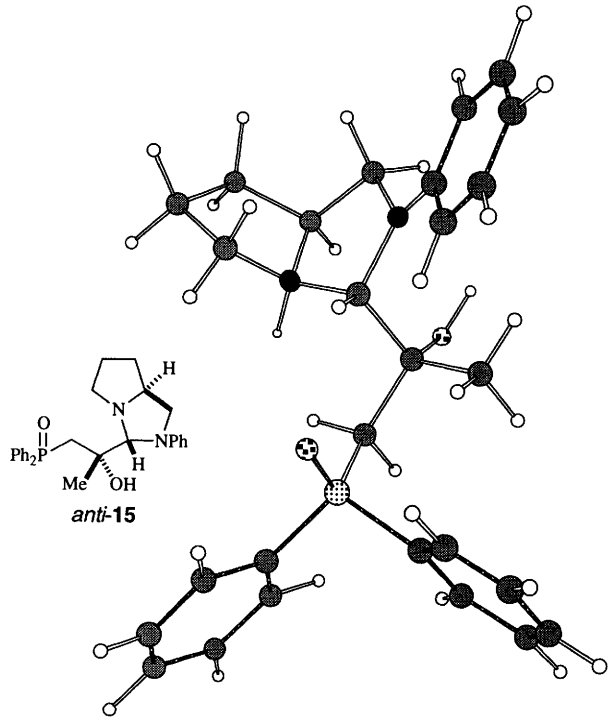
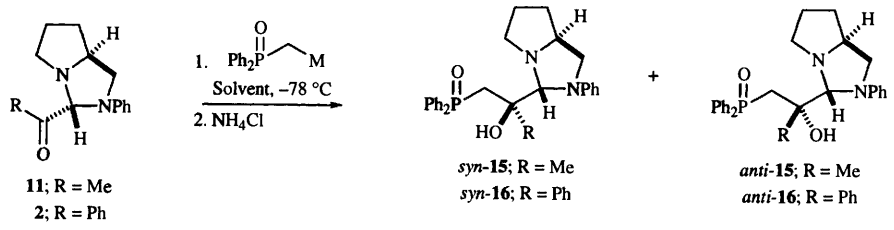


Fig. 2 Chem3D representation of crystal structure of alcohol *anti*-**15**

enabled us to identify the minor diastereoisomeric alcohol obtained from the addition reaction as alcohol *anti*-**15**. Also isolated from the chromatographic process was recovered starting methyl ketone **11** in 17% yield and a 54% yield of a 90:10 mixture of alcohols *syn*- and *anti*-**15**. Unfortunately, repeated recrystallisation of this mixture only returned the same 90:10 mixture of alcohols *syn*- and *anti*-**15**. We were, however, pleased to observe that the combined yield of alcohols **15** was 78% or 93% based on recovered starting material.

Both the sense and degree of asymmetric induction obtained from the addition of lithiated methyldiphenylphosphine oxide to methyl ketone **11** were essentially the same as we had obtained when we added methyllithium to phenyl ketone **2** in THF (entry 3 in Table 1). It appears that the combination of lithium as the counterion and THF as the solvent favours a Felkin non-chelation controlled addition reaction. This is consistent with the selectivity obtained by Mukaiyama when he added a lithium enolate to phenyl ketone **2** (Scheme 3).[24] Still



11; R = Me
2; R = Ph

syn-**15**; R = Me
syn-**16**; R = Ph

anti-**15**; R = Me
anti-**16**; R = Ph

Table 2 Stereoselectivity of addition of metallated methyldiphenylphosphine oxides to keto aminals **11** and **2**

				Methyl ketone **11**		Phenyl ketone **2**	
Entry	M	Conditions	Solvent	Prod:SM[a]	*syn*-**15** *anti*-**15**	Prod:SM[a]	*syn*-**16** *anti*-**16**
1	Li	$Ph_2P(O)Me$, BuLi	THF	82:18	64:36	No SM	68:32
2	Li	$Ph_2P(O)Me$, BuLi, TMEDA	THF	94:6	77:23	No SM	54:46
3	$CeCl_2$	$Ph_2P(O)Me$, BuLi then transmetallation with $CeCl_3$	THF	76:24	73:27	—[b]	—[b]
4	$TiCl_3$	$Ph_2P(O)Me$, BuLi then transmetallation with $TiCl_4$	THF	—[c]	—[c]	—[b]	—[b]
5	Li	$Ph_2P(O)Me$, BuLi	Toluene	78:22	28:72	73:27	40:60
6	Li·LiBr	$Ph_2P(O)Me$, MeLi·LiBr[d]	THF	75:25	29:71	No SM	36:64
7	Li·LiBr	$Ph_2P(O)Me$, MeLi·LiBr[d]	Toluene	93:7	14:86	No SM	16:84
8	MgBr	$Ph_2P(O)Me$, BuLi then transmetallation with $MgBr_2$[e]	THF	38:62	18:82	21:79	5:95

[a] Ratio of products **15** or **16** to starting material. [b] Reaction not carried out. [c] No aminal products in the crude reaction mixture. [d] Lithiation at 0 °C. [e] Lithiation, transmetallation and reaction at 0 °C.

has noticed a similar trend in the addition of butyllithium to a protected α-hydroxy ketone when the reaction was carried out in pentane, Et_2O and THF.[33] Recently, a theoretical study into the factors affecting chelation controlled reactions has been described.[34]

By varying both the solvent and the metal counterion as well as carrying out the addition reaction in the presence of different additives, we hoped to improve the stereoselectivity of the reaction and discover complementary reaction conditions for the synthesis of alcohol *anti*-**15**. The full results of the addition of differently metallated methyldiphenylphosphine oxides to the methyl and phenyl ketones **11** and **2** are presented in Table 2. The extent of conversion and the ratios of the diastereomeric alcohols **15** and **16** were determined by ^1H NMR spectroscopy on the crude product mixtures. The relative stereochemistry of alcohols **16** was assigned by comparison with the results obtained from the methyl ketone **11** reactions. Due to the limited solubility of phosphine oxides in Et_2O, we did not carry out any addition reactions in this solvent.‡

Carrying out the addition reaction of lithiated methyldiphenylphosphine oxide to methyl ketone **11** in THF with added TMEDA or after transmetallation with cerium(III) chloride (using the method described by Imamoto)[35] led to a slight improvement in the stereoselectivity (entries 2 and 3). Transmetallation of the lithiated phosphine oxide with titanium tetrachloride (using Reetz's method)[36] and subsequent reaction with methyl ketone **11** (entry 4) generated a crude product which contained no bicyclic aminal compounds whatsoever. Clearly, aminal hydrolysis had occurred.§

Some synthetic transformations using Grignard reagents of phosphine oxides have been reported by Seyferth who generated them by refluxing a THF solution of phenylmagnesium bromide with methyldiphenylphosphine oxide for 4–6 h.[37] However, we preferred to generate the Grignard reagents by transmetallating the lithiated phosphine oxide with magnesium bromide[38] at 0 °C. Subsequent addition of the methyl and phenyl ketones **11** and **2** generated alcohols *anti*-**15** and *anti*-**16** respectively with high levels of stereoselectivity (entry 8). With magnesium as the counterion, even in THF, chelation control *via* the intermediate depicted in Fig. 1 (M = Mg) is the dominant pathway. However, the conversion into products was only moderate using this phosphine oxide Grignard reagent. Apparently, the Grignard reagent is very unreactive and, although we had found conditions for the highly selective synthesis of alcohols *anti*-**15** and *anti*-**16**, the yields obtained from these reactions meant that they were not going to be synthetically useful.

What we required was a new set of reaction conditions for the synthesis of alcohols *anti*-**15** and *anti*-**16** with good levels of both stereoselectivity and conversion. We had noticed that carrying out the reaction of lithiated methyldiphenylphosphine oxide in toluene generated alcohols **15** and **16** with reasonable *anti* selectivity (entry 5) presumably *via* chelation control. This was similar to the result obtained when we added methyllithium to phenyl ketone **2** in Et_2O as solvent (see entry 3 in Table 1). We therefore reasoned that dissolving up some additional lithium cations in the toluene solution might promote 'extra chelation'.

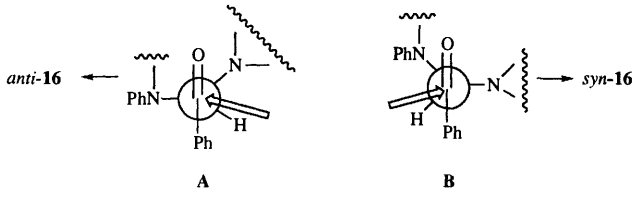
To investigate this, we lithiated methyldiphenylphosphine oxide not with butyllithium in the usual way but with methyllithium as a complex with lithium bromide. The lithiation was best carried out at 0 °C whereupon a precipitate formed which slowly dissolved on stirring for 30 min to give a yellow solution. At this point, the solution was cooled to −78 °C and the methyl or phenyl ketones **11** and **2** were added. Analysis of the crude product mixtures by ^1H NMR spectroscopy indicated the highly stereoselective formation of alcohols *anti*-**15** and *anti*-**16** with excellent levels of conversion (entry 7).[39]

As can be seen from Table 2, the inherent *syn* selectivity observed with the usual Horner–Wittig reaction conditions (entry 1) can be overturned by the use of either toluene as the solvent (entry 5) or lithium bromide as an additive (entry 6) as the chelation controlled pathway becomes more significant. Finally, combination of the two effects (toluene as the solvent and lithium bromide as an additive) gives useful levels of stereoselectivity (entry 7) and synthetically useful reactions.

