Investigation of the configurational stability of lithiated phosphine oxides using the Hoffmann test: X-ray structures of (2*S**,3*S**,4*R**)-2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-ol and (2*S**,4*S**)-2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-one

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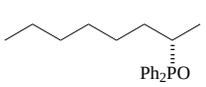
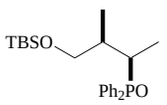
The Hoffmann test (reaction of a racemic organolithium with a phenylalanine-derived aldehyde) is used to show that lithiated diphenylphosphine oxides are not configurationally stable in THF at −78 °C (usual reaction conditions) on the timescale of their rate of reaction with the aldehyde. The test is carried out by reacting lithiated ethyldiphenylphosphine oxide with a phenylalanine-derived aldehyde and because all four diastereoisomeric alcohols are obtained, it is necessary to determine the relative stereochemistry of the products. This is done using a combination of synthesis and X-ray crystallography of (2*S,3*S**,4*R**)-2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-ol and (2*S**,4*S**)-2-(*N*,*N*-dibenzylamino)-2-diphenylphosphinoyl-1-phenylpentan-3-one.**

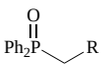
Recently,[1,2] we demonstrated that lithium derivatives of diphenylphosphine oxides are not configurationally stable under the usual conditions that they are used in synthesis (THF solution, −78 °C). In other words, a chiral centre at a carbon *α* to phosphorus in diphenylphosphine oxides such as **1** does not maintain its configuration when it is lithiated and then reacted with an electrophile. Prior to our study, virtually nothing was known about the configurational stability of phosphorus-stabilised organolithium derivatives.† In an isolated example, Denmark and Dorow showed that a lithiated phosphonamide was not configurationally stable.[4]



(*S*)-**1**



syn-**2**



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Most of the previously reported configurational stability investigations[5] have concentrated on oxygen-,[6,7] nitrogen-,[8,9] sulfur- and selenium-stabilised[10,11] organolithium derivatives. In general, sulfur- and selenium-stabilised organolithiums require a low temperature (*e.g.* below −78 °C) and/or a short timescale of investigation (*e.g. in situ* electrophilic quenches) for configurational stability. This is in contrast to oxygen- and nitrogen-stabilised organolithiums which are typically configurationally stable at −78 °C and sometimes at even higher temperatures.[6–9] In situations where lithiation is followed by racemisation, some suggestions for possible racemisation mechanisms have been proposed.[8,12]

Three different methods are usually used to determine whether organolithum compounds are configurationally stable or not. Of these, lithiation of enantiomerically enriched or diastereoisomerically pure compounds has been used most often. Indeed, we initially used phosphine oxides (*S*)- and (*R*)-**1** as well as *syn*- and *anti*-**2** to study the configurational stability of our lithiated phosphine oxides.[1,2] However, in 1987, Hoffmann introduced a new and superior method for investigating configurational stability: the 'Hoffmann test'.[13,14] We now report in full[15] the successful application of this test to investigate the configurational stability of lithiated diphenylphosphine oxides.

The Hoffmann test is completely different from the 'classical' methods that we[1,2] and others[6–11] have previously used to investigate configurational stability. Perhaps its most important attribute is that it uses a racemic organolithium compound generated from a prochiral precursor (*e.g.* phosphine oxide **3**); the test requires neither enantiomerically enriched nor diastereoisomerically pure precursors to the organolithium compounds under investigation. So far, Hoffmann has used the test to gain information on the configurational stability of organolithiums derived from sulfides,[16,17] selenides,[16] sulfones[17] and some benzyl-substituted compounds.[17,18] More recently, other research groups have also found such a test useful: Beak has used it to investigate a benzyl-substituted organolithium compound[19] and we[15] have used it with our lithiated phosphine oxides.

We wanted to use the Hoffmann test to study the configurational stability of lithiated phosphine oxides because it directly addressed two remaining issues. First of all, our studies so far[1,2] have provided us with information on the configurational stability of lithium derivatives of secondary phosphine oxides (*e.g.* **1** and **2**) only. No information had been obtained about the corresponding primary phosphine oxides **3** but the Hoffmann test would allow us to study these directly. Secondly, as we shall see, the Hoffmann test is essentially an internal aldehyde electrophilic quench and we reasoned that this was the shortest possible intermolecular timescale available for investigating configurational stability. Previously, by using internal electrophilic quenches,[1,2] we had shown that lithiated phosphine oxides were not configurationally stable on the timescale of their reaction with cyclobutanone[20] but our attempts at carrying out internal quenches with aldehydes had been unsuccessful.‡

Before we describe our own Hoffmann test experiments, it is useful to summarise the important features of the test. This is primarily because the theoretical and practical basis of the test

† The configurational stability of a free carbanion generated from a diphenylphosphine oxide using potassium *tert*-butoxide in refluxing polar solvents (*e.g.* 2-methylpropan-2-ol, methanol and DMSO) was investigated some time ago by Cram and co-workers.[3]

‡ Seebach has successfully used benzaldehyde as an internal electrophile to trap a lithium enolate derived from an amino acid.[21] However, we did not observe any addition products when we added LDA to a THF solution of butyldiphenylphosphine oxide and benzaldehyde.[2]

Table 1 Hoffmann test with organolithium **5** and aldehyde **4**

Entry	R	Aldehyde	Ratios [a] (yield, %)	Conclusion
1	Ph	*rac*-**4** [b]	36:61 (90)	—
2	Ph	(*S*)-**4** [b]	40:60 (90)	Config. unstable
3	Pr	*rac*-**4** [c]	70:30 (87)	—
4	Pr	(*S*)-**4** [c]	52:48 (81)	Config. stable

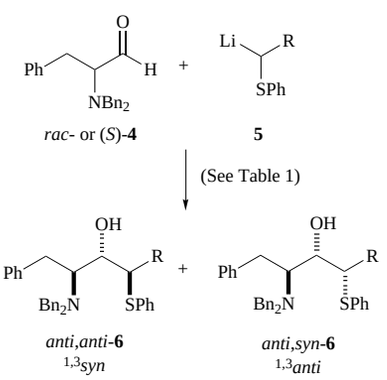
[a] Ratio of ^{1,3}*anti*:^{1,3}*syn*. [b] THF, −78 °C. [c] Methyl-THF, −120 °C.

is completely different to that of the 'classical' methods that are usually used to study configurational stability.

Introduction to the Hoffmann test

The test is composed of two separate experiments. In the first experiment, a *racemic* organolithium is reacted with a *racemic* chiral electrophile (aldehyde **4** is almost always used§) and the ratio of diastereoisomeric products is determined (experiment 1). Then, exactly the same experiment is carried out but with a *racemic* organolithium and an *enantiomerically enriched* electrophile and the ratio of products determined (experiment 2). Perhaps surprisingly, a comparison of these two ratios allows one to determine whether the organolithium is configurationally stable or not *on the timescale of its rate of reaction with the electrophile*.

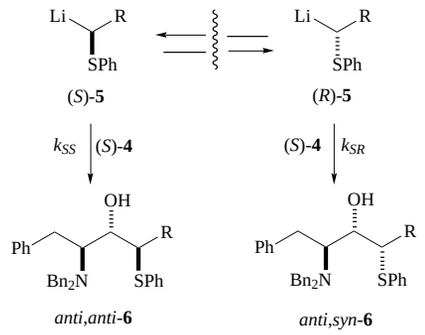
In order to investigate the configurational stability of sulfur-stabilised organolithiums **5** (R = Ph and Pr), Hoffmann carried out the reactions depicted in Scheme 1 and his results are shown



Scheme 1

in Table 1.[16,17] Since reaction of organolithium **5** (R = Ph) with *rac*- and (*S*)-**5** generated essentially the same ratio of alcohols **6** (Entries 1 and 2), Hoffmann concluded that organolithium **5** (R = Ph) was not configurationally stable.[17] In contrast, with organolithium **5** (R = Pr), the ratios of alcohols **6** obtained from the two experiments were significantly different¶ (Entries 3 and 4) indicating that organolithium **5** (R = Pr) was configurationally stable under these conditions.[16] The ratio of interest in the Hoffmann test is the ^{1,3}*syn*:^{1,3}*anti* ratio and in these two examples, only two products were obtained because of the excellent Felkin[22] selectivity exhibited by aldehyde **4**.[23,24] When this occurs, the Hoffmann test can even be used to investigate configurational stability without identifying the products. However, this is not always the case.[13] Sometimes the diastereoisomeric products need to be identified so that the ^{1,3}*anti*:^{1,3}*syn* ratio can be accurately determined.

