Mechanistic and synthetic aspects of stereoselective reactions of lithium derivatives of chiral phosphine oxides: X-ray crystal structure of (1*R**,2*S**,1′*S**,2′*R**)-1-(1′-diphenylphosphinoyl-2′-phenylpropyl)-2-phenylsulfanylcyclohexan-1-ol

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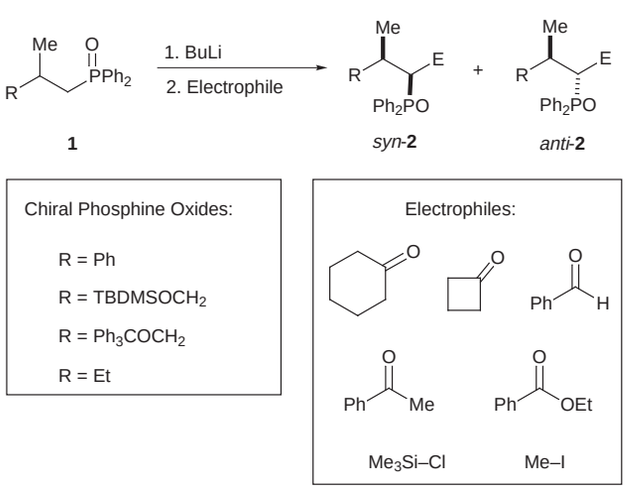
Lithiation of four different chiral phosphine oxides and reaction with seven different electrophiles has been carried out in order to discover what factors govern the sense and degree of asymmetric induction imparted by the resident chiral centre. Provided the groups at the chiral centre are significantly different in steric size (*e.g.* Ph and Me) and ketones, esters or Me_3SiCl are used as the electrophile, surprisingly high levels of *syn*-diastereoselectivity are observed. Reactions with benzaldehyde or methyl iodide proved to be rather unselective. The stereochemistry of the reaction of lithiated 1-diphenylphosphinoyl-2-phenylpropane **9** with cyclohexanone was elucidated by conversion into (1*R**,2*S**,1′*S**,2′*R**)-1-(1′-diphenylphosphinoyl-2′-phenylpropyl)-2-phenylsulfanylcyclohexan-1-ol *syn*,*syn*,*anti*-**39** and subsequent X-ray crystal structure analysis. The stereochemistry of the remainder of the compounds were determined by analogy and by using a reliable ^{13}C NMR spectroscopy $^3J_{PC}$ coupling constant correlation. A detailed (and potentially general) mechanistic interpretation of the results which combines knowledge of the structure and configurational stability of lithiated phosphine oxides is discussed. In particular, it is suggested that a dynamic kinetic diastereoselection of rapidly equilibrating diastereomeric lithiated phosphine oxides explains the observed high levels of stereocontrol; a tentative transition state model is proposed to explain the *syn*-selectivity. Finally, the use of one of the addition products in the concise and stereoselective synthesis of an alkene with 1,4-disposed chiral centres is described.

Introduction

Our programme of research investigating the use of the diphenylphosphinoyl (Ph_2PO) group in stereocontrolled organic synthesis has spanned nearly 20 years.[1] During that time, we have discovered many new methods for the control of relative stereochemistry using the diphenylphosphinoyl group[2] and, more recently, have applied our methodology in the area of asymmetric synthesis.[3] However, a detailed study of the reactions of lithium derivatives of chiral phosphine oxides **1** is an area of stereocontrolled synthesis that has so far been neglected. In such reactions, we wanted to discover what effect the stereogenic centre in a range of chiral (but racemic) phosphine oxides **1** had on the formation of adducts *syn*- and *anti*-**2** (Scheme 1).



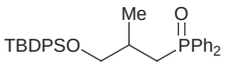
Scheme 1

In order to investigate the general reaction outlined in Scheme 1, we have studied the reactions of four chiral phosphine oxides **1** with seven different electrophiles and in this paper we report our findings in full.[4,5] The stereoselectivity observed in these reactions (the so-called β′ selectivity†), coupled with our expanding knowledge of the structure[6,7] and configurational stability[8,9] of lithiated phosphine oxides, have allowed us to comment on some of the mechanistic aspects which are described in detail in this paper. As well as being of mechanistic interest, stereoselective reactions of lithium derivatives of chiral phosphine oxides **1** (particularly with carbonyl electrophiles) are also of considerable synthetic value. One example of the use of such reactions in the stereocontrolled synthesis of an alkene with flanking 1,4-related chiral centres is described at the end of this paper.