‡ We do, however, use this limited solubility to good effect—trituration with Et_2O is an excellent way of inducing oils to crystallise.
§ In contrast, Agami was able to add allyl silane to a keto oxazolidine in the presence of titanium tetrachloride.[19]

Rationalisation of the sense of asymmetric induction

So far, we have differentiated between chelation and non-chelation controlled processes and we have described how the chelation controlled reaction gives rise to *anti* selectivity in reactions with metallated phosphine oxides by invoking a chelated intermediate (Fig. 1; M = Mg or Li·LiBr) as suggested by Mukaiyama. However, we have not attempted to explain the source of the *syn* selectivity from Felkin non-chelation controlled reactions. To try and do this, we have considered the two possible Felkin transition states **A** and **B** for the addition reactions (Scheme 7): both of these conformations have a



A **B**

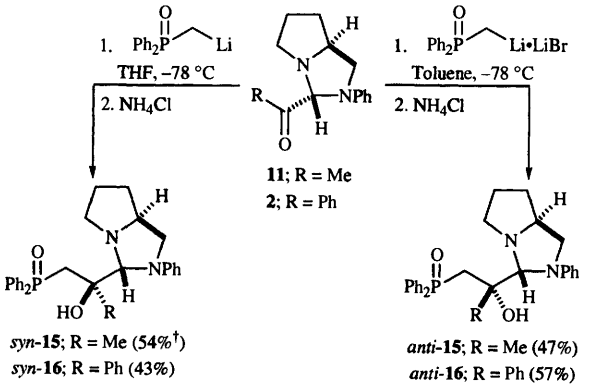
Scheme 7

carbon–nitrogen bond perpendicular to the carbonyl group but it is not clear which conformation will be the more reactive.

Assuming that the reaction is under Felkin control, we know that, since the addition of lithiated methyldiphenylphosphine oxide to phenyl ketone **2** in THF gives alcohol *syn*-**16** as the major product, it must be formed *via* transition state **B**. This pathway for the reaction must overcome competition from the other Felkin transition state (**A**) and from the chelation controlled pathway which both lead to alcohol *anti*-**16**. We have no explanation for origin of the selectivity (and the preferential reaction *via* transition state **B**) but it can be seen that in both the chelation and non-chelation controlled reactions, it is the same nitrogen atom that determines the stereoselectivity *i.e.* the aniline nitrogen never appears to be involved directly.

Conclusions—optimised conditions for the stereoselective synthesis of single diastereoisomers of alcohols 15 and 16

We have thus been able to show that by suitable choice of metallation conditions, each one of the four alcohols *syn*- and *anti*-**15** and *syn*- and *anti*-**16** can be selectively synthesised. Single diastereoisomers of alcohols **15** and **16** are, of course, direct precursors to β-hydroxy phosphine oxides **1** of high enantiomeric excess. The optimum reaction conditions used for carrying out these syntheses are summarised in Scheme 8.



† 90:10 ratio of *syn*- and *anti*-**15**

Scheme 8

Addition of lithiated phosphine oxide in THF to the methyl and phenyl ketones **11** and **2** gave a 54% yield of an inseparable 90:10 mixture of alcohols *syn*- and *anti*-**15** and a 43% yield of alcohol *syn*-**16** respectively. In contrast, addition of lithiated phosphine oxide in toluene in the presence of lithium bromide to the methyl and phenyl ketones **11** and **2** gave a 47% yield of alcohol *anti*-**15** and a 57% yield of alcohol *anti*-**16** respectively.

Experimental

All solvents were distilled before use. THF and Et_2O were freshly distilled from lithium aluminium hydride whilst CH_2Cl_2 and toluene were freshly distilled from calcium hydride. Triphenylmethane was used as indicator for THF. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was dried by stirring over and distilling from calcium hydride and was then stored over activated 4 Å molecular sieves. Butyllithium was titrated against diphenylacetic acid before use. All non-aqueous reactions were carried out under argon using oven-dried glassware.

Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) according to the method of Still, Kahn and Mitra.[40] Thin layer chromatography was carried out on commercially available pre-coated plates (Merck silica Kieselgel $60F_{254}$). Proton and carbon NMR spectra were recorded on a Bruker WM 200, WM 250, WM 400 or AMX 500 Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield of tetramethylsilane and values of coupling constants (*J*) are given in Hz. The symbol * after the proton NMR chemical shift indicates that the signal disappears after a D_2O 'shake'. Carbon NMR spectra were recorded with broad band proton decoupling and Attached Proton Test. The symbols $^+$ and $^-$ after the carbon NMR chemical shift indicate odd and even numbers of attached protons respectively.

Melting points were measured on a Reichart hot stage microscope or a Buchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 (FT-IR) spectrophotometer. Mass spectra were recorded on a Kratos double-beam mass spectrometer using a DS503 data system for high resolution analysis. Microanalyses were carried out by the staff of the University Chemical Laboratory using Carlo Erba 1106 or Perkin-Elmer 240 automatic analysers. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter (using the sodium D line; 589 nm) and $[\alpha]_D^{20}$ are given in units of 10^{-1} deg cm^2 g^{-1}.

Although some of the reactions described in this paper have been carried out by Mukaiyama, we include full experimental details of reactions where our procedure differs significantly from that reported. In addition, we report the first ever full characterisation of the products of all of these reactions. The carbon atoms in the bicyclic aminals are referred to by numbers as shown in Fig. 3 for methyl ester **10**.

(*S*)-*N*-(Benzyloxycarbonyl)proline 5

Using Mukaiyama's method,[28] (*S*)-*N*-(benzyloxycarbonyl)proline **5**¶ was prepared in 93% yield as a colourless oil which crystallised on standing as cubes, mp 75–76 °C (from 1:1 Et_2O–hexane) (lit.,[41] 76–77 °C); $[\alpha]_D^{20}$ −38.9 (*c* 1.0 in EtOH) {lit.,[28] $[\alpha]_D^{22}$ −40.4 (*c* 1.027 in EtOH)} (Found: C, 62.6; H, 6.05; N, 5.65%; M$^+$, 249.1004. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%; *M*, 249.1001); ν_{max}(Nujol)/cm^{-1} 2700–2300br (OH), 1757 (C=O, CO_2H), 1648 (C=O, NCO_2Bn) and 1593 (Ph); both the ^{1}H and ^{13}C NMR show that the two carbamate rotamers are present in solution at room temperature: δ_H(250 MHz, $CDCl_3$) 10.20 (1 H, br s, OH), 7.35–7.29 (5 H, m, Ph), 5.23–5.10 (2 H, m, $PhCH_2O$), 4.47–4.34 (1 H, m, $NCHCO_2H$), 3.67–3.41 (2 H, m, NCH_2) and 2.32–1.86 (4 H, m, CH_2CH_2); δ_C(100 MHz, $CDCl_3$)

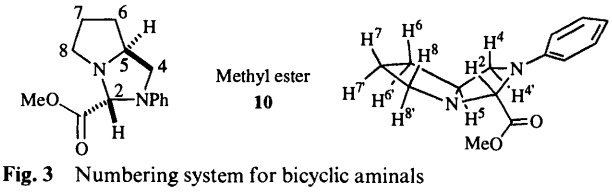


Fig. 3 Numbering system for bicyclic aminals

¶ Full characterisation of **5** has not previously been described.

178.2$^-$ and 176.6$^-$ (C=O, CO_2H), 155.6$^-$ and 154.3$^-$ (C=O, NCO_2Bn), 136.3$^-$ and 136.2$^-$ (*ipso*-Ph), 128.4$^+$, 128.3$^+$, 128.0$^+$, 127.8$^+$, 127.5$^+$, 67.4$^-$ and 67.0$^-$ ($PhCH_2O$), 59.1$^+$ and 58.5$^+$ ($NCHCO_2H$), 46.8$^-$ and 46.5$^-$ (NCH_2), 30.8$^-$ and 29.3$^-$ (CH_2CH_2) and 24.2$^-$ and 23.3$^-$ (CH_2CH_2); *m*/*z* 249 (20%, M$^+$), 204 (60, M − CO_2H), 160 (70), 114 (80, M − CO_2Bn), 92 (75), 91 (100, $PhCH_2$) and 77 (20, Ph).