It is perhaps surprising to observe a difference in the ratio of alcohols **6** obtained from the reactions of organolithium **5** (R = Pr) with aldehyde *rac*-**4** and (*S*)-**4** (Entries 3 and 4). An explanation of the observed 52:48 ratio of alcohols **6** obtained from the reaction with aldehyde (*S*)-**4** (Entry 4) is shown in Scheme 2. Intially there is a 50:50 mixture of organolithiums



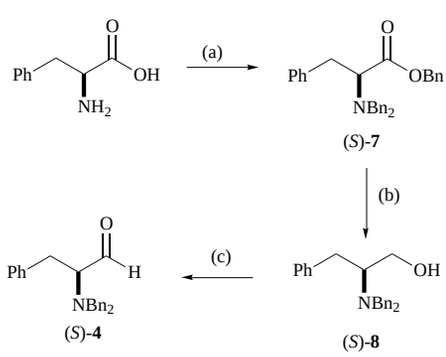
Scheme 2 Configurationally stable organolithium **5**

(*R*)- and (*S*)-**5** and as the organolithium is configurationally stable [*i.e.* (*R*)- and (*S*)-**5** do not interconvert], a 50:50 mixture of alcohols **6** should (in theory) be obtained.

However, there are two potential traps. First of all, the rates of formation of the two diastereoisomeric products (k_{SS} and k_{SR}) are not necessarily the same and so the two products will accumulate at different rates. Thus, intercepting the reaction before it has reached completion could give a non-50:50 ratio even though the organolithium is configurationally stable. For this reason, a good yield (*i.e.* high conversion) from the second experiment is a prerequisite of an accurate Hoffmann test. Secondly, if the rates k_{SS} and k_{SR} are not sufficiently different, then an approximately 50:50 ratio of products could be obtained from the second experiment even though the organolithium is *not* configurationally stable. This is the reason for the first experiment. The ratio of diastereoisomeric products obtained from the first experiment merely reflects the relative rates of their formation (*i.e.* k_{SS} and k_{SR})—if this deviates from 50:50 [*e.g.* the ratio was 70:30 for **5** (R = Pr); Entry 3] then the Hoffmann test can be used to investigate configurational stability. Using a more detailed mathematical analysis, Hoffmann has shown that the results are most meaningful when the ratio of diastereoisomeric products falls in the range of 60:40 to 75:25.[13]

Background synthetic work

For our Hoffmann test studies, we needed to prepare aldehydes *rac*- and (*S*)-**4** and a route described by Reetz *et al.*[23] was used (although, to our knowledge, the full details have not previously been reported); it is outlined in Scheme 3 for the synthesis of



Scheme 3 *Reagents and conditions:* (a) 3 equiv. K_2CO_3, 3.5 equiv. BnBr, EtOH–water (5:1), reflux, 12 h (83%); (b) $LiAlH_4$, THF, 0 °C, 1 h (80%); (c) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; (ii) $Et_3N \longrightarrow 0$ °C; (iii) water (93%)

aldehyde (*S*)-**4**. Initially, (−)-phenylalanine was converted into benzyl ester (*S*)-**7** using 3 equiv. of potassium carbonate and benzyl bromide, a method described by Lagu *et al.*[25] (and modified from that originally reported by Reetz *et al.*[23]). Reduction of benzyl ester (*S*)-**7** with lithium aluminium hydride gave alcohol (*S*)-**8** which was oxidised to the required aldehyde (*S*)-**4** using Swern conditions.[26] Dess–Martin periodinane oxidation[27] was also successful but as aldehyde **4**

§ The Hoffmann test has, however, been carried out with other electrophiles.[18,19]

¶ In particular, an essentially 50:50 ratio of alcohols **6** was obtained from the reaction between organolithium **5** (R = Pr) and aldehyde (*S*)-**4**.

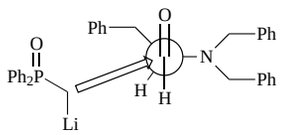
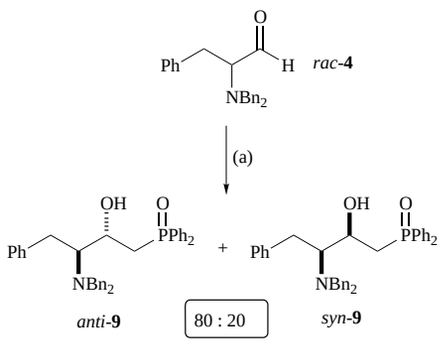


Fig. 1

obtained in this way was of lower purity, we preferred the Swern conditions. For reactions of aldehydes *rac*- and (*S*)-**4** described in this paper, the aldehydes were always freshly prepared by Swern oxidation of the corresponding alcohols *rac*- and (*S*)-**8**.‖

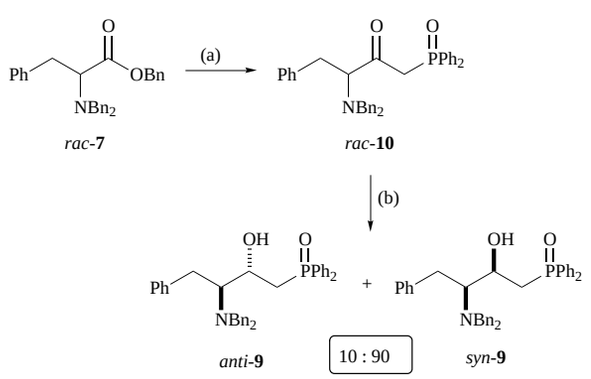
Before we carried out the Hoffmann test experiments, the inherent Felkin selectivity of aldehyde **4** in reactions with lithiated phosphine oxides was established. Thus, methyldiphenylphosphine oxide was lithiated and reacted with aldehyde *rac*-**4** to give a 50% yield of an 80:20 mixture of alcohols *anti*- and *syn*-**9** (Scheme 4); purification by HPLC gave a 22% yield of



Scheme 4 *Reagents and conditions:* (a) (i) $Ph_2P(O)Me$, BuLi, THF, −78 °C, 2 h; (ii) NH_4Cl (50%)

pure alcohol *anti*-**9**. The *anti* stereochemistry of the major product was assigned from precedent[23,24] and assumes that reaction occurs *via* the Felkin–Anh[22] transition state depicted in Fig. 1 (the sterically demanding and electronegative dibenzylamino group is perpendicular to the carbonyl group). In fact, the selectivity was not as high as we had expected and our result can be contrasted with the high levels of Felkin selectivity observed in other reactions (see Scheme 1).

The stereochemical assignment in the phosphine oxide addition reaction described above was corroborated by a synthesis of the other diastereoisomer of alcohol **9** (Scheme 5). An acyl-

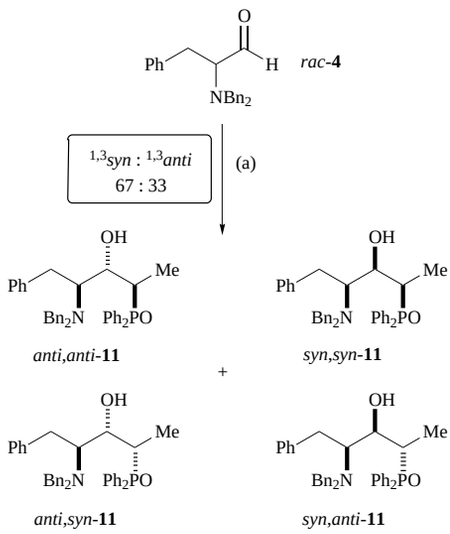


Scheme 5 *Reagents and conditions:* (a) (i) $Ph_2P(O)Me$, BuLi, THF, −78 °C, 2 h; (ii) NH_4Cl (58%); (b) $NaBH_4$, MeOH, −20 °C, 3 h (100% crude; 58% yield of pure *syn*-**9**)

ation reaction between lithiated methyldiphenylphosphine oxide and benzyl ester *rac*-**7** generated a 58% yield of β-keto phosphine oxide *rac*-**10** which was reduced using conditions described by Reetz *et al.*[30] (sodium borohydride, MeOH, −20 °C) to give a quantitative yield of a 90:10 mixture of alcohols *syn*- and *anti*-**9**. Recrystallisation afforded pure *syn*-**9**. The stereoselectivity was once again assigned from precedent[30] and can be rationalised in terms of a Felkin[22] non-chelation controlled reduction.