Background

Prior to the work described in this paper, we and others had reported a few isolated examples of the reactions of chiral phosphine oxides **1**. For example, reaction of lithiated **3** or **4** with unsaturated aldehydes led to the non-selective formation of all four diastereomeric products in each case.[10,11] In contrast, slightly better levels of β′ stereocontrol were disclosed by Fleming *et al.* for reactions between lithiated **5** or **6** and aldehydes or methyl iodide.[12] Finally, it was also found that good to excellent levels of β′ stereocontrol could be achieved if the chiral phosphine oxide contains groups capable of internal chelation in the

† Because of the way that we label the carbon atoms in β-hydroxy phosphine oxides [*e.g.* **2** in which E = C(OH)R^2], "β′ selectivity" is the term we prefer to describe the way in which the stereogenic centre of phosphine oxides **1** controls the relative stereochemistry between the α and β′ stereogenic centres in adducts **2**; see also structures *syn*- and *anti*-**35** in Scheme 8.



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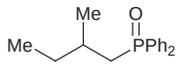

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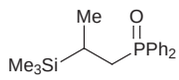

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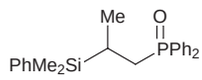

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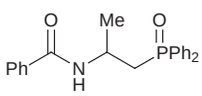

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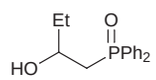

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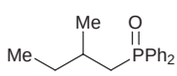
organolithium species. Thus, the dilithiated form of phosphine oxide **7** reacts stereoselectively with a range of electrophiles (methyl iodide, ketones, aldehydes)[13] whilst reaction of dilithiated **8** with aldehydes is stereoselective but to a lesser degree.[14]

Systematic study of the reactions of lithium derivatives of chiral phosphine oxides

Four chiral phosphine oxides **4**, **9**, **10** and **11** were selected for



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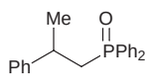

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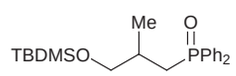

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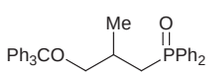

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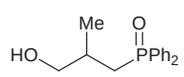

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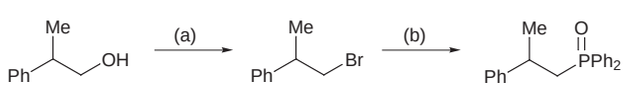
our study of β′ selectivity. Phosphine oxide **4** had been prepared previously in our reseach group[11] and the synthesis of phosphine oxide **10** (silylation of the hydroxy group in phosphine oxide **12**) has been described elsewhere.[8] In a similar manner, standard tritylation of alcohol **12** afforded phosphine oxide **11** and we have also developed a useful synthesis of phosphine oxide **9**. Thus, conversion of commercially available alcohol **13** into the known[15] bromide **14** (*via* the corresponding tosylate) and reaction with lithium diphenylphosphinide (prepared according to the method of Ashby *et al*.[16]) followed by hydrogen peroxide work-up gave phosphine oxide **9** in 77% overall yield (Scheme 2).



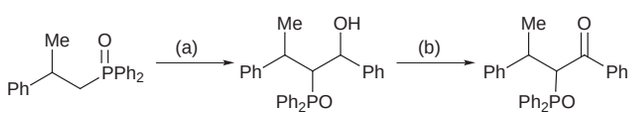
13 14 9

Scheme 2 *Reagents and conditions*: (a) i, Pyridine, *p*-TsCl, CH_2Cl_2, rt, 8 h; ii, LiBr, acetone, reflux, 8 h (83%); (b) i, Ph_2PLi, THF, 0 °C, 1 h; ii, H_2O_2; iii, NH_4Cl (93%).