(*S*)-*N*-(Benzyloxycarbonyl)prolinanilide 6

Using Mukaiyama's method,[28] (*S*)-*N*-(benzyloxycarbonyl)prolinanilide **6**‖ was prepared in 92% yield as cubes, mp 141–142 °C (from acetone) (lit.,[28] 141–141.5 °C); R_f(EtOAc) 0.6; $[\alpha]_D^{20}$ −57.3 (*c* 1.1 in EtOH) {lit.,[28] $[\alpha]_D^{23}$ −63.2 (*c* 0.997 in EtOH)} (Found: C, 70.2; H, 6.3; N, 8.6%; M$^+$, 324.1467. $C_{19}H_{20}N_2O_3$ requires C, 70.3; H, 6.2; N, 8.6%; *M*, 324.1474); ν_{max}(Nujol)/cm^{-1} 3274 (NH), 1699 (C=O, amide I), 1666 (C=O, NCO_2Bn), 1601 (Ph) and 1551 (NH bend, amide II); The ^{1}H NMR is very broad due to carbamate rotamer interconversion: δ_H(250 MHz, $CDCl_3$) 9.2 (1 H, br s, NH), 7.5–7.0 (10 H, br m, 2 × Ph), 5.3–5.0 (2 H, br m, $PhCH_2O$), 4.6–4.5 (1 H, br m, NC*H*CONH), 3.7–3.4 (2 H, br m, NCH_2) and 2.6–1.8 (4 H, br m, CH_2CH_2); δ_C(100 MHz, $CDCl_3$) 169.3$^-$ (C=O, CONH), 156.9$^-$ (C=O, NCO_2Bn), 138.1$^-$ (*ipso*-NPh), 136.2$^-$ (*ipso*-Ph), 128.8$^+$, 128.6$^+$, 128.2$^+$, 128.0$^+$, 124.0$^+$ (*p*-NPh), 119.7$^+$ (*o*-NPh), 67.6$^-$ ($PhCH_2O$), 61.0$^+$ (N*C*HCONH), 47.1$^-$ (NCH_2), 27.3$^-$ (CH_2CH_2) and 24.6$^-$ (CH_2CH_2); *m*/*z* 324 (40%, M$^+$), 205 (30, M − $PhCH_2$), 204 (70, M − CONHPh), 160 (70), 92 (80, PhNH), 91 (100, $PhCH_2$) and 77 (40, Ph).

(*S*)-*N*-Prolinanilide 7

Using a method modified from that reported by Mukaiyama,[28] a solution of amide (*S*)-**6** (34.7 g, 107.0 mmol) in MeOH (175 cm^3) was added carefully to 10% palladium on charcoal (1.45 g) in a 250 cm^3 Dreschel bottle under nitrogen. Hydrogen was bubbled vigorously through the suspension at room temperature and the expelled carbon dioxide was detected using a second Dreschel bottle containing limewater.[42] After 5 h at room temperature, the catalyst was removed by filtration through Celite and the solution evaporated under reduced pressure to give the crude product as a white solid. Recrystallisation from cyclohexane gave amine (*S*)-**7**** (18.4 g, 90%) as fibrous needles, mp 76–78 °C (from cyclohexane) (lit.,[28] 76–77 °C); R_f(EtOAc) 0.1; $[\alpha]_D^{20}$ −71.4 (*c* 1.0 in EtOH) {lit.,[28] $[\alpha]_D^{27}$ −71.0 (*c* 1.025 in EtOH)} (Found: C, 69.4; H, 7.4; N, 14.7%; M$^+$, 190.1101. $C_{11}H_{14}N_2O$ requires C, 69.4; H, 7.4; N, 14.7%; *M*, 190.1106); ν_{max}(Nujol)/cm^{-1} 3348 (NH), 3212 (NH), 1662 (C=O, amide I), 1600 (Ph) and 1520 (NH bend, amide II); δ_H(250 MHz, $CDCl_3$) 9.7 (1 H, br s, amide NH), 7.6 (2 H, dd, *J* 1.2 and 7.7, *o*-NPh), 7.3 (2 H, dd, *J* 7.0 and 7.7, *m*-NPh), 7.1 (1 H, tt, *J* 1.2 and 7.0, *p*-NPh), 3.84 (1 H, dd, *J* 5.2 and 9.2, NC*H*CONH), 3.06 (1 H, td, *J* 6.8 and 10.2, NCH_AH_B), 2.97 (1 H, td, *J* 6.2 and 10.2, NCH_AH_B), 2.20 (1 H, tdd, *J* 7.6, 9.1 and 12.9, $NCHCH_AH_B$), 2.05 (1 H, dtd, *J* 5.2, 6.7 and 13.0, $NCHCH_AH_B$), 1.95 (1 H, br s, NH) and 1.81–1.69 (2 H, m, CH_2); δ_C(100 MHz, $CDCl_3$) 173.3$^-$ (C=O), 137.7$^-$ (*ipso*-NPh), 128.8$^+$ (*m*-NPh), 123.8$^+$ (*p*-NPh), 119.1$^+$ (*o*-NPh), 60.9$^+$ (N*C*HCONH), 47.2$^-$ (NCH_2), 30.6$^-$ (CH_2CH_2) and 26.2$^-$ (CH_2CH_2); *m*/*z* 190 (60%, M$^+$), 93 (50), 77 (20, Ph) and 70 (100, M − CONHPh).

(*S*)-(+)-2-(Anilinomethyl)pyrrolidine 8

Using Mukaiyama's method,[28] (*S*)-(+)-2-(anilinomethyl)pyrrolidine **8**†† was prepared in 78% yield as a colourless oil, bp 92–93 °C/0.25 mmHg (lit.,[28] 111–112 °C/0.55 mmHg); $[\alpha]_D^{20}$ +15.3 (*c* 1.0 in EtOH) {lit.,[28] $[\alpha]_D^{24}$ +19.7 (*c* 1.087 in EtOH)} (Found: M$^+$, 176.1309. $C_{11}H_{16}N_2$ requires *M*, 176.1313); δ_C(63 MHz, $CDCl_3$) 148.5$^-$ (*ipso*-NPh), 129.1$^+$ (*m*-NPh), 117.2$^+$ (*p*-NPh), 112.9$^+$ (*o*-NPh), 57.6$^+$ (NCH), 48.6$^-$ (NCH_2), 46.5$^-$ (NCH_2), 29.5$^-$ (CH_2CH_2) and 25.7$^-$ (CH_2CH_2). The ^{1}H NMR was in agreement with that described by Mukaiyama.[28]

Methyl glyoxylate 9

Using Hook's method,[29] methyl dimethoxyacetate (24.8 g, 185.0 mmol), glyoxylic acid monohydrate (13.8 g, 187.0 mmol) and toluene-*p*-sulfonic acid (0.11 g, 0.6 mmol) were heated at 80 °C for 18 h. After cooling to 0 °C, phosphorus pentoxide (18.2 g, 128.0 mmol) was added in portions (**care**—exothermic) and the mixture was then heated at 80 °C for 4 h. Additionally, we found that the mixture could be stored indefinitely in the freezer and distilled when required to give methyl glyoxylate **9** as a colourless oil, bp 42–43 °C/23 mmHg (lit.,[43] 45–50 °C/29 mmHg); δ_H(200 MHz, $CDCl_3$) 9.4 (1 H, s, CHO) and 3.9 (3 H, s, OMe).

2-Methoxycarbonyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane 10

Methyl glyoxylate **9** (528 mg, 6.0 mmol) was added dropwise to a stirred solution of diamine (*S*)-**8** (892 mg, 5.1 mmol) in toluene (5 cm^3) at room temperature. After 15 min at room temperature, the toluene was evaporated under reduced pressure and the residue purified by chromatography on silica with Et_2O as eluent to give methyl ester **10**‡‡ (1.19 g, 95%) as a colourless oil, R_f(EtOAc) 0.4; $[\alpha]_D^{20}$ −31.7 (*c* 1.2 in $CHCl_3$) (Found: C, 68.0; H, 7.3; N, 11.2%; M$^+$, 246.1377. $C_{14}H_{18}N_2O_2$ requires C, 68.3; H, 7.4; N, 11.4%; *M*, 246.1368); ν_{max}(film)/cm^{-1} 1751 (C=O), 1599 (Ph), 1574 (Ph) and 1502 (Ph); δ_H(500 MHz, $CDCl_3$) 7.2 (2 H, dd, *J* 7.5 and 8.5, *m*-NPh), 6.75 (1 H, t, *J* 7.4, *p*-NPh), 6.55 (2 H, d, *J* 7.9, *o*-NPh), 4.85 (1 H, s, H^2), 4.1 (1 H, dtd, *J* 4.0, 6.6 and 8.0, H^5), 3.72 (3 H, s, OMe), 3.67 (1 H, t, *J* 8.0, H$^{4'}$), 3.32 (1 H, ddd, *J* 4.05, 7.1 and 9.6, H$^{8'}$), 3.19 (1 H, dd, *J* 6.6 and 8.0, H^4), 2.74 (1 H, dt, *J* 7.7 and 8.9, H^8), 2.21–2.15 (1 H, m, H$^{6'}$), 1.96–1.86 (2 H, m, H^7 and H$^{7'}$) and 1.82–1.77 (1 H, m, H^6); δ_C(100 MHz, $CDCl_3$) 171.8$^-$ (C=O), 145.5$^-$ (*ipso*-NPh), 129.4$^+$ (*m*-NPh), 117.5$^+$ (*p*-NPh), 112.6$^+$ (*o*-NPh), 80.7$^+$ (C^2), 62.7$^+$ (C^5), 55.2$^-$ (C^4 or C^8), 52.6$^-$ (C^4 or C^8), 52.2$^+$ (OMe), 30.5$^-$ (C^6 or C^7) and 24.9$^-$ (C^6 or C^7); *m*/*z* 246 (60%, M$^+$), 187 (100, M − CO_2Me), 145 (45), 104 (50), 91 (60, NPh) and 77 (70, Ph).