Hoffmann test reactions with lithiated phosphine oxides

For the first of our Hoffmann test experiments, lithiated ethyldiphenylphosphine oxide was reacted with aldehyde *rac*-**4** to give all four possible diastereoisomeric alcohol products **11** (Scheme 6). We were not too surprised by this because we had



Scheme 6 *Reagents and conditions:* (a) (i) $Ph_2P(O)Et$, BuLi, THF, −78 °C, 6 h; (ii) NH_4Cl (63%)

already established that the Felkin selectivity of aldehyde **4** in reactions with lithiated phosphine oxides was not particularly good (see Scheme 4). Using ^1H NMR spectroscopy, the ratio was accurately determined as 27:40:28:5. When all four diastereoisomeric products are obtained in a Hoffmann test experiment, it is necessary to assign the relative stereochemistry and to identify the alcohols with the same 1,3 relative stereochemistry.** By repeated chromatography, we isolated a pure sample of the major product from this reaction and identified it as alcohol *anti*,*anti*-**11** using X-ray crystallography (Fig. 2). Despite this, we were unable to identify the relative stereochemistry of the other three diastereoisomeric alcohols and so attention was switched to a reduction approach to the same alcohols **11**.

An acylation reaction between lithiated ethyldiphenylphosphine oxide and benzyl ester *rac*-**4** actually proceeded with high stereoselectivity to give a 66% isolated yield of a 90:10 mixture of β-keto phosphine oxides *rac*-**12** (Scheme 7). The major product was obtained pure by recrystallisation and identified as β-keto phosphine oxide *anti*-**12** by X-ray crystallography (Fig. 3).†† Subsequent sodium borohydride reduction to alcohols *anti*,*syn*- and *syn*,*anti*-**11** (90:10 ratio but diastereoisomers not assigned) enabled us to identify which of alcohols **11** had the same 1,3 relative stereochemistry (Scheme 7). In this way, we assigned a 67:33 ^{1,3}*syn*:^{1,3}*anti* ratio of alcohols **11** obtained from the first of our Hoffmann test experiments (Scheme 6). As discussed in an earlier section, this ratio is in fact in the optimum range for carrying out the test.[13]

‖ An alternative synthesis of aldehyde (*S*)-**4** suitable for large-scale preparations has very recently been reported.[28] This new route minimises the use of benzyl bromide, avoids the use of pyrophoric lithium aluminium hydride and uses a pyridine–sulfur trioxide oxidation[29] at 10–15 °C in place of the low temperature (−78 °C) Swern oxidation.

** Hoffmann had found himself in the same unfortunate situation when he first used the test to comment on configurational stability.[13]

†† Some of the synthetic and mechanistic points of interest in this reaction (including a suggested explanation for the observed selectivity) are described in the next section.

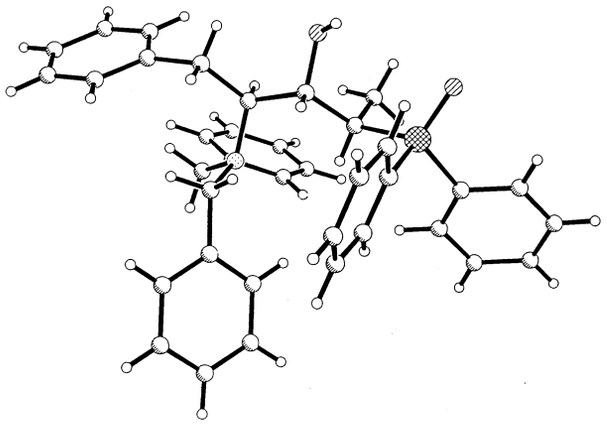


Fig. 2 X-Ray crystal structure of *anti*,*anti*-**11**

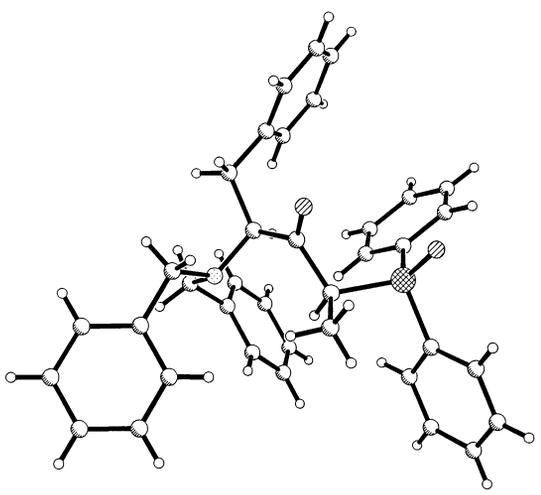
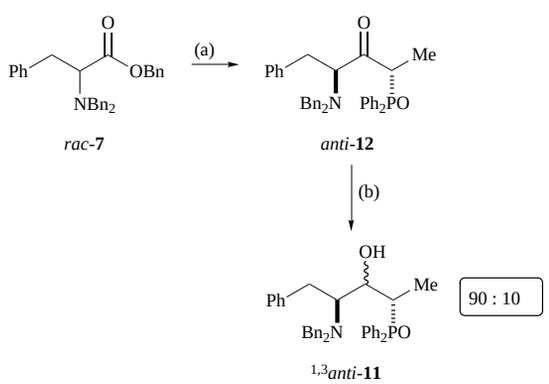
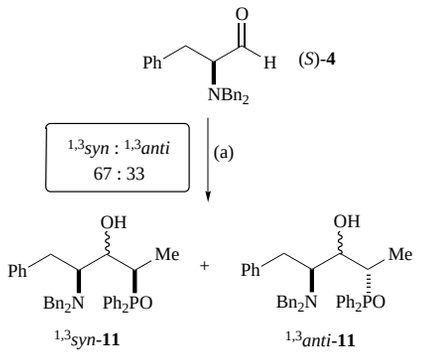


Fig. 3 X-Ray crystal structure of *anti*-**12**



Scheme 7 *Reagents and conditions:* (a) (i) $Ph_2P(O)Et$, BuLi, THF, −78 °C, 6 h; (ii) NH_4Cl (66% yield of a 90 : 10 mixture of *anti*- and *syn*-**12**); (b) $NaBH_4$, EtOH, room temp., 16 h (100%)

With the second experiment of the Hoffmann test, there are two important practical considerations:[13] (i) a pre-cooled solution of the organolithium is added to a solution of the electrophile (inverse addition) to ensure that the timescale of the test is indeed the rate of reaction with the electrophile; (ii) a ten-fold excess of the electrophile is used to ensure that the reaction reaches completion. Thus, a solution of lithiated ethyldiphenylphosphine oxide was added to a stirred solution of ten equivalents of aldehyde (*S*)-**4** in THF at −78 °C to give a 28 : 39 : 27 : 6 ratio of alcohols **11** at ≥95% completion as judged by ^{1}H NMR spectroscopy of the crude reaction mixture (Scheme 8). The ^{1,3}*syn* : ^{1,3}*anti* ratio was determined to be 67 : 33, identical to that obtained from the first experiment. Significantly, purification by chromatography afforded a 93% yield of essentially the same mixture of alcohols **11**.

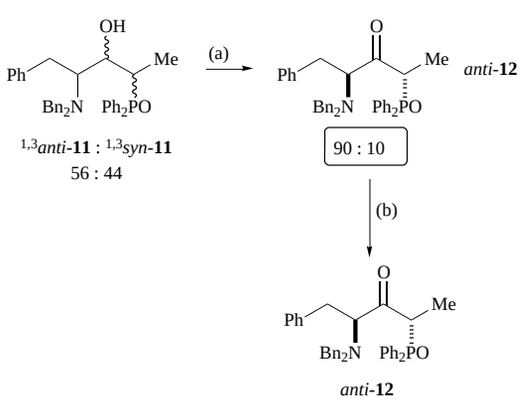


Scheme 8 *Reagents and conditions:* (a) (i) $Ph_2P(O)Et$, BuLi, THF, −78 °C, 6 h; (ii) NH_4Cl (93%)

Since the conversion of ethyldiphenylphosphine oxide into alcohols **11** is complete using aldehyde (*S*)-**4** (≥95% conversion by ^{1}H NMR spectroscopy; chemical yield, 93%) and since the ^{1,3}*syn* : ^{1,3}*anti* ratio was 67 : 33 in both of the Hoffmann test experiments, we are able to conclude that organolithium compounds derived from primary phosphine oxides (*e.g.* **3**) are not configurationally stable in THF at −78 °C even on the timescale of their reaction with aldehyde **4**. This result is consistent with our earlier findings.[1,2]