The reactions of the chiral phosphine oxides **4** and **9**–**11** with a range of electrophiles were all carried out in the same way. Thus, the lithiated phosphine oxide was generated in THF at −78 °C and reacted with the appropriate electrophile. After one hour, the reaction mixture was quenched with ammonium chloride solution and standard aqueous work-up gave the crude product mixture which was analysed by ^{1}H NMR spectroscopy to determine the β′ selectivity. In most cases, single diastereomers of the addition products were obtained after purification by chromatography and/or recrystallisation. The results are shown in Tables 1 and 2.‡

The relative stereochemistry of the addition products described in Tables 1 and 2 were assigned using a combination of X-ray crystallography and NMR methods. For example, the sole product of the reaction between lithiated phosphine oxide **9** and cyclohexanone (Entry 5; Table 1) was identified as alcohol *syn*-**19** by X-ray crystallographic analysis of a derivative, the details of which are described later. By analogy with this result, we were happy to assign the relative β′ stereochemistry in alcohols **18**, **20** and **21** (Entries 4, 6 and 7; Table 1). However, in order to establish the stereochemistry of the other addition products, we had to make use of ^{13}C NMR spectroscopy: by comparing the X-ray crystal structures of alcohol *syn*-**19** and three other related compounds with their ^{13}C NMR spectra, we noticed that the values of the $^3J_{PC}$ coupling constants were consistently dependent on their relative β′ stereochemistry. Compounds with *syn* relative stereochemistry between the diphenylphosphinoyl group and the β′ substituent have $^3J_{PC}$ = 4.5–13 Hz and those with *anti*-stereochemistry have $^3J_{PC}$ = 0–2 Hz.[4] In this way, we have assigned the β′ stereochemistry of *all* of the addition products described in this paper.

The results of hydroxyalkylation and acylation reactions of chiral phosphine oxides **9**–**11** are summarised in Table 1; there are a number of interesting trends. The reaction between lithiated **9** and benzaldehyde (Entry 1; Table 1) is completely non-selective: all four diastereomeric β-hydroxy phosphine oxides **15** were generated in essentially the same amounts. Indeed, it was only by conversion of the mixture into the β-keto phosphine oxides **17** (using Dess–Martin periodinane-mediated oxidation[18]) that the *anti* β′ selectivity (of only 55:45) could be determined (Scheme 3).



9 15 17

(*anti* : *syn* 55 : 45)

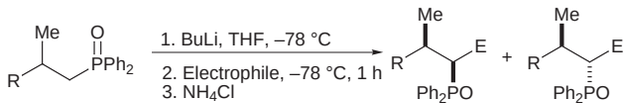
Scheme 3 *Reagents and conditions*: (a) i, LDA, THF, −78 °C, 30 min; ii, PhCHO, −78 °C, 30 min; iii, NH_4Cl (100%); (b) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 1 h (84%).

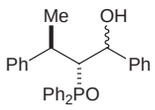
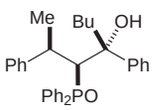
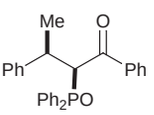
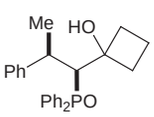
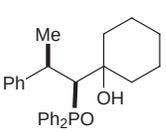
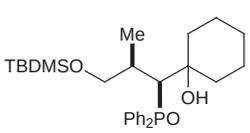
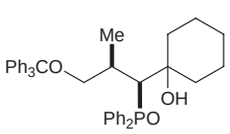
In contrast to the reaction of lithiated **9** with an aldehyde, hydroxyalkylation of chiral phosphine oxides **9**–**11** with ketones or acylation of **9** with ethyl benzoate§ all proceeded with high levels of *syn* β′ stereocontrol (Entries 2–7; Table 1). In particular, *only one* diastereomer of β-hydroxy phosphine oxide **16** was obtained from the reaction of lithiated **9** with valerophenone (Entry 2; Table 1). This is particularly surprising when one considers the stereorandom reaction of lithiated **9** with benzaldehyde (Entry 1; Table 1) coupled with the fact that reactions of β′ branched phosphine oxides with aldehydes generally proceed with low levels of diastereoselectivity.[20] The single diastereomer

‡ In the original communication reported in 1989[17] and in the review article published in 1996,[1] the stereochemistry of compounds **16**, **17** and **19** was incorrectly reported. It is important to emphasise that these errors have been corrected in our recent communications[4,5] and in the present full paper.