The ^{1}H NMR spectrum was fully assigned using the results obtained from 500 MHz COSY and NOESY analyses. Initially, we assigned δ_H 4.1 as H^5 on the basis of its multiplicity. Then, using the COSY experiment, it was possible to identify the pairs of protons on C^4 since δ_H 4.1 (H^5) was coupled to δ_H 3.67 (H$^{4'}$) and δ_H 3.19 (H^4) as well as to the backbone protons on C^6 [δ_H 2.2 (H$^{6'}$) and δ_H 1.8 (H^6)]. From this, it was possible to identify the pairs of protons (H^8/H$^{8'}$) on C^8 since they only coupled to each other and to the two backbone protons on C^7 [δ_H 1.96–1.86 (H^7 and H$^{7'}$)]. The multiplicities and coupling constants of H^4, H$^{4'}$, H^8 and H$^{8'}$ were consistent with these assignments. From the NOESY experiment, we were able to distinguish between H^4/H$^{4'}$ as well as between H^8/H$^{8'}$: for example, a NOE was observed between δ_H 4.1 (H^5) and δ_H 3.67 (H$^{4'}$) but not between δ_H 4.1 (H^5) and δ_H 3.19 (H^4). Applying these assignments to the remaining NOEs, we were actually able to identify all of the backbone protons H^6, H$^{6'}$, H^7 and H$^{7'}$. The NOEs could then be traced around the two faces of the bicyclic aminal structure: *endo* face—H^2→H^8→H^7→H^6→H^4; *exo* face—H$^{8'}$→H$^{7'}$→H^5→H$^{6'}$→H$^{4'}$. From these analyses, we concluded that we had obtained the expected *exo* diastereoisomer of methyl ester **10**. This was subsequently confirmed when we obtained the X-ray crystal structure of alcohol *anti*-**15**.

¶ Full characterisation of **5** has not previously been described.
‖ Full characterisation of amide **6** has not previously been described.
** Full characterisation of amine **7** has not previously been described.
†† Mukaiyama has reported most of the characterisation of diamine **8**.[28]

‡‡ Mukaiyama has previously reported only ^{1}H NMR (in CCl_4) and combustion analysis of methyl ester **10**.[23] Our synthesis of methyl ester **10** uses methyl glyoxylate **9**; Mukaiyama's synthesis used methyl hydroxymethoxyacetate.

Exactly the same features were observed in the COSY and NOESY analyses of alcohol *anti*-**15**. The full assignments of all the ^{1}H NMR spectra in this paper are based on the results obtained from analysing methyl ester **10** and alcohol *anti*-**15**.

2-(*N*-Methoxy-*N*-methylaminocarbonyl)-3-phenyl-1,3-diazabicyclo[3.3.0]octane 13

Trimethylaluminium (2.9 cm^3 of a 2 M solution in hexanes, 5.8 mmol) was added dropwise to a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride (574 mg, 5.9 mmol) in THF (20 cm^3) under argon at 0 °C. The resulting solution was allowed to warm to room temperature over 1 h and a solution of methyl ester **10** (962 mg, 3.9 mmol) in THF (10 cm^3) was added dropwise. After 60 h at room temperature, the mixture was cooled to 0 °C and saturated aqueous ammonium chloride (20 cm^3) was added. The mixture was extracted with EtOAc (5 × 20 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification by chromatography on silica with EtOAc–MeOH (15:1) as eluent gave *Weinreb amide* **13** (868 mg, 81%) as a colourless oil, R_f(EtOAc) 0.1; $[\alpha]_D^{20}$ +78.5 (*c* 1.6 in $CHCl_3$) (Found: C, 64.7; H, 7.9; N, 15.2%; M$^+$, 275.1635. $C_{15}H_{21}N_3O_2$ requires C, 65.4; H, 7.7; N, 15.3%; *M*, 275.1634); ν_{max}(film)/cm^{-1} 1670 (C=O), 1599 (Ph), 1573 (Ph) and 1505 (Ph); δ_H(400 MHz, $CDCl_3$) 7.18 (2 H, dd, *J* 7.4 and 8.6, *m*-NPh), 6.69 (1 H, t, *J* 7.3, *p*-NPh), 6.48 (2 H, d, *J* 7.8, *o*-NPh), 5.36 (1 H, s, H^2), 4.08 (1 H, dtd, *J* 3.7, 6.6 and 8.0, H^5), 3.87 (3 H, s, OMe), 3.75 (1 H, t, *J* 8.0, H$^{4'}$), 3.30 (1 H, ddd, *J* 3.9, 6.9 and 10.9, H$^{8'}$), 3.20 (3 H, s, NMe), 3.17 (1 H, dd, *J* 6.6 and 8.0, H^4), 2.76 (1 H, td, *J* 7.5 and 8.9, H^8), 2.19–2.13 (1 H, m, C*H*$_A$H$_B$CH$_2$) and 1.95–1.77 (3 H, m, CH$_A$*H*$_B$CH$_2$); δ_C(100 MHz, $CDCl_3$) No C=O peak, 145.8$^-$ (*ipso*-NPh), 129.3$^+$ (*m*-NPh), 116.9$^+$ (*p*-NPh), 112.3$^+$ (*o*-NPh), 77.3$^+$ (C^2), 62.3$^+$ (C^5), 61.5$^+$ (OMe), 55.2$^-$ (C^4 or C^8), 53.3$^-$ (C^4 or C^8), 32.2$^+$ (NMe), 30.6$^-$ (C^6 or C^7) and 24.8$^-$ (C^6 or C^7); *m/z* 275 (30%, M$^+$), 187 [100, M − CON(Me)OMe], 145 (10) and 77 (30, Ph).

2-Acetyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane 11

Using a method modified from that reported by Mukaiyama,[23] a suspension of anhydrous magnesium chloride (135 mg, 1.4 mmol) and methyl ester **10** (293 mg, 1.3 mmol) in THF (5 cm^3) under argon was heated under reflux for 15 min. After cooling to −78 °C, methylmagnesium bromide (0.5 cm^3 of a 3 M solution in Et_2O, 1.5 mmol) was added dropwise and the resulting solution was stirred for 1 h at −78 °C. Saturated aqueous ammonium chloride (1 cm^3) was added and the mixture extracted with Et_2O (3 × 10 cm^3). The diethyl ether extracts were washed with saturated brine (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil which contained a 3:18:79 ratio of methyl ester **10**, alcohol **12** and methyl ketone **11** (by ^{1}H NMR). Purification by chromatography on silica with Et_2O as eluent gave methyl ketone **11**§§ (181 mg, 66%) as a colourless oil, R_f(EtOAc) 0.5; $[\alpha]_D^{20}$ −45.3 (*c* 1.2 in $CHCl_3$) (Found: C, 72.9; H, 7.9; N, 12.3%; M$^+$, 230.1432. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%; *M*, 230.1425); ν_{max}(film)/cm^{-1} 1714 (C=O), 1599 (Ph), 1574 (Ph) and 1505 (Ph); δ_H(400 MHz, $CDCl_3$) 7.21 (2 H, dd, *J* 7.4 and 8.7, *m*-NPh), 6.75 (1 H, t, *J* 7.3, *p*-NPh), 6.48 (2 H, d, *J* 8.7, *o*-NPh), 4.37 (1 H, s, H^2), 3.92 (1 H, dtd, *J* 4.8, 6.6 and 7.2, H^5), 3.78 (1 H, dd, *J* 7.2 and 8.5, H$^{4'}$), 3.20 (1 H, ddd, *J* 5.2, 7.1 and 10.1, H$^{8'}$), 3.13 (1 H, dd, *J* 6.6 and 8.5, H^4), 2.83 (1 H, td, *J* 7.3 and 10.1, H^8), 2.15–2.08 (1 H, m, C*H*$_A$H$_B$CH$_2$), 2.11 (3 H, s, Me) and 1.95–1.67 (3 H, m, CH$_A$*H*$_B$CH$_2$); δ_C(100 MHz, $CDCl_3$) 208.1$^-$ (C=O), 145.7$^-$ (*ipso*-NPh), 129.9$^+$ (*m*-NPh), 117.6$^+$ (*p*-NPh), 112.5$^+$ (*o*-NPh), 86.5$^+$ (C^2), 62.9$^+$ (C^5), 55.0$^-$ (C^4 or C^8), 53.1$^-$ (C^4 or C^8), 30.9$^-$ (C^6 or C^7), 25.0$^-$ (C^6 or C^7) and 24.3$^+$ (Me); *m/z* 230 (20%, M$^+$), 187 (100, M − COMe), 109 (70), 97 (70) and 77 (30, Ph) and alcohol **12** (34 mg, 12%) as a colourless oil, R_f(Et_2O) 0.15; ν_{max}(film)/cm^{-1} 3445 (OH), 1598 (Ph) and 1504 (Ph); δ_H(250 MHz, $CDCl_3$) 7.21 (2 H, dd, *J* 7.1 and 8.9, *m*-NPh), 6.70–6.67 (3 H, m, *o*- and *p*-NPh), 4.51 (1 H, s, H^2), 3.90 (1 H, dtd, *J* 4.3, 6.5 and 7.8, H^5), 3.74 (1 H, dd, *J* 7.8 and 9.1, H$^{4'}$), 3.20 (1 H, ddd, *J* 4.3, 5.7 and 9.9, H$^{8'}$), 3.15 (1 H, dd, *J* 6.5 and 9.1, H^4), 2.95 (1 H, br s, OH), 2.60 (1 H, dt, *J* 7.0 and 8.7, H^8), 2.18–2.08 (1 H, m, C*H*$_A$H$_B$CH$_2$), 1.83–1.56 (3 H, m, CH$_A$*H*$_B$CH$_2$), 1.24 (3 H, s, Me) and 1.18 (3 H, s, Me); δ_C(100 MHz, $CDCl_3$) 148.4$^-$ (*ipso*-NPh), 128.9$^+$ (*m*-NPh), 116.7$^+$ (*p*-NPh), 113.2$^+$ (*o*-NPh), 88.3$^+$ (C^2), 75.1$^-$ (COH), 62.4$^+$ (C^5), 56.7$^-$ (C^4 or C^8), 56.6$^-$ (C^4 or C^8), 32.0$^-$ (C^6 or C^7), 27.2$^+$ (Me), 25.5$^+$ (Me) and 25.0$^-$ (C$_6$ or C$_7$); *m/z* 246 (40%, M$^+$), 188 (60), 187 (100, M − Me$_2$COH) and 77 (30, Ph) (Found: M$^+$, 246.1741. $C_{15}H_{22}N_2O$ requires *M*, 246.1732).