Additional results

The highly stereoselective formation of β-keto phosphine oxide *anti*-**12** from an acylation reaction between benzyl ester *rac*-**4** and lithiated ethyldiphenylphosphine oxide (Scheme 7) merits further discussion. In fact, such an acylation reaction could have been used in a Hoffmann test study as this reaction would not have suffered from the complication of multiple diastereoisomeric products (unlike reaction with aldehyde **4**). However, the observed 90:10 ratio is not in the optimum range[13] for the test and, more importantly, we believe that the observed selectivity is due to a thermodynamically driven equilibration of ketones *anti*- and *syn*-**12** by enolisation of the now quite acidic proton on the carbon between the diphenylphosphinoyl and ketone groups. We suggest this because the same 90 : 10 ratio of β-keto phosphine oxides *anti*- and *syn*-**12** was obtained when we oxidised a 44 : 56 mixture of alcohols ^{1,3}*syn*- and ^{1,3}*anti*-**11** using Dess–Martin's periodinane[27] (Scheme 9). Even with this mild



Scheme 9 *Reagents and conditions:* (a) Dess–Martin periodinane, CH_2Cl_2, room temp., 12 h (49%); (b) (i) BuLi, THF, −78 °C, 30 min; (ii) MeOH (77%)

oxidising reagent, epimerisation has occurred to give what we presume to be a thermodynamic mixture of β-keto phosphine oxides.[31]

As we described earlier, β-keto phosphine oxide *anti*-**12** was obtained pure by recrystallisation of the crude acylation product. However, we also uncovered an alternative way of generating pure *anti*-**12**. Lithiation of a 90 : 10 mixture of β-keto phosphine oxides *anti*- and *syn*-**12** followed by kinetic

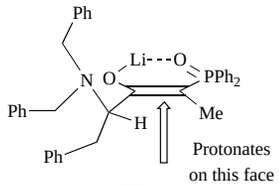
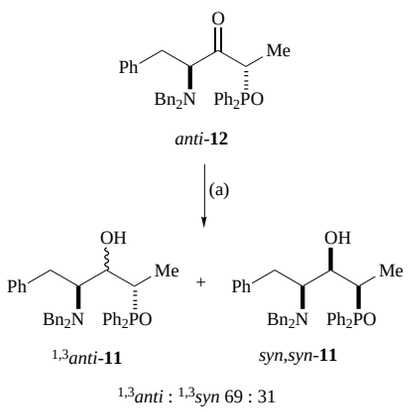


Fig. 4

reprotonation with methanol gave a 77% isolated yield of β-keto phosphine oxide *anti*-**12** only (Scheme 9). Presumably, only the lithium enolate depicted in Fig. 4 will form as it is stabilised by chelation to the diphenylphosphinoyl group. Then, stereoselective protonation on the least hindered face (opposite to the dibenzylamino group) of the lithium enolate in a Houk conformation[32] (Fig. 4) rationalises the specific formation of ketone *anti*-**12**.[33]

Finally, we have also reduced β-keto phosphine oxide *anti*-**12** using Luche's conditions[34] of sodium borohydride in the presence of cerium(III) chloride (Scheme 10): we obtained



Scheme 10 *Reagents and conditions:* (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 30 min (100%)

three alcohols **11** in a ratio of 63:31:6. Although not unambiguously identified, the most abundant ^{1,3}*anti* alcohol obtained from the Luche reduction was actually the minor alcohol product from the sodium borohydride reduction (see Scheme 7). The next most abundant alcohol was recognised as *syn*,*syn*-**11** and must have been generated by epimerisation of the starting ketone and subsequent highly stereoselective reduction. Epimerisation of β-keto phosphine oxides during Luche reductions is unprecedented.

Conclusion

The results presented herein and elsewhere[1,2] indicate that lithiated phosphine oxides are not configurationally stable in THF at −78 °C. However, all is not lost: configurationally unstable organolithium compounds can still be used in diastereo- and enantio-selective synthesis and there are many reported examples.

For example, Beak has carried out some highly enantioselective reactions of benzylic organolithiums in the presence of the chiral ligand (−)-sparteine[19,35] and Hoffmann has recently reported enantioselective reactions of a configurationally labile α-phenylseleno-alkyllithium compound in the presence of a different chiral diamine.[36] In these cases, the selectivity can arise either from a dynamic kinetic resolution[37] of rapidly interconverting organolithium compounds or from the trapping of a thermodynamic mixture of the diastereoisomeric organolithiums. Unfortunately, our attempts at reactions of lithiated phosphine oxides in the presence of chiral ligands have met with little success.[38] Stereoselective reactions of organolithiums derived from chiral precursors (*e.g.* sulfides[10] and, from our own work, phosphine oxides[31,39–40]) are also known. In these cases, the stereoselectivity of the lithiation step is unimportant and only that of reaction with the electrophile matters.

Experimental

General methods have been described previously.[41] Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) according to the method of Still *et al.*[42] High performance liquid chromatography (HPLC) was performed using a Dynamax prepacked silica column (25 cm × 21.4 mm internal diameter) with a Gilson model 303 pump and a Cecil Instruments CE212A UV detector at 254 nm. The symbols + and − after the carbon NMR chemical shift indicate odd and even numbers of attached protons respectively. Ester **7**, alcohol **8** and aldehyde **4** are known[23,28] compounds but, to the best of our knowledge, details of their preparation and full characterisation have not previously been reported.

(*S*)-*N*,*N*-Dibenzylphenylalanine benzyl ester 7

A solution of benzyl bromide (26.0 cm^3, 218.6 mmol) in EtOH (80 cm^3) was added dropwise to a stirred solution of (*S*)-(−)-phenylalanine (10.0 g, 60.5 mmol) and potassium carbonate (29.3 g, 212.0 mmol) in EtOH–water (5:1; 500 cm^3) at room temperature. The resulting solution was heated under reflux for 12 h, cooled to room temperature and then extracted with Et_2O (3 × 200 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by chromatography on silica with hexane–Et_2O (4:1) as eluent gave benzyl ester (*S*)-**7** (21.8 g, 83%) as a colourless oil which could not be crystallised, R_f (4:1 hexane–Et_2O) 0.5; $[\alpha]_D^{20}$ −72.9 (*c* 1.8 in $CHCl_3$) (Found: C, 82.8; H, 6.8; N, 3.3%; $M^+ - PhCH_2$, 344.1630. $C_{30}H_{29}NO_2$ requires C, 82.7; H, 6.7; N, 3.2%; $M - PhCH_2$, 344.1651); ν_{max}(film)/cm^{-1} 1729 (C=O), 1602 (Ph), 1585 (Ph) and 1495 (Ph); δ_H(400 MHz, $CDCl_3$) 7.41–7.35 (5 H, m, Ph), 7.23–7.21 (9 H, m, Ph), 7.20–7.13 (4 H, m, Ph), 7.03–7.01 (2 H, m, Ph), 5.25 (1 H, d, *J* 12.2, PhCH_AH$_B$O), 5.13 (1 H, d, *J* 12.2, PhCH$_A$$H_B$O), 3.94 (2 H, d, *J* 14.0, 2 × PhCH_AH$_B$N), 3.73 (1 H, t, *J* 7.8 CHN), 3.55 (2 H, d, *J* 14.0, 2 × PhCH$_A$$H_B$N), 3.15 (1 H, dd, *J* 7.4 and 14.0, PhCH_AH$_B$) and 3.02 (1 H, dd, *J* 8.2 and 14.0, PhCH$_A$$H_B$); δ_C(50 MHz, $CDCl_3$) 172.1$^-$ (C=O), 139.2$^-$ (2 × *ipso*-*Ph*CH$_2$N), 138.0$^-$ (*ipso*-Ph), 135.9$^-$ (*ipso*-Ph), 129.4$^+$, 128.7–128.1$^+$, 127.7–126.9$^+$, 126.2$^+$, 66.0$^-$ (Ph*C*H$_2$O), 62.3$^+$ (CHN), 54.4$^-$ (2 × PhCH$_2$N) and 35.6$^-$ (Ph*C*H$_2$); *m*/*z* 344 (70, M − PhCH$_2$), 300 (40, M − PhCH$_2$OCO) and 91 (100, PhCH$_2$).

In the same way, benzyl ester *rac*-**7** was obtained in 73% yield as plates, mp 68–70 °C (from hexane) (Found: C, 82.85; H, 6.8; N, 3.1%; M^+, 435.2183. $C_{30}H_{29}NO_2$ requires C, 82.7; H, 6.7; N, 3.2%; *M*, 435.2198).