§ Reaction of lithiated **9** with ethyl benzoate at −78 °C followed by an ammonium chloride quench afforded a 38% yield of a 92:8 mixture of ketones *syn*- and *anti*-**17** which could be recrystallised to a single diastereomer. However, and to our surprise, if we allowed the same reaction to warm up to 0 °C *before* quenching, we obtained an improved 51% yield of a mixture of ketones **17** enriched in the other diastereomer (76:24 mixture of *anti*- and *syn*-**17**). To explain this, we suggest that the usual product, a *syn* lithium alkoxide, forms but at the higher temperature it decomposes to give a lithium enolate which undergoes a stereoselective protonation in a Houk-like conformation[19] to give ketone *anti*-**17**.[5]

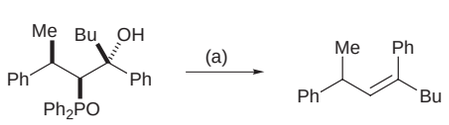
Table 1 Hydroxyalkylation and acylation reactions of chiral phosphine oxides



Entry	R	SM[a]	Electrophile	Major addition product	*syn*:*anti*[b]	Isolated yield (%)
1	Ph	**9**[c]	Benzaldehyde	 *anti*-**15**	45:55	—
2	Ph	**9**	Valerophenone	 *syn*,*anti*-**16**	≥95:5	46
3	Ph	**9**	Ethyl benzoate	 *syn*-**17**	92:8	38
4	Ph	**9**	Cyclobutanone	 *syn*-**18**	80:20	40
5	Ph	**9**	Cyclohexanone	 *syn*-**19**	≥95:5	44
6	$TBDMSOCH_2$	**10**	Cyclohexanone	 *syn*-**20**	80:20	63 (13)[d]
7	Ph_3COCH_2	**11**	Cyclohexanone	 *syn*-**21**	96:4	65

[a] Starting material. [b] By ^1H NMR spectroscopy of the crude product mixture. [c] LDA used for the lithiation step. [d] Isolated yield of *anti*-**20** in brackets.

of β-hydroxy phosphine oxide **16** obtained from this reaction was identified as *syn*,*anti*-**16**: the β′ stereochemistry was assigned using the β′ coupling constant rule and the relative stereochemistry between the α and β stereogenic centres was established by conversion into alkene (*Z*)-**22** (*via* Horner–Wittig elimination[2]) and subsequent NOE analysis (Scheme 4).



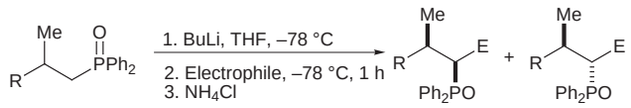
syn,*anti*-**16** (*Z*)-**22**

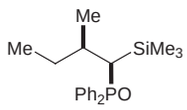
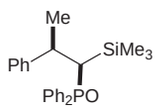
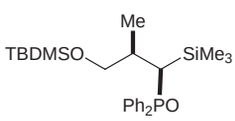
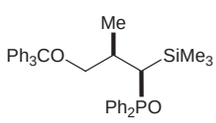
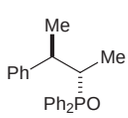
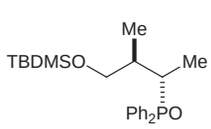
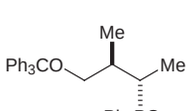
Scheme 4 *Reagents and conditions*: (a) KOH, DMSO, 50 °C, 45 min (44%).

The reactions of lithiated chiral phosphine oxides with ethyl benzoate, cyclobutanone and cyclohexanone (Entries 3–7; Table 1) were easier to analyse as there were only two diastereomeric products and, in all these cases, high levels of *syn* β′ stereocontrol were observed. However, only 38–76% isolated yields of the adducts were obtained and some starting material was always recovered. To rationalise this, we suggest that steric hindrance in these β′ branched lithiated phosphine oxides reduces their reactivity and, in the reactions with cyclic ketones, a detrimental amount of ketone enolisation occurs. Consistent with this suggestion is the fact that reaction of lithiated **9** with the much more readily enolised cyclopentanone led to less than 10% of the corresponding β-hydroxy phosphine oxide as judged by ^1H NMR spectroscopy of the crude reaction mixture.