2-Acetyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane 11

Methylmagnesium bromide (0.9 cm^3 of a 3 M solution in Et_2O, 2.7 mmol) was added dropwise to a stirred solution of Weinreb amide **13** (399 mg, 1.45 mmol) in THF (20 cm^3) under argon at −78 °C. After 1 h at −78 °C, saturated aqueous ammonium chloride (1 cm^3) was added and the solution allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with Et_2O (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification by chromatography on silica with Et_2O as eluent gave methyl ketone **11** (328 mg, 98%) as a colourless oil identical (TLC and ^{1}H NMR) to that obtained previously.

2-Benzoyl-3-phenyl-1,3-diazabicyclo[3.3.0]octane 2

Using Mukaiyama's method,[22] phenyl ketone **2**¶¶ was prepared in 83% yield using benzene as solvent (Dean–Stark head) as a yellow foam, R_f(EtOAc) 0.7; ν_{max}(Nujol)/cm^{-1} 1694 (C=O), 1598 (Ph) and 1504 (Ph); δ_H(400 MHz, $CDCl_3$) 8.08 (2 H, d, *J* 7.1, *o*-PhCO), 7.6 (1 H, tt, *J* 1.0 and 7.4, *p*-PhCO), 7.5 (2 H, t, *J* 7.3, *m*-PhCO), 7.15 (2 H, dd, *J* 7.4 and 8.5, *m*-NPh), 6.7 (1 H, t, *J* 7.3, *p*-NPh), 6.4 (2 H, d, *J* 7.8, *o*-NPh), 5.66 (1 H, s, H^2), 3.92 (1 H, dtd, *J* 3.3, 7.1 and 8.0, H^5), 3.79 (1 H, t, *J* 8.0, H$^{4'}$), 3.47 (1 H, ddd, *J* 4.1, 7.2 and 9.3, H$^{8'}$), 3.26 (1 H, t, *J* 7.9, H^4), 2.91 (1 H, dt, *J* 8.0 and 8.6, H^8) and 2.18–1.83 (4 H, m, CH$_2$CH$_2$); δ_C(100 MHz, $CDCl_3$) 195.6$^-$ (C=O), 145.9$^-$ (*ipso*-NPh), 135.3$^-$ (*ipso*-PhCO), 133.2$^+$, 129.3$^+$, 129.0$^+$, 128.7$^+$, 116.9$^+$ (*p*-NPh), 112.4$^+$ (*o*-NPh), 81.7$^+$ (C^2), 62.2$^+$ (C^5), 54.7$^-$ (C^4 or C^8), 53.4$^-$ (C^4 or C^8), 30.3$^-$ (C^6 or C^7) and 24.9$^-$ (C^6 or C^7); *m/z* 292 (40%, M$^+$), 187 (100, M − PhCO), 105 (30, PhCO) and 77 (40, Ph) (Found: M$^+$, 292.1583. $C_{19}H_{20}N_2O$ requires *M*, 292.1576).

In most reactions, phenyl ketone **2** was prepared immediately before use by the following procedure: phenylglyoxal monohydrate (1.0 mmol) was added in one portion to a stirred solution of diamine (*S*)-**8** (1.0 mmol) in toluene (15 cm^3) at room temperature. The resulting mixture was heated at reflux for 45 min with continuous removal of water by means of a Dean–Stark head. After cooling to room temperature, the toluene was evaporated under reduced pressure and the crude product used without further purification.

2-[(1′*S*)-1′-Hydroxy-1′-phenylethyl]-3-phenyl-1,3-diazabicyclo-[3.3.0]octane *syn*-14

Methylmagnesium bromide (0.25 cm^3 of a 3 M solution in Et_2O, 0.75 mmol) was added dropwise to a stirred solution of phenyl ketone **2** (118 mg, 0.4 mmol) in Et_2O (3 cm^3) under argon at −78 °C. After 30 min at −78 °C, saturated aqueous ammonium chloride (1 cm^3) was added and the solution allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with Et_2O (3 × 10 cm^3). The combined organic

§§ Full characterisation of methyl ketone **11** has not previously been described.

¶¶ Mukaiyama has reported most of the characterisation of phenyl ketone **2**.[22]

extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil which contained a ≥97:3 ratio of alcohols *syn*-**14** and *anti*-**14** (by ^{1}H NMR). Purification by chromatography on silica with Et_2O–hexane (1:1) as eluent gave alcohol *syn*-**14**‖‖ (62 mg, 50%) as a pale yellow oil, R_f(1:1 Et_2O–hexane) 0.3; ν_{max}(film)/cm^{-1} 3428 (OH), 1597 (Ph), 1572 (Ph) and 1503 (Ph); δ_H(200 MHz, $CDCl_3$) 7.41–7.37 (2 H, m, Ph), 7.25–7.11 (5 H, m, Ph and *m*-NPh), 6.75–6.68 (3 H, m, *o*- and *p*-NPh), 4.80 (1 H, s, H^2), 3.21–3.11 (1 H, m, H^5), 2.96–2.84 (1 H, m, H$^{4'}$), 2.76–2.62 (2 H, m, H^4 and H$^{8'}$), 2.48 (1 H, td, *J* 7.8 and 8.9, H^8), 1.91–1.25 (4 H, m, CH_2CH_2) and 1.59 (3 H, s, Me); δ_C(50 MHz, $CDCl_3$) 147.7$^-$ (*ipso*-NPh), 145.3$^-$ (*ipso*-Ph), 129.6$^+$ (*m*-NPh), 127.5$^+$, 126.6$^+$, 126.4$^+$, 116.8$^+$ (*p*-NPh), 112.9$^+$ (*o*-NPh), 89.2$^+$ (C^2), 76.0$^-$ (COH), 61.0$^+$ (C^5), 56.4$^-$ (C^4 or C^8), 55.8$^-$ (C^4 or C^8), 31.0$^-$ (C^6 or C^7), 27.9$^+$ (Me) and 24.4$^-$ (C^6 or C^7); *m*/*z* 308 (5%, M$^+$), 290 (40, M − H_2O), 275 (60), 264 (50), 187 [100, M − Ph(Me)COH] and 77 (60, Ph) (Found: M$^+$, 308.1883. $C_{20}H_{24}N_2O$ requires *M*, 308.1889).

2-[(1′*R*)-1′-Hydroxy-1′-phenylethyl]-3-phenyl-1,3-diazabicyclo-[3.3.0]octane *anti*-14

In the same way, phenylmagnesium bromide (0.1 cm^3 of a 3 M solution in Et_2O, 0.3 mmol) and methyl ketone **11** (53 mg, 0.2 mmol) in Et_2O (2 cm^3) gave the crude product as an oil which contained a ≥97:3 ratio of alcohols *anti*-**14** and *syn*-**14** (by ^{1}H NMR). Purification by chromatography on silica with Et_2O–hexane (1:1) as eluent gave alcohol *anti*-**14** (58 mg, 82%) as a colourless oil, R_f(1:1 Et_2O–hexane) 0.3; ν_{max}(film)/cm^{-1} 3428 (OH), 1597 (Ph), 1572 (Ph) and 1503 (Ph); δ_H(200 MHz, $CDCl_3$) 7.53–7.47 (2 H, m, Ph), 7.34–7.20 (3 H, m, Ph), 7.06 (2 H, dd, *J* 7.4 and 8.2, *m*-NPh), 6.64 (1 H, t, *J* 7.1, *p*-NPh), 6.37 (2 H, d, *J* 8.2, *o*-NPh), 4.70 (1 H, s, H^2), 3.90* (1 H, br s, OH), 3.84–3.59 (2 H, m, H$^{4'}$ and H^5), 3.23–3.08 (2 H, m, H^4 and H$^{8'}$), 2.50 (1 H, td, *J* 7.7 and 9.4, H^8), 2.14–2.03 (1 H, m, C*H*$_A$H$_B$CH$_2$), 1.82–1.51 (3 H, m, CH$_A$*H*$_B$C*H*$_2$) and 1.60 (3 H, s, Me); δ_C(50 MHz, $CDCl_3$) 148.1$^-$ (*ipso*-NPh), 145.9$^-$ (*ipso*-Ph), 128.6$^+$ (*m*-NPh), 127.9$^+$, 127.8$^+$, 126.1$^+$, 116.6$^+$ (*p*-NPh), 112.9$^+$ (*o*-NPh), 89.7$^+$ (C^2), 77.3$^-$ (COH), 62.3$^+$ (C^5), 56.4$^-$ (C^4 or C^8), 56.1$^-$ (C^4 or C^8), 31.8$^-$ (C^6 or C^7), 25.1$^-$ (C^6 or C^7) and 24.6$^+$ (Me); *m*/*z* 290 (10%, M − H_2O), 187 [100, M − Ph(Me)COH] and 77 (20, Ph) (Found: M$^+$ − H_2O, 290.1781. $C_{20}H_{24}N_2O$ requires *M* − H_2O, 290.1783).