(*S*)-2-(*N*,*N*-Dibenzylamino)-3-phenylpropan-1-ol 8

A solution of benzyl ester (*S*)-**7** (11.45 g, 26.3 mmol) in THF (50 cm^3) was added dropwise to a stirred suspension of lithium aluminium hydride (2.09 g, 55.3 mmol) in THF (200 cm^3) under argon at 0 °C. After 1 h at 0 °C, water was added until effervescence ceased and the reaction mixture was extracted with Et_2O (3 × 200 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by chromatography on silica with Et_2O–hexane (1:1) as eluent gave alcohol (*S*)-**8** (7.0 g, 80%) as plates, mp 69–71 °C (from 1:1 Et_2O–hexane); R_f (1:1 hexane–Et_2O) 0.4; $[\alpha]_D^{20}$ +38.4 (*c* 1.5 in $CHCl_3$) (Found: C, 83.3; H, 7.6; N, 4.1%; $M^+ - CH_2OH$, 300.1752. $C_{23}H_{25}NO$ requires C, 83.3; H, 7.6; N, 4.2%; $M - CH_2OH$, 300.1752); ν_{max}(Nujol)/cm^{-1} 3458 (OH), 1601 (Ph), 1582 (Ph) and 1493 (Ph); δ_H(400 MHz, $CDCl_3$) 7.35–7.21 (13 H, m, Ph), 7.17 (1 H, t, *J* 7.4, Ph), 7.10 (1 H, t, *J* 7.1, Ph), 3.93 (2 H, d, *J* 13.3, 2 × PhCH_AH$_B$N), 3.51 (1 H, t, *J* 10.4, CH_AH$_B$OH), 3.49 (2 H, d, *J* 13.3, 2 × PhCH$_A$$H_B$N), 3.33 (1 H, br dd, *J* 7.0 and 10.5,

CH_AH_BOH), 3.15–3.04 (2 H, m, CHN and $PhCH_AH_B$), 3.02 (1 H, br s, OH) and 2.44 (1 H, dd, *J* 9.5 and 13.0, $PhCH_AH_B$); δ_C(50 MHz, $CDCl_3$) 139.1$^-$ (*ipso*-Ph), 139.0$^-$ (2 × *ipso*-*Ph*CH_2N), 129.0$^+$, 128.5$^+$, 127.3$^+$, 126.2$^+$, 60.8$^+$ (CHN), 60.4$^-$ (CH_2OH), 53.2$^-$ (2 × Ph*C*H_2N) and 31.7$^-$ (Ph*C*H_2); *m/z* 331 (10%, M^+), 300 (60, M − CH_2OH), 240 (80, M − $PhCH_2$) and 91 (100, $PhCH_2$).

In the same way, alcohol *rac*-**8** was obtained in 93% yield as plates, mp 99–101 °C (from 1:1 Et_2O–hexane) (Found: C, 83.5; H, 7.7; N, 4.1%; M^+, 331.1934. $C_{23}H_{25}NO$ requires C, 83.3; H, 7.6; N, 4.2%; M, 331.1936).

(*S*)-2-(*N*,*N*-Dibenzylamino)-3-phenylpropanal 4

DMSO (35 µl, 0.5 mmol) was added dropwise to a stirred solution of oxalyl chloride (45 µl, 0.5 mmol) in CH_2Cl_2 (2 cm^3) under argon at −78 °C. After 5 min, a solution of alcohol (*S*)-**8** (155 mg, 0.5 mmol) in CH_2Cl_2 (4 cm^3) was added dropwise by means of a cannula. After a further 10 min at −78 °C, triethylamine (350 µl, 2.4 mmol) was added dropwise and the resulting solution was allowed to warm to room temperature. Water (5 cm^3) was added, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were washed quickly with hydrochloric acid (3 M; 10 cm^3) and then water (15 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give aldehyde (*S*)-**4** (144 mg, 93%) as a colourless oil which was unstable to chromatography on silica, R_f (1:1 hexane–Et_2O) 0.65; ν_{max}(film)/cm^{-1} 1729 (C=O), 1601 (Ph), 1584 (Ph) and 1494 (Ph); δ_H(200 MHz, $CDCl_3$) 9.63 (1 H, s, CHO), 7.49–7.09 (15 H, m, 3 × Ph), 3.88 (2 H, d, *J* 13.7, 2 × $PhCH_AH_BN$), 3.72 (2 H, d, *J* 13.7, 2 × $PhCH_AH_BN$), 3.62 (1 H, t, *J* 6.4, CHN), 3.20 (1 H, dd, *J* 7.3 and 13.9, $PhCH_AH_B$) and 3.00 (1 H, dd, *J* 6.2 and 13.9, $PhCH_AH_B$); δ_C(50 MHz, $CDCl_3$) 202.0 (C=O), 139.1$^-$ (*ipso*-Ph), 138.8$^-$(2 × *ipso*-*Ph*CH_2N),129.4$^+$,129.0$^+$,128.7$^+$,128.5$^+$,128.4$^+$, 127.5$^+$, 127.3$^+$, 126.2$^+$, 68.5$^+$ (CHN), 54.8$^-$ (2 × Ph*C*H_2N) and 30.0$^-$ (Ph*C*H_2); *m/z* 329 (25%, M^+), 300 (30, M − CHO), 240 (50, M − $PhCH_2$) and 91 (100, $PhCH_2$) (Found: M^+, 329.1780. $C_{23}H_{23}NO$ requires *M*, 329.1772).

(2*S**,3*S**)-3-(*N*,*N*-Dibenzylamino)-1-diphenylphosphinoyl-4-phenylbutan-2-ol *anti*-9

Butyllithium (1.4 cm^3 of a 1.5 M solution in hexane, 2.1 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (454 mg, 2.1 mmol) in THF (40 cm^3) under argon at −78 °C. The resulting red solution was stirred at −78 °C for 30 min and then a solution of aldehyde *rac*-**4** [prepared from alcohol *rac*-**8** (529 mg, 1.6 mmol)] in THF (5 cm^3) was added dropwise. After 2 h at −78 °C, the yellow solution was allowed to warm to room temperature and saturated aqueous ammonium chloride (1.0 cm^3) was added. The THF was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 30 cm^3). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by chromatography on silica with EtOAc–hexane (1:1) as eluent gave an 80:20 ratio (by ^{1}H NMR spectroscopy) of alcohols *anti*- and *syn*-**9** (439 mg, 50%) as an off-white solid. Further purification by HPLC gave *alcohol anti*-**9** (190 mg, 22%) as fine needles, mp 169–171 °C (from EtOAc); R_f (1:1 EtOAc–hexane) 0.2 (Found: C, 79.4; H, 6.7; N, 2.5; P, 5.7%; M^+, 545.2461. $C_{36}H_{36}NO_2P$ requires C, 79.2; H, 6.7; N, 2.6; P, 5.7%; *M*, 545.2484); ν_{max}(Nujol)/cm^{-1} 3449 (OH), 1601 (Ph), 1492 (Ph), 1436 (P–Ph) and 1177 (P=O); δ_H(400 MHz, $CDCl_3$) 7.75–7.70 (2 H, m, *o*-Ph_2PO), 7.61–7.53 (2 H, m, *o*-Ph_2PO), 7.51–7.44 (5 H, m, Ph), 7.31–7.16 (12 H, m, Ph), 7.11–6.94 (4 H, m, Ph), 4.59 (1 H, br s, OH), 4.34 (1 H, dt, *J* 5.9 and 10.5, C*H*OH), 3.57 (2 H, d, *J* 13.8, 2 × $PhCH_AH_BN$), 3.53 (2 H, d, *J* 13.3, 2 × $PhCH_AH_BN$), 3.15 (1 H, dd, *J* 4.4 and 14.2, $PhCH_AH_B$), 3.00 (1 H, dd, *J* 8.3 and 14.2, $PhCH_AH_B$), 2.90 (1 H, td, *J* 5.0 and 9.0, CHN), 2.55 (1 H, dd, *J* 6.1 and 14.8, PCH_AH_B) and 2.08 (1 H, td, *J* 11.9 and 14.8, PCH_AH_B); δ_C(100 MHz, $CDCl_3$) 141.4$^-$ (*ipso*-Ph), 139.9$^-$ (2 × *ipso*-*Ph*CH_2N), 133.9–125.8 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 66.8$^+$ (d, *J* 4.6, CHOH), 64.6$^+$ (d, *J* 13.7, CHN), 60.4$^-$ (2 × Ph*C*H_2N), 34.9$^-$ (d, *J* 71.3, P*C*H_2) and 32.1$^-$ (Ph*C*H_2); *m/z* 545 (10%, M^+), 454 (30, M − $PhCH_2$), 300 (90, M − $PhCH_2OCO$), 201 (Ph_2PO) and 91 (100, $PhCH_2$).