In a similar fashion, reaction of lithiated **9**, **10** or **11** with Me_3SiCl furnished silylated products **24**, **25** or **26** with high degrees of *syn* β′ selectivity (Entries 2–4; Table 2). On close inspection, the actual diastereoselectivity observed for the reactions of these three phosphine oxides with Me_3SiCl parallels

Table 2 Silylation and alkylation reactions of chiral phosphine oxides



Entry	R	SM[a]	Electrophile	Major addition product		*syn*:*anti*[b]	Isolated yield (%)
1	Et	**4**	Me_3SiCl		*syn*-**23**	56:44	85[c]
2	Ph	**9**	Me_3SiCl		*syn*-**24**	93:7	57[d]
3	$TBDMSOCH_2$	**10**	Me_3SiCl		*syn*-**25**	85:15	79[c]
4	Ph_3COCH_2	**11**	Me_3SiCl		*syn*-**26**	96:4	89[c]
5	Ph	**9**	MeI		*anti*-**27**	38:62	100[e]
6	$TBDMSOCH_2$	**10**	MeI		*anti*-**28**	44:55	100[e]
7	Ph_3COCH_2	**11**	MeI		*anti*-**29**	45:55	100[e]

[a] Starting material. [b] By ^1H NMR spectroscopy of the crude product mixture. [c] Yield of mixture of diastereomers after chromatography. [d] Yield of pure *syn*-**24** after recrystallisation. [e] Yield of crude product mixture.

their selectivities in reactions with cyclohexanone (compare Entries 5–7; Table 1 with Entries 2–4; Table 2). Thus, on the basis of this evidence, it appears that Me_3SiCl and cyclohexanone have a comparable reactivity in reactions with lithiated **9**, **10** or **11** which is perhaps surprising. When the two substituents at the stereogenic centre in the chiral phosphine oxide are similar in size (*e.g.* in phosphine oxide **4**), the β′ selectivity drops considerably as would be expected (Entry 1; Table 2).

Finally, we found that reactions of lithiated **9**, **10** or **11** with methyl iodide (Entries 5–7; Table 2) behaved completely differently to those with Me_3SiCl (Entries 2–4; Table 2). The methylation reactions were only marginally *anti*-stereoselective contrasting with the *syn* β′ selectivity observed in virtually all of the other examples in Tables 1 and 2. There is precedent for the observed *anti*-selectivity in reactions with methyl iodide: Fleming *et al.* have previously reported *anti*-selective methylations of β′-silyl chiral phosphine oxides **5** and **6** using methyl iodide at 0 °C.[12]

In summary, it appears that good to excellent levels of β′ stereocontrol can be obtained when chiral phosphine oxides **9**, **10** or **11** are lithiated and reacted with ketones, esters or Me_3SiCl. Not surprisingly, a lower level of stereoselectivity is observed if the stereogenic centre in the chiral phosphine oxide bears similarly sized groups (as in **4**). However, reactions of lithium derivatives of chiral phosphine oxides with aldehydes or methyl iodide are also particularly non-selective.

Mechanistic rationale for the observed β′ stereoselectivity

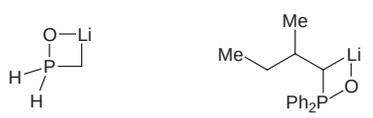
It is clear from the results presented so far that the β′ stereo-

selectivity observed in our study is somewhat variable. The underlying trend is, however, one of *syn* β′ stereocontrol. To emphasise this, we have summarised the results obtained from the reactions of lithiated **9** with a range of electrophiles (Table 3). In order to make sense of the results in Table 3 and hence to provide a general explanation of the sense and degree of the asymmetric induction, we need to consider what happens when the chiral phosphine oxides are lithiated and then what factors govern the stereoselectivity of reaction with the electrophiles.