Addition of methyllithium to phenyl ketone 2 in Et_2O

In the same way, methyllithium (0.2 cm^3 of a 1.4 M solution in Et_2O, 0.28 mmol) and phenyl ketone **2** (48 mg, 0.16 mmol) in Et_2O (3 cm^3) gave the crude product as an oil which contained a 95:5 ratio of alcohols *syn*-**14** and *anti*-**14** (by ^{1}H NMR).

Addition of methyllithium to phenyl ketone 2 in THF

In the same way, methyllithium (0.15 cm^3 of a 1.4 M solution in Et_2O, 0.21 mmol) and phenyl ketone **2** (32 mg, 0.11 mmol) in THF (2 cm^3) gave the crude product as an oil which contained a 61:39 ratio of alcohols *anti*-**14** and *syn*-**14** (by ^{1}H NMR).

Addition of lithiated phosphine oxide to methyl ketone 11 in THF. 2-[(1′*R*)-2′-Diphenylphosphinoyl-1′-hydroxy-1′-methylethyl]-3-phenyl-1,3-diazabicyclo[3.3.0]octane *syn*-15 and 2-[(1′*S*)-2′-diphenylphosphinoyl-1′-hydroxy-1′-methylethyl]-3-phenyl-1,3-diazabicyclo[3.3.0]octane *anti*-15

Butyllithium (1.0 cm^3 of a 1.6 M solution in hexane, 1.6 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (334 mg, 1.6 mmol) in THF (4 cm^3) under argon at −78 °C to give an orange coloured solution. After 30 min at −78 °C, a solution of methyl ketone **11** in THF (2 cm^3) was added dropwise and the resulting solution was stirred at −78 °C for 1.5 h. Saturated aqueous ammonium chloride (2 cm^3) was added and the mixture allowed to warm to room temperature. The THF was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 50 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil which contained an 18:53:29 ratio of methyl ketone **11**, alcohol *syn*-**15** and alcohol *anti*-**15** (by ^{1}H NMR) *i.e.* a 64:36 ratio of alcohols *syn*-**15** and *anti*-**15**. Purification by chromatography on silica with EtOAc–MeOH (20:1) as eluent gave recovered methyl ketone **11** (41 mg, 17%) and, by combining the first four fractions, a 90:10 ratio (by ^{1}H NMR) of alcohols *anti*-**15** and *syn*-**15** (112 mg, 24%). Combining the remaining fractions gave a 90:10 ratio (by ^{1}H NMR) of alcohols *syn*-**15** and *anti*-**15** (254 mg, 54%).

Recrystallisation from EtOAc–MeOH (2:1) of the 90:10 mixture of alcohols *anti*-**15** and *syn*-**15** gave *alcohol anti*-**15** (58 mg, 12%) as cubes, mp >235 °C (from 2:1 EtOAc–MeOH); R_f(EtOAc) 0.2; $[\alpha]_D^{20}$ +17.6 (*c* 1.0 in $CHCl_3$) (Found: C, 72.6; H, 7.0; N, 6.3; P, 7.1%; M$^+$, 446.2111. $C_{27}H_{31}N_2O_2P$ requires C, 72.6; H, 7.0; N, 6.3; P, 6.9%; *M*, 446.2123); ν_{max}(Nujol)/cm^{-1} 3312 (OH), 1595 (Ph), 1504 (Ph), 1440 (P–Ph) and 1160 (P=O); δ_H(400 MHz, $CDCl_3$) 7.81–7.73 (4 H, m, *o*-Ph_2PO), 7.50–7.43 (6 H, m, *m*- and *p*-Ph_2PO), 7.18 (2 H, dd, *J* 7.3 and 8.7, *m*-NPh), 6.83 (2 H, d, *J* 8.0, *o*-NPh), 6.67 (1 H, t, *J* 7.3, *p*-NPh), 4.95 (1 H, s, H^2), 4.22 (1 H, br s, OH), 3.93–3.90 (1 H, m, H^5), 3.75 (1 H, dd, *J* 7.7 and 9.0, H$^{4'}$), 3.13 (1 H, dd, *J* 6.3 and 9.0, H^4), 3.10–3.05 (1 H, m, H$^{8'}$), 2.82 (1 H, dd, *J* 11.0 and 14.9, PC*H*$_A$H$_B$), 2.72 (1 H, dd, *J* 10.5 and 14.8, PCH$_A$*H*$_B$), 2.61 (1 H, td, *J* 7.1 and 9.0, H^8), 2.11–2.04 (1 H, m, H$^{6'}$), 1.78–1.73 (1 H, m, H^7), 1.72–1.61 (1 H, m, H$^{7'}$), 1.60–1.54 (1 H, m, H^6) and 1.19 (3 H, s, Me); δ_C(100 MHz, $CDCl_3$) 148.8$^-$ (*ipso*-NPh), 135.3–128.5 (*m*-NPh and Ph_2PO), 116.7$^+$ (*p*-NPh), 113.5$^+$ (*o*-NPh), 87.0$^+$ (d, *J* 6.7, C^2), 78.1$^-$ (COH), 62.9$^+$ (C^5), 56.7$^-$ (C^4 or C^8), 56.2$^-$ (C^4 or C^8), 37.6$^-$ (d, *J* 70.2, PCH_2), 31.9$^-$ (C^6 or C^7), 26.1$^+$ (d, *J* 3.8, Me) and 25.1$^-$ (C^6 or C^7); *m*/*z* 446 (20%, M$^+$), 428 (80, M − H_2O), 259 [50, $Ph_2P(O)CH_2C(Me)OH$], 227 (70), 201 (40, Ph_2PO), 187 [100, M − $Ph_2P(O)CH_2C(Me)OH$] and 77 (30, Ph).

Repeated recrystallisation from EtOAc–MeOH (2:1) of the 90:10 mixture of alcohols *syn*-**15** and *anti*-**15** returned only the same 90:10 ratio (by ^{1}H NMR) of *alcohols syn*-**15** and *anti*-**15** as plates, mp 195–201 °C (from 2:1 EtOAc–MeOH); R_f(EtOAc) 0.2 (Found: C, 72.2; H, 7.0; N, 6.0; P, 7.1%; M$^+$, 446.2123. $C_{27}H_{31}N_2O_2P$ requires C, 72.6; H, 7.0; N, 6.3; P, 6.9%; *M*, 446.2123); ν_{max}(Nujol)/cm^{-1} 3313 (OH), 1595 (Ph), 1504 (Ph), 1440 (P–Ph) and 1160 (P=O); δ_H(400 MHz, $CDCl_3$) Major diastereoisomer, alcohol *syn*-**15** 7.80–7.74 (4 H, m, *o*-Ph_2PO), 7.50–7.42 (6 H, m, *m*- and *p*-Ph_2PO), 7.18 (2 H, dd, *J* 7.4 and 8.6, *m*-NPh), 6.88 (2 H, d, *J* 8.1, *o*-NPh), 6.68 (1 H, t, *J* 7.3, *p*-NPh), 4.73 (1 H, s, H^2), 4.67 (1 H, br s, OH), 3.82 (1 H, dtd, *J* 3.3, 6.9 and 8.8, H^5), 3.69 (1 H, dd, *J* 7.8 and 8.9, H$^{4'}$), 3.03 (1 H, dd, *J* 7.5 and 8.9, H^4), 2.88 (1 H, dd, *J* 11.2 and 15.0, PC*H*$_A$H$_B$), 2.77 (1 H, dd, *J* 9.4 and 15.0, PCH$_A$*H*$_B$), 2.72 (1 H, ddd, *J* 3.4, 6.9 and 9.8, H$_{8'}$), 2.30 (1 H, td, *J* 7.3 and 9.2, H^8), 2.15–2.03 (1 H, m, C*H*$_A$H$_B$CH$_2$), 1.67–1.61 (3 H, m, CH$_A$*H*$_B$C*H*$_2$) and 1.25 (3 H, s, Me); δ_C(100 MHz, $CDCl_3$) major diastereoisomer, alcohol *syn*-**15** 149.1$^-$ (*ipso*-NPh), 135.2–128.6 (*m*-NPh and Ph_2PO), 116.9$^+$ (*p*-NPh), 113.6$^+$ (*o*-NPh), 88.1$^+$ (d, *J* 9.5, C^2), 79.0$^-$ (d, *J* 5.7, COH), 62.3$^+$ (C^5), 56.9$^-$ (C^4 or C^8), 55.7$^-$ (C^4 or C^8), 37.8$^-$ (d, *J* 70.6, PCH_2), 31.2$^-$ (C^6 or C^7), 25.4$^+$ (d, *J* 6.6, Me) and 25.4$^-$ (C^6 or C^7); *m*/*z* 446 (20%, M$^+$), 428 (40, M − H_2O), 259 [40, $Ph_2P(O)CH_2C(Me)OH$], 227 (50), 215 (70), 201 (40,

‖‖ Alcohol **14** has previously been synthesised by Mukaiyama but it was not isolated.[22,23]

Ph_2PO), 187 [100, M − $Ph_2P(O)CH_2C(Me)OH$] and 77 (20, Ph).