3-(*N*,*N*-Dibenzylamino)-1-diphenylphosphinoyl-4-phenylbutan-2-one 10

Butyllithium (0.6 cm^3 of a 1.5 M solution in hexane, 0.9 mmol) was added dropwise to a stirred solution of methyldiphenylphosphine oxide (187 mg, 0.9 mmol) in THF (5 cm^3) under argon at −78 °C. The resulting red solution was stirred at −78 °C for 30 min and then a solution of benzyl ester *rac*-**7** (343 mg, 0.8 mmol) in THF (3 cm^3) was added dropwise. After 2 h at −78 °C, the colourless solution was allowed to warm to room temperature and saturated aqueous ammonium chloride (0.5 cm^3) was added. The THF was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 30 cm^3). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by chromatography on silica with EtOAc–hexane (1:1) as eluent gave the *ketone rac*-**10** (248 mg, 58%) as a waxy non-crystallisable foam, R_f (EtOAc) 0.6; ν_{max}($CHCl_3$)/cm^{-1} 1713, (C=O), 1602 (Ph), 1592 (Ph), 1495 (Ph), 1438 (P–Ph) and 1212 (P=O); δ_H(200 MHz, $CDCl_3$) 7.52–7.10 (23 H, m, Ph_2PO and Ph), 6.99–6.94 (2 H, m, Ph), 4.04 (1 H, dd, *J* 13.9 and 14.5, PCH_AH_B), 3.73 (2 H, d, *J* 13.4, 2 × $PhCH_AH_BN$), 3.60 (1 H, dd, *J* 5.4 and 7.7, CHN), 3.48 (2 H, d, *J* 13.5, 2 × $PhCH_AH_BN$), 3.41 (1 H, dd, *J* 14.3 and 16.0, PCH_AH_B), 2.98 (1 H, dd, *J* 7.8 and 13.7, $PhCH_AH_B$) and 2.85 (1 H, dd, *J* 5.3 and 13.7, $PhCH_AH_B$); δ_C(50 MHz, $CDCl_3$) 201.6$^-$ (d, *J* 4.8, C=O), 138.9$^-$ (*ipso*-Ph), 138.8$^-$ (2 × *ipso*-*Ph*CH_2N), 131.8–125.8 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 69.3$^+$ (CHN), 54.5$^-$ (2 × Ph*C*H_2N), 43.2$^-$ (d, *J* 59.0, P*C*H_2) and 29.0$^-$ (Ph*C*H_2); *m/z* 452 (50%, M − $PhCH_2$), 300 (50, M − $PhCH_2OCO$) and 91 (100, $PhCH_2$) (Found: M$^+$ − $PhCH_2$, 452.1778. $C_{36}H_{34}NO_2P$ requires *M* − $PhCH_2$, 452.1780).

In the same way, ketone (*S*)-**10** was obtained in 53% yield; $[\alpha]_D^{20}$ −81.2 (*c* 1.0 in $CHCl_3$); *m/z* 452 (50%, M − $PhCH_2$), 300 (50, M − $PhCH_2OCO$) and 91 (100, $PhCH_2$) (Found: M$^+$ − $PhCH_2$, 452.1778. $C_{36}H_{34}NO_2P$ requires *M* − $PhCH_2$, 452.1780). Also isolated was unadulterated benzyl ester (*S*)-**7**; $[\alpha]_D^{20}$ −72.6 (*c* 1.75 in $CHCl_3$).

(2*R**,3*S**)-3-(*N*,*N*-Dibenzylamino)-1-diphenylphosphinoyl-4-phenylbutan-2-ol *syn*-9

Sodium borohydride (38 mg, 1.0 mmol) was added in one portion to a stirred solution of ketone *rac*-**10** (233 mg, 0.4 mmol) in MeOH (10 cm^3) under argon at −20 °C. After 3 h at −20 °C, water (2 cm^3) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid (234 mg, 100%) which contained a 90:10 ratio (by ^{1}H NMR spectroscopy) of alcohols *syn*- and *anti*-**9**. Recrystallisation from EtOAc gave *alcohol syn*-**9** (135 mg, 58%) as plates, mp 165–167 °C (from 1:1 EtOAc–hexane); R_f (1:1 EtOAc–hexane) 0.2 (Found: C, 79.2; H, 6.75; N, 2.4; P, 5.7%; M^+ − $PhCH_2$, 454.1940. $C_{36}H_{36}NO_2P$ requires C, 79.2; H, 6.7; N, 2.6; P, 5.7%; *M* − $PhCH_2$, 454.1936); ν_{max}(Nujol)/cm^{-1} 3252 (OH), 1601 (Ph), 1492 (Ph), 1436 (P–Ph) and 1177 (P=O); δ_H(400 MHz, $CDCl_3$) 7.66–7.61 (2 H, m, *o*-Ph_2PO), 7.53–7.14 (23 H, m, *o*-, *m*- and *p*-Ph_2PO and Ph), 4.33 (1 H, br s, OH), 4.14 (2 H, d, *J* 13.3, 2 × $PhCH_AH_BN$), 4.02 (1 H, dt, *J* 4.8 and 9.9, C*H*OH), 3.45 (2 H, d, *J* 13.3, 2 × $PhCH_AH_BN$), 3.11 (1 H, dd, *J* 4.9 and 13.5, $PhCH_AH_B$), 2.98 (1 H, dd, *J* 9.0 and 13.5, $PhCH_AH_B$), 2.75 (1 H,

td, *J* 10.1 and 15.3, PCH_AH_B), 2.68 (1 H, td, *J* 4.9 and 9.3, CHN) and 1.79 (1 H, ddd, *J* 0.9, 9.3 and 10.3, PCH_AH_B); δ_C(50 MHz, $CDCl_3$) 140.2$^-$ (*ipso*-Ph), 140.0$^-$ (2 × *ipso*-*Ph*CH_2N), 131.7–125.8 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 67.0$^+$ (d, *J* 4.1, CHOH), 64.3$^+$ (d, *J* 13.2, CHN), 55.1$^-$ (2 × Ph*C*H_2N), 34.8$^-$ (d, *J* 72.5, PCH_2) and 31.0$^-$ (Ph*C*H_2); *m/z* 454 (10%, M$^+$ − PCH_2), 300 (50, M − PCH_2OCO) and 91 (100, PCH_2).

Hoffmann test experiment 1: 2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-ol 11

Butyllithium (0.2 cm^3 of a 1.5 M solution in hexane, 0.3 mmol) was added dropwise to a stirred solution of ethyldiphenylphosphine oxide (59 mg, 0.3 mmol) in THF (2 cm^3) under argon at −78 °C. The resulting red solution was stirred at −78 °C for 30 min and then a solution of aldehyde *rac*-**4** [prepared from alcohol *rac*-**8** (155 mg, 0.5 mmol)] in THF (2 cm^3) was added dropwise. After 1 h at −78 °C, saturated aqueous ammonium chloride (1.0 cm^3) was added and the yellow solution was 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; 30 cm^3). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Analysis of the crude product by ^{1}H NMR spectroscopy indicated that the reaction had gone to approximately 80% completion and that the crude product contained a 27:40:28:5 ratio of *alcohols* **11** *i.e.* a 67:33 ratio of ^{1,3}*syn*:^{1,3}*anti*. The four diastereoisomers exhibited δ_H(400 MHz, $CDCl_3$) *syn*,*syn*-**11**: 0.69 (3 H, dd, *J* 7.0 and 16.9, CH*Me*); *anti*,*anti*-**11**: 4.11 (1 H, t, *J* 9.7, C*H*OH) and 0.63 (3 H, dd, *J* 7.0 and 17.2, CH*Me*); ^{1,3}*anti*: 4.40 (1 H, t, *J* 9.6, C*H*OH) and 0.53 (3 H, dd, *J* 7.3 and 18.05, CH*Me*); ^{1,3}*anti*: 0.12 (3 H, dd, *J* 7.2 and 18.1, CH*Me*). Purification by chromatography on silica with hexane–EtOAc (4:1) and then EtOAc–hexane (1:1) as eluent gave a 44:48:8:0 ratio of alcohols **11** (91 mg, 63%) as a white solid, R_f (EtOAc) 0.5–0.6. Although we did not attempt to separate the diastereoisomers, there clearly had been some separation.