Table 3 β′ Selectivity of reactions of lithiated **9** with different electrophiles

Entry	Electrophile	*syn*:*anti*
1	Cyclohexanone	≥95:5
2	Me_3SiCl	93:7
3	Ethyl benzoate	92:8
4	Cyclobutanone	80:20
5	Benzaldehyde	45:55
6	Methyl iodide	38:62

Recent results reported by our group have resulted in a greater knowledge of the nature and properties of lithiated phosphine oxides in THF. For example, our predictive *ab initio* calculations[6] suggested a four-membered lithium–oxygen–phosphorus–carbon structure for lithiated phosphine oxides which was subsequently proved when we obtained an X-ray structure of lithiated **4**.[7] In addition, using a number of



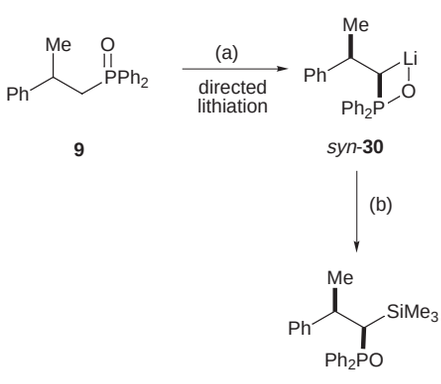
Ab initio calculation

X-ray crystal structure of lithiated **4**

Structures of lithiated phosphine oxides.

methods,[8,9] we have demonstrated that lithium derivatives of diphenylphosphine oxides are not configurationally stable[21,22] under the usual conditions that they are used (THF solution, −78 °C).

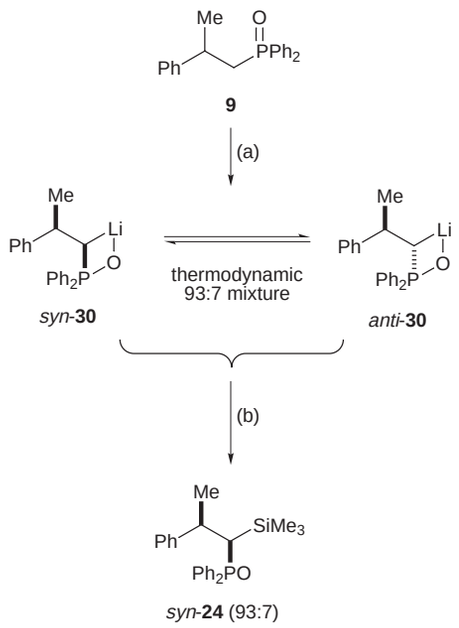
A mechanism which could account for the stereoselective formation of silyl phosphine oxide *syn*-**24** from phosphine oxide **9** and Me_3SiCl is depicted in Scheme 5. The first step



Scheme 5 *Reagents and conditions*: (a) BuLi, THF, −78 °C, 30 min; (b) i, Me_3SiCl, −78 °C, 1 h; ii, NH_4Cl.

involves lithiation of **9** (directed by the resident chiral centre) to give a configurationally stable lithium derivative *syn*-**30** which is trapped stereospecifically (with retention) by Me_3SiCl to give silyl phosphine oxide *syn*-**24**. This directed lithiation mechanism (which Hoppe and Schwerdtfeger[23] used to rationalise stereoselective reactions of lithiated carbamates) cannot however be operating in our case since it is highly unlikely that organolithium **30** is configurationally stable.¶

An alternative mechanism which could account for the formation of silyl phosphine oxide *syn*-**24** is shown in Scheme 6.



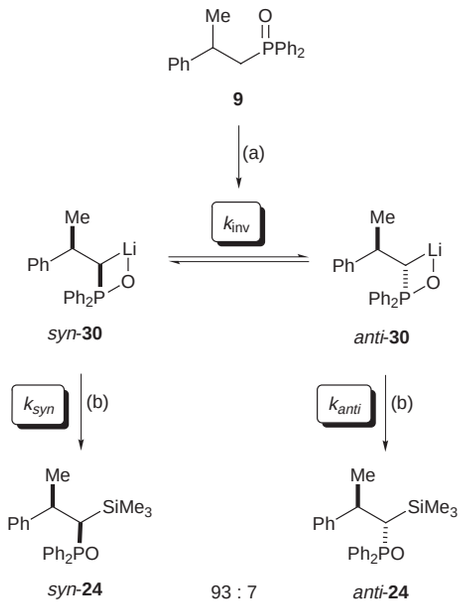
Scheme 6 *Reagents and conditions*: (a) BuLi, THF, −78 °C, 30 min; (b) i, Me_3SiCl, −78