Addition of lithiated phosphine oxide to phenyl ketone 2 in THF. 2-[(1′*R*)-2′-Diphenylphosphinoyl-1′-hydroxy-1′-phenylethyl]-3-phenyl-1,3-diazabicyclo[3.3.0]octane *syn*-16 and 2-[(1′*S*)-2′-diphenylphosphinoyl-1′-hydroxy-1′-phenylethyl]-3-phenyl-1,3-diazabicyclo[3.3.0]octane *anti*-16

In the same way, butyllithium (1.6 cm^3 of a 1.6 M solution in hexane, 2.6 mmol), methyldiphenylphosphine oxide (531 mg, 2.5 mmol) and phenyl ketone **2** [prepared from phenylglyoxal monohydrate (259 mg, 1.7 mmol) and diamine (*S*)-**8** (295 mg, 1.7 mmol)] in THF (13 cm^3) gave the crude product as a white solid which contained a 68:32 ratio of alcohols *syn*-**16** and *anti*-**16** (by ^1H NMR). Purification by chromatography on silica with EtOAc–hexane (3:2) as eluent gave *alcohol syn*-**16** (371 mg, 43%) as needles, mp 188–190 °C (from 10:1 EtOAc–MeOH); R_f(EtOAc) 0.55; $[\alpha]_D^{20}$ −41.2 (*c* 0.5 in $CHCl_3$) (Found: $M^+ - H_2O$, 490.2154. $C_{32}H_{33}N_2O_2P$ requires $M - H_2O$, 490.2174); ν_{max}(Nujol)/cm^{-1} 3310 (OH), 1595 (Ph), 1501 (Ph), 1438 (P–Ph) and 1238 (P=O); δ_H(200 MHz, $CDCl_3$) 7.87–7.76 (2 H, m, *o*-Ph_2PO), 7.54–7.16 (12 H, m, Ph and *m*- and *p*-Ph_2PO), 7.10–6.91 (3 H, m, Ph and *m*-NPh), 6.84 (2 H, d, *J* 7.3, *o*-NPh), 6.68 (1 H, t, *J* 7.2, *p*-NPh), 5.68* (1 H, br s, OH), 5.06 (1 H, s, H^2), 3.45–3.21 (1 H, m, H^5), 3.38 (1 H, dd, *J* 11.8 and 14.7, PCH_AH_B), 2.93–2.69 (4 H, m, H^4, $H^{4'}$, $H^{8'}$ and PCH_AH_B), 2.38 (1 H, td, *J* 7.2 and 8.9, H^8), 1.86–1.50 (3 H, m, $CH_AH_BCH_2$) and 1.40–1.23 (1 H, m, $CH_AH_BCH_2$); δ_C(50 MHz, $CDCl_3$) 148.6$^-$ (*ipso*-NPh), 142.7$^-$ (d, *J* 5.5, *ipso*-Ph), 133.6–125.9 (Ph, *m*-NPh and Ph_2PO), 116.3$^+$ (*p*-NPh), 113.3$^+$ (*o*-NPh), 89.3$^+$ (d, *J* 9.6, C^2), 81.1$^-$ (d, *J* 5.7, COH), 62.1$^+$ (C^5), 56.4$^-$ (C^4 or C^8), 55.5$^-$ (C^4 or C^8), 37.4$^-$ (d, *J* 70.4, PCH_2), 31.8$^-$ (C^6 or C^7) and 25.1$^-$ (C^6 or C^7); *m*/*z* 490 (20%, M − H_2O), 334 [40, $Ph_2P(O)CH_2C$-(Ph)(OH)CH], 321 [50, $Ph_2P(O)CH_2C(Ph)OH$], 201 (100, Ph_2PO), 187 [20, M − $Ph_2P(O)CH_2C(Ph)OH$] and 77 (80, Ph) and *alcohol anti*-**16** (170 mg, 20%) as plates, mp 218–220 °C decomp. (from 10:1 EtOAc–MeOH); R_f(EtOAc) 0.45; $[\alpha]_D^{20}$ +8.4 (*c* 0.6 in $CHCl_3$) (Found: C, 75.6; H, 6.5; N, 5.3; P, 6.1%; M^+, 508.2300. $C_{32}H_{33}N_2O_2P$ requires C, 75.6; H, 6.5; N, 5.5; P, 6.1%; *M*, 508.2280); ν_{max}(Nujol)/cm^{-1} 3311 (OH), 1594 (Ph), 1501 (Ph), 1438 (P–Ph) and 1238 (P=O); δ_H(200 MHz, $CDCl_3$) 7.71–7.21 (14 H, m, Ph and Ph_2PO), 7.17–7.05 (3 H, m, Ph and *m*-NPh), 6.94 (2 H, d, *J* 8.1, *o*-NPh), 6.68 (1 H, t, *J* 7.2, *p*-NPh), 5.63 (1 H, s, H^2), 5.48* (1 H, br s, OH), 3.25 (1 H, dd, *J* 14.4 and 15.0, PCH_AH_B), 3.20–3.13 (1 H, m, H^5), 3.07–2.87 (2 H, m, H^4 and $H^{8'}$), 2.95 (1 H, dd, *J* 6.6 and 15.2, PCH_AH_B), 2.77 (1 H, dd, *J* 5.4 and 6.8, H^4), 2.53 (1 H, td, *J* 8.4 and 9.0, H^8), 1.94–1.81 (1 H, m, $CH_AH_BCH_2$) and 1.72–1.42 (3 H, m, $CH_AH_BCH_2$); δ_C(50 MHz, $CDCl_3$) 148.3$^-$ (*ipso*-NPh), 144.5$^-$ (d, *J* 6.6, *ipso*-Ph), 136.5–126.8 (Ph, *m*-NPh and Ph_2PO), 116.7$^+$ (*p*-NPh), 113.5$^+$ (*o*-NPh), 87.3$^+$ (d, *J* 5.7, C^2), 78.1$^-$ (d, *J* 6.0, COH), 61.5$^+$ (C^5), 57.0$^-$ (C^4 or C^8), 55.9$^-$ (C^4 or C^8), 37.7$^-$ (d, *J* 70.9, PCH_2), 31.5$^-$ (C^6 or C^7) and 24.5$^-$ (C^6 or C^7); *m*/*z* 508 (10%, M^+), 490 (40, M − H_2O), 321 [10, $Ph_2P(O)CH_2C(Ph)OH$], 201 (60, Ph_2PO), 187 [100, M − $Ph_2P(O)CH_2C(Ph)OH$] and 77 (70, Ph).

Addition of lithiated phosphine oxide to methyl ketone 11 in toluene

In the same way, methyldiphenylphosphine oxide (33 mg, 0.15 mmol), butyllithium (0.1 cm^3 of a 1.6 M solution in hexane, 0.16 mmol) and methyl ketone **11** (20 mg, 0.09 mmol) in toluene (2 cm^3) gave the crude product as a colourless oil which contained a 22:56:22 ratio of methyl ketone **11**, alcohol *anti*-**15** and alcohol *syn*-**15** (by ^1H NMR) *i.e.* a 72:28 ratio of alcohols *anti*-**15** and *syn*-**15**.

Addition of lithiated phosphine oxide to phenyl ketone 2 in toluene

In the same way, methyldiphenylphosphine oxide (83 mg, 0.4 mmol), butyllithium (0.3 cm^3 of a 1.3 M solution in hexane, 0.4 mmol) and phenyl ketone **2** (100 mg, 0.34 mmol) in toluene (11 cm^3) gave the crude product as a colourless oil which contained a 27:44:29 ratio of phenyl ketone **2**, alcohol *anti*-**16** and alcohol *syn*-**16** (by ^1H NMR) *i.e.* a 60:40 ratio of alcohols *anti*-**16** and *syn*-**16**.

Addition of lithiated phosphine oxide to methyl ketone 11 in THF in the presence of TMEDA

In the same way, methyldiphenylphosphine oxide (69 mg, 0.3 mmol), TMEDA (50 mm^3, 0.3 mmol), butyllithium (0.25 cm^3 of a 1.4 M solution in hexane, 0.35 mmol) and methyl ketone **11** (49 mg, 0.2 mmol) in THF (2 cm^3) gave the crude product as a colourless oil which contained a 6:72:22 ratio of methyl ketone **11**, alcohol *syn*-**15** and alcohol *anti*-**15** (by ^1H NMR) *i.e.* a 77:23 ratio of alcohols *syn*-**15** and *anti*-**15**. Purification by chromatography on silica with EtOAc–MeOH (40:1) as eluent gave recovered methyl ketone **11** (3 mg, 6%) and an 85:15 ratio (by ^1H NMR) of alcohols *syn*-**15** and *anti*-**15** (63 mg, 67%). In this case, recrystallisation from EtOAc–MeOH (100:1) of the 85:15 mixture of alcohols *syn*-**15** and *anti*-**15** gave alcohol *syn*-**15** (14 mg, 15%) as a single diastereoisomer by ^1H and ^{13}C NMR spectroscopy.