In a separate experiment, further purification by chromatography on silica with EtOAc–hexane (1:1) as eluent gave *alcohol anti*,*anti*-**11** as plates, mp 212–214 °C (from EtOAc); R_f (EtOAc) 0.55; ν_{max}($CHCl_3$)/cm^{-1} 3369 (OH), 1602 (Ph), 1495 (Ph), 1438 (P–Ph) and 1160 (P=O); δ_H(400 MHz, $CDCl_3$) 7.72–7.63 (4 H, m, *o*-Ph_2PO), 7.54–7.09 (21 H, m, *m*- and *p*-Ph_2PO and Ph), 4.11 (1 H, t, *J* 9.7, C*H*OH), 3.50 (2 H, d, *J* 13.8, 2 × PhCH_AH_BN), 3.41 (2 H, br d, *J* 13.45, 2 × PhCH_AH_BN), 3.17 (1 H, dd, *J* 3.5 and 14.2, PhCH_AH_B), 3.10 (1 H, ddd, *J* 3.75, 8.1 and 9.1, CHN), 3.00–2.89 (2 H, m, PCH and PhCH_AH_B) and 0.63 (3 H, dd, *J* 7.0 and 17.2, CH*Me*); δ_C(100 MHz, $CDCl_3$) 140.3$^-$ (*ipso*-Ph), 139.5$^-$ (2 × *ipso*-*Ph*CH_2N), 132.3–125.8 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 70.35$^+$ (CHOH), 60.5$^+$ (d, *J* 12.0, CHN), 53.2$^-$ (2 × PhCH_2N), 33.25$^+$ (d, *J* 70.9, PCH), 32.7$^-$ (PhCH_2) and 5.3$^+$ (CH*Me*); *m/z* 468 (30, M − PCH_2), 300 [80, M − MeCH(Ph_2PO)CHOH], 201 (20, Ph_2PO) and 91 (100, PCH_2) (Found: M$^+$ − PCH_2, 468.2095. $C_{37}H_{38}NO_2P$ requires *M* − PCH_2, 468.2092) and a product enriched in one of the ^{1,3}*anti* alcohols **11** as an oil, R_f (EtOAc) 0.5; ν_{max}($CHCl_3$)/cm^{-1} 3369 (OH), 1602 (Ph), 1495 (Ph), 1438 (P–Ph) and 1160 (P=O); δ_H(400 MHz, $CDCl_3$) 7.72–6.86 (25 H, m, Ph_2PO and 3 × Ph), 4.91 (1 H, br s, OH), 4.40 (1 H, t, *J* 9.6, C*H*OH), 3.84 (2 H, d, *J* 14.5, 2 × PhCH_AH_BN), 3.57 (2 H, br d, *J* 14.3, 2 × PhCH_AH_BN), 3.15–2.85 (3 H, m, PhCH_2 and CHN), 2.54 (1 H, qd, *J* 7.4 and 15.0, PCH) and 0.53 (3 H, dd, *J* 7.3 and 18.05, CH*Me*); δ_C(100 MHz, $CDCl_3$) 140.7$^-$ (*ipso*-Ph), 140.4$^-$ (2 × *ipso*-*Ph*CH_2N), 132.8–125.8 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 71.2$^+$ (CHOH), 59.2$^+$ (d, *J* 10.0, CHN), 54.3$^-$ (2 × PhCH_2N), 36.1$^+$ (d, *J* 69.8, PCH), 31.2$^-$ (PhCH_2) and 12.3$^+$ (CH*Me*); *m/z* 560 (5%, M + H), 300 [70, M − MeCH(Ph_2-PO)CHOH], 201 (40, Ph_2PO) and 91 (100, PCH_2) (Found: M$^+$ + H, 560.2708. $C_{37}H_{38}NO_2P$ requires *M* + H, 560.2718).

Hoffmann test experiment 2: 2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-ol 11

The title compound was prepared using the Hoffmann test conditions of reverse addition with 10 equiv. of the electrophile:[14] butyllithium (0.2 cm^3 of a 1.5 M solution in hexane, 0.3 mmol) was added dropwise to a stirred solution of ethyldiphenylphosphine oxide (56 mg, 0.25 mmol) in THF (2 cm^3) under argon at −78 °C. The resulting red solution was stirred at −78 °C for 30 min and then added dropwise by means of a cannula to a stirred solution of aldehyde (*S*)-**4** [prepared from alcohol (*S*)-**8** (155 mg, 0.5 mmol)] in THF (2 cm^3) under argon at −78 °C. After 1 h at −78 °C, saturated aqueous ammonium chloride (1.0 cm^3) was added and the yellow solution was 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). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Analysis of the crude product by ^{1}H NMR spectroscopy indicated that the reaction had gone to ≥95% completion and that the crude product contained a 28:39:27:6 ratio of alcohols **11** *i.e.* a 67:33 ratio of ^{1,3}*anti*:^{1,3}*syn*. Purification by chromatography on silica with hexane–EtOAc (4:1) and then EtOAc–hexane (1:1) as eluent gave an 18:43:33:6 ratio (by ^{1}H NMR spectroscopy) of alcohols **11** (125 mg, 93%) as a white solid, R_f (EtOAc) 0.5–0.6. Although we did not attempt to separate the diastereoisomers, there clearly had been some loss of alcohol *syn*,*syn*-**11**.

(2*S,4*S**)-2-(*N*,*N*-Dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-one *anti*-12**

Butyllithium (0.35 cm^3 of a 1.5 M solution in hexane, 0.5 mmol) was added dropwise to a stirred solution of ethyldiphenylphosphine oxide (123 mg, 0.5 mmol) in THF (2.5 cm^3) under argon at −78 °C. The resulting orange solution was stirred at −78 °C for 30 min and then a solution of benzyl ester *rac*-**7** (238 mg, 0.55 mmol) in THF (2.5 cm^3) was added dropwise. After 1 h at −78 °C, saturated aqueous ammonium chloride (0.5 cm^3) was added and the colourless solution was 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; 30 cm^3). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by chromatography on silica with EtOAc–hexane (2:1) as eluent gave a 90:10 ratio (by ^{1}H NMR spectroscopy) of ketones *anti*- and *syn*-**12** (196 mg, 66%) as a white solid. Recrystallisation from EtOAc gave *ketone anti*-**12** as rectangular plates, mp 138–140 °C (from EtOAc); R_f (EtOAc) 0.6; ν_{max}($CHCl_3$)/cm^{-1} 1710.5 (C=O), 1602 (Ph), 1592 (Ph), 1438 (P–Ph) and 1118 (P=O); δ_H(400 MHz, $CDCl_3$) 7.47–7.12 (23 H, m, Ph_2PO and Ph), 6.88–6.86 (2 H, m, Ph), 4.33 (1 H, qd, *J* 6.9 and 13.9, PCH), 3.70 (2 H, d, *J* 13.5, 2 × PhCH_AH_BN), 3.48–3.40 (1 H, m, CHN), 3.42 (2 H, d, *J* 13.95, 2 × PhCH_AH_BN), 2.89 (1 H, dd, *J* 6.0 and 13.9, PhCH_AH_B), 2.81 (1 H, dd, *J* 7.3 and 13.8, PhCH_AH_B) and 1.39 (3 H, dd, *J* 7.0 and 15.9, CH*Me*); δ_C(50 MHz, $CDCl_3$) 204.9$^-$ (C=O), 138.9$^-$ (2 × *ipso*-*Ph*CH_2N), 131.7–125.7 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 69.0$^+$ (CHN), 54.3$^-$ (2 × PhCH_2N), 44.9$^+$ (d, *J* 57.0, PCH), 29.0$^-$ (Ph*C*H_2) and 12.1$^+$ (d, *J* 2.9, Me); *m/z* 557 (20%, M$^+$), 529 (30, M − CO), 466 (70, M − PCH_2), 362 (50), 300 [90, M − MeCH(Ph_2PO)CO], 201 (20, Ph_2PO) and 91 (100, PCH_2) (Found: M$^+$, 557.2493. $C_{37}H_{36}NO_2P$ requires *M*, 557.2484). Diagnostic signals for *ketone syn*-**12**: δ_H(400 MHz, $CDCl_3$) 7.80–7.71 (4 H, m, *o*-Ph_2PO), 3.96 (1 H, qd, *J* 7.7 and 15.2, PCH), 3.85–3.75 (1 H, m, CHN), 3.70 (2 H, d, *J* 13.9, 2 × PhCH_AH_BN), 3.50 (2 H, d, *J* 13.9, 2 × PhCH_AH_BN), 3.10 (1 H, dd, *J* 9.6 and 13.1, PhCH_AH_B) and 0.76 (3 H, dd, *J* 7.7 and 15.6, CH*Me*).

Sodium borohydride reduction of ketone *anti*-12: 2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-ol 11

Sodium borohydride (3.5 mg, 0.1 mmol) was added in one portion to a stirred solution of ketone *anti*-**12** (10 mg, 0.02 mmol) in EtOH (1 cm^3) at room temperature. After 12 h at room temperature, water (2 cm^3) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 5 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid (12 mg, 100%) which contained a 90:10 ratio (by ^{1}H NMR spectroscopy) of alcohols ^{1,3}*anti*-**11**. Diagnostic signals for the major isomer of alcohol **11**: δ_H(400 MHz, $CDCl_3$) 7.70–7.65 (2 H, m, *o*-Ph_2PO), 7.54–7.09 (23 H, m, Ph_2PO and Ph), 4.84 (1 H, br s, OH), 4.29–4.20 (2 H, br s, 2 × PhCH_AH_BN), 3.61 (1 H, br s, C*H*OH), 3.49 (2 H, br d, *J* 13.6, 2 × PhCH_AH_BN), 3.20 (1 H, quintet d, *J* 7.4 and 15.9, PCH), 3.17 (1 H, dd, *J* 9.8 and 12.7, PhCH_AH_B), 3.11 (1 H, dd, *J* 4.5 and 12.5, PhCH_AH_B), 2.86 (1 H, td, *J* 4.0 and 8.6, CHN) and 0.12 (3 H, dd, *J* 7.2 and 18.1, CH*Me*); δ_C(100 MHz, $CDCl_3$) 140.35$^-$ (2 × *ipso*-*Ph*CH_2N), 131.7–125.9 (Ph, 2 × *Ph*CH_2N and Ph_2PO), 73.2$^+$ (CHOH), 59.75$^+$ (CHN), 55.7$^-$ (2 × Ph*C*H_2N), 34.3$^+$ (d, *J* 72.1, PCH), 29.7$^-$ (Ph*C*H_2) and 11.0$^+$ (CH*Me*). Diagnostic signal for the minor isomer of alcohol **11**: δ_H(400 MHz, $CDCl_3$) 0.53 (3 H, dd, *J* 7.3 and 18.05, CH*Me*).

Luche reduction of ketone *anti*-12: 2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-ol 11

Sodium borohydride (10 mg, 0.1 mmol) was added in one portion to a stirred solution of ketone *anti*-**12** (10 mg, 0.02 mmol) and $CeCl_3$·$7H_2O$ (8 mg, 0.02 mmol) in EtOH (1 cm^3) under argon at −78 °C. After 30 min at −78 °C, water (2 cm^3) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 5 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid (12 mg, 100%) which contained a 63:6:31 (by ^{1}H NMR spectroscopy) ratio of alcohols **11**. The major product was the same as the minor product of the sodium borohydride reaction. The second most abundant alcohol was identified as *syn*,*syn*-**11**: δ_H(400 MHz, $CDCl_3$) 0.69 (3 H, dd, *J* 7.0 and 16.9, CH*Me*).

Dess–Martin periodinane oxidation of a mixture of alcohols 11: (2*S,4*S**)-2-(*N*,*N*-dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-one *anti*-12**

A 56:44 mixture of alcohols ^{1,3}*anti*- and ^{1,3}*syn*-**11** (41 mg, 0.1 mmol) in CH_2Cl_2 (2 cm^3) was added dropwise by means of a cannula to a stirred solution of Dess–Martin periodinane (50 mg, 0.15 mmol) in CH_2Cl_2 (2 cm^3) under argon at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 12 h. Then, the mixture was diluted with CH_2Cl_2 (5 cm^3) and carefully poured into a solution of sodium thiosulfate (8 equiv. with respect to the periodinane) in saturated aqueous sodium hydrogen carbonate (10 cm^3). After 30 min, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (10 cm^3) and then saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography on silica with EtOAc–hexane (2:1) as eluent gave a 90:10 ratio (by ^{1}H NMR spectroscopy) of ketones *anti*- and *syn*-**12** (20 mg, 49%) as a non-crystallisable foam identical (TLC and ^{1}H NMR spectroscopy) to that obtained previously.

(2*S,4*S**)-2-(*N*,*N*-Dibenzylamino)-4-diphenylphosphinoyl-1-phenylpentan-3-one *anti*-12**

Butyllithium (0.05 cm^3 of a 1.5 M solution in hexane, 0.075 mmol) was added dropwise to a stirred solution of a 90:10 mixture of ketones *anti*- and *syn*-**12** (35 mg, 0.06 mmol) in THF (3 cm^3) under argon at −78 °C. The resulting orange solution was stirred at −78 °C for 30 min and then MeOH (200 μl) was added dropwise and the colourless solution was 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). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as an oil. Purification by chromatography on silica with EtOAc as eluent gave a ≥97:3 ratio (by ^{1}H NMR spectroscopy) of ketones *anti*- and *syn*-**12** (27 mg, 77%) as a white solid.

X-Ray structure analysis of alcohol *anti*,*anti*-11

Molecular formula $C_{37}H_{38}NO_2P$ (M_r = 559.65), crystals grown by slow evaporation from EtOAc–MeOH as plates, crystal size 0.44 × 0.37 × 0.25 mm^3, monoclinic, space group $P2_1/c$, a = 15.032(4), b = 12.989(3), c = 16.694(7) Å, β = 111.58(2)°, V = 3031(2) $Å^3$, Z = 4, D_x = 1.226 g cm^{-3}, μ(Mo-Kα) = 0.125 mm^{-1}, $F(000)$ = 1192; 4567 unique reflections were collected on a RIGAKU AFC7R sequential diffractometer, $2\theta_{max}$ = 47.5°. The structure was solved by direct methods and the H atoms were placed geometrically and allowed to ride on the relevant non-H atom. The structure was refined by full-matrix least-squares (on F^2) of 371 parameters with SHELXL-93,[43] all non-H atoms anisotropic, H atoms isotropic with fixed individual displacement parameters [U(H) = 1.2 U_{eq}(C)]. Refinement converged at wR = 0.120 corresponding to R = 0.042 for 3817 observed reflections on all data with $|F| > 4\sigma(F)$, $w = 1/[\sigma^2F_o^2 + (0.0498P)^2 + 2.48P]$ where $P = (F_o^2 + 2F_c^2)/3$, S = 1.001, $\Delta\rho$ in final difference map within 0.265 and −0.287 e $Å^{-3}$, all relevant data are deposited with the Cambridge Crystallographic Data Centre.‡‡

X-Ray structure analysis of ketone *anti*-12·H_2O

Molecular formula $C_{37}H_{38}NO_3P$ (M_r = 575.65), crystals grown by slow evaporation from EtOAc–MeOH as rectangular plates, crystal size 0.32 × 0.23 × 0.07 mm^3, triclinic, space group P1 (no. 2), a = 12.541(2), b = 13.482(2), c = 9.338(13) Å, α = 99.88(10), β = 99.64(6), γ = 87.78(7)°, V = 1533(3) $Å^3$, Z = 2, D_x = 1.247 g cm^{-3}, μ(Mo-Kα) = 0.127 mm^{-1}, $F(000)$ = 612; 4746 unique reflections were collected on a RIGAKU R-AXIS IIc area detector diffractometer, $2\theta_{max}$ = 50.9°. The structure was solved by direct methods and the H atoms were placed geometrically and allowed to ride on the relevant non-H atom. The structure was refined by full-matrix least-squares (on F^2) of 380 parameters with SHELXL-93,[43] all non-H atoms anisotropic, H atoms isotropic with fixed individual displacement parameters [U(H) = 1.2 U_{eq}(C)]. Refinement converged at wR_2 = 0.182 corresponding to R = 0.065 for 4447 observed reflections on all data with $|F| > 4\sigma(F)$, the weighting scheme was $w = 1/[\sigma^2F_o^2 + (0.0784P)^2 + 1.8932P]$ where $P = (F_o^2 + 2F_c^2)/3$, S = 1.109, $\Delta\rho$ in final difference map within 0.283 and −0.587 e $Å^{-3}$, all relevant data are deposited with the Cambridge Crystallographic Data Centre.‡‡

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‡‡ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/93.

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