Addition of lithiated phosphine oxide to phenyl ketone 2 in THF in the presence of TMEDA

In the same way, methyldiphenylphosphine oxide (50 mg, 0.2 mmol), TMEDA (70 mm^3, 0.4 mmol), butyllithium (0.15 cm^3 of a 1.5 M solution in hexane, 0.2 mmol) and phenyl ketone **2** (48 mg, 0.16 mmol) in THF (2 cm^3) gave the crude product as a colourless oil which contained a 54:46 ratio of alcohols *syn*-**16** and *anti*-**16** (by ^1H NMR).

Addition of the phosphine oxide cerate reagent to methyl ketone 11 in THF

Butyllithium (0.19 cm^3 of a 1.4 M solution in hexane, 0.27 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (58 mg, 0.27 mmol) in THF (2 cm^3) under argon at −78 °C. After 30 min at −78 °C, this orange coloured solution was added to a suspension of dry $CeCl_3$ [prepared in the following way:[35] $CeCl_3 \cdot 7H_2O$ (101 mg, 0.3 mmol) was stirred at 140 °C and 1 mmHg pressure for 4 h; after cooling to 0 °C, cold THF (5 cm^3) was added and the resulting suspension stirred for 12 h at room temperature] and stirred at −78 °C for a further 1 h. Then, a solution of methyl ketone **11** (50 mg, 0.22 mmol) in THF (2 cm^3) was added dropwise and the resulting solution was stirred at −78 °C for 1.5 h. Saturated aqueous ammonium chloride (2 cm^3) was added and the mixture allowed to warm to room temperature. The THF was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 20 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid which contained a 24:55:21 ratio of methyl ketone **11**, alcohol *syn*-**15** and alcohol *anti*-**15** (by ^1H NMR) *i.e.* a 73:27 ratio of alcohols *syn*-**15** and *anti*-**15**.

Attempted addition of the phosphine oxide titanium reagent to methyl ketone 11 in CH_2Cl_2

Butyllithium (0.25 cm^3 of a 1.4 M solution in hexane, 0.35 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (71 mg, 0.3 mmol) in CH_2Cl_2 (2 cm^3) under argon at −78 °C. After 30 min at −78 °C, titanium tetrachloride (40 mm^3, 0.4 mmol) was added dropwise and the resulting solution stirred at −78 °C for a further 1 h. Then, a solution of methyl ketone **11** (38 mg, 0.17 mmol) in CH_2Cl_2 (1 cm^3) was added dropwise and the resulting solution was stirred at −78 °C for 30 min and then allowed to warm to 0 °C. Saturated aqueous ammonium chloride (2 cm^3) was

added and the mixture allowed to warm to room temperature. The mixture was added to CH_2Cl_2–water (1:1; 20 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil which contained no aminal products whatsoever (by ^1H NMR).

Addition of lithiated methyldiphenylphosphine oxide to methyl ketone 11 in toluene in the presence of lithium bromide. 2-[(1′*S*)-2′-Diphenylphosphinoyl-1′-hydroxy-1′-methylethyl]-3-phenyl-1,3-diazabicyclo[3.3.0]octane *anti*-15

Methyllithium as a complex with lithium bromide (1.4 cm^3 of a 1.5 M solution in Et_2O, 2.1 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (462 mg, 2.14 mmol) in toluene (8 cm^3) under argon at 0 °C. A white precipitate immediately formed which slowly dissolved over 30 min to give a pale yellow solution. After cooling to −78 °C, a solution of methyl ketone **11** (332 mg, 1.40 mmol) in toluene (2 cm^3) was added dropwise and the resulting solution stirred at −78 °C for 1.5 h. Saturated aqueous ammonium chloride (1 cm^3) was added and the mixture allowed to warm to room temperature. The toluene was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 50 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid which contained a 7:80:13 ratio of methyl ketone **11**, alcohol *anti*-**15** and alcohol *syn*-**15** (by ^1H NMR) *i.e.* an 86:14 ratio of alcohols *anti*-**15** and *syn*-**15**. Purification by chromatography on silica with EtOAc–MeOH (20:1) as eluent gave recovered methyl ketone **11** (13 mg, 4%) and a 91:9 ratio (by ^1H NMR) of alcohols *anti*-**15** and *syn*-**15** (396 mg, 62%). Recrystallisation from EtOAc–MeOH (2:1) of the 91:9 mixture of alcohols *anti*-**15** and *syn*-**15** gave alcohol *anti*-**15** (304 mg, 47%) as a single diastereomer by ^1H and ^{13}C NMR spectroscopy.

Addition of lithiated phosphine oxide to phenyl ketone 2 in toluene in the presence of lithium bromide. 2-[(1′*S*)-2′-Diphenylphosphinoyl-1′-hydroxy-1′-phenylethyl]-3-phenyl-1,3-diazabicyclo[3.3.0]octane *anti*-16

In the same way, methyllithium as a complex with lithium bromide (0.9 cm^3 of a 1.5 M solution in Et_2O, 1.35 mmol), methyldiphenylphosphine oxide (292 mg, 1.35 mmol) and phenyl ketone **2** [prepared from phenylglyoxal monohydrate (141 mg, 0.9 mmol) and diamine (*S*)-**8** (160 mg, 0.9 mmol)] in toluene (7 cm^3) gave the crude product as a white solid which contained an 84:16 ratio of alcohols *anti*-**16** and *syn*-**16** (by ^1H NMR). Purification by chromatography on silica with EtOAc–hexane (3:2) as eluent gave alcohol *syn*-**16** (25 mg, 5%) identical (TLC and ^1H NMR) to that obtained previously and alcohol *anti*-**16** (264 mg, 57%) identical (TLC and ^1H NMR) to that obtained previously.

Addition of lithiated phosphine oxide to methyl ketone 11 in THF in the presence of lithium bromide

In the same way, methyldiphenylphosphine oxide (31 mg, 0.14 mmol), methyllithium as a complex with lithium bromide (0.1 cm^3 of a 1.5 M solution in Et_2O, 0.15 mmol) and methyl ketone **11** (17 mg, 0.07 mmol) in THF (2 cm^3) gave the crude product as a colourless oil which contained a 25:53:22 ratio of methyl ketone **11**, alcohol *anti*-**15** and alcohol *syn*-**15** (by ^1H NMR) *i.e.* a 71:29 ratio of alcohols *anti*-**15** and *syn*-**15**.

Addition of lithiated phosphine oxide to phenyl ketone 2 in THF in the presence of lithium bromide

In the same way, methyldiphenylphosphine oxide (50 mg, 0.23 mmol), methyllithium as a complex with lithium bromide (0.15 cm^3 of a 1.5 M solution in Et_2O, 0.23 mmol) and phenyl ketone **2** (49 mg, 0.17 mmol) in THF (2 cm^3) gave the crude product as a white solid which contained a 64:36 ratio of alcohols *anti*-**16** and *syn*-**16** (by ^1H NMR).

Addition of the phosphine oxide Grignard reagent to methyl ketone 11 in THF

Butyllithium (0.25 cm^3 of a 1.4 M solution in hexane, 0.35 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (72 mg, 0.3 mmol) in THF (1.5 cm^3) under argon at 0 °C. After 30 min, solid magnesium bromide (65 mg, 0.5 mmol) was added in one portion and the resulting yellow solution stirred at 0 °C for 30 min. Then, a solution of methyl ketone **11** (57 mg, 0.25 mmol) in THF (0.5 cm^3) was added dropwise and the resulting solution was stirred at 0 °C for 2 h. Saturated aqueous ammonium chloride (2 cm^3) was added and the mixture allowed to warm to room temperature. The THF was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 20 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid which contained a 62:31:7 ratio of methyl ketone **11**, alcohol *anti*-**15** and alcohol *syn*-**15** (by ^1H NMR) *i.e.* an 82:18 ratio of alcohols *anti*-**15** and *syn*-**15**. Purification by chromatography on silica with EtOAc as eluent gave recovered methyl ketone **11** (17 mg, 30%) and a 91:9 ratio (by ^1H NMR) of alcohols *anti*-**15** and *syn*-**15** (40 mg, 36%).

Addition of the phosphine oxide Grignard reagent to phenyl ketone 2 in THF

In the same way, methyldiphenylphosphine oxide (86 mg, 0.4 mmol), butyllithium (0.25 cm^3 of a 1.6 M solution in hexane, 0.4 mmol), magnesium bromide (76 mg, 0.4 mmol) and phenyl ketone **2** (57 mg, 0.25 mmol) in THF (2 cm^3) gave the crude product as a colourless oil which contained a 79:20:1 ratio of phenyl ketone **2**, alcohol *anti*-**16** and alcohol *syn*-**16** (by ^1H NMR) *i.e.* a 95:5 ratio of alcohols *anti*-**16** and *syn*-**16**.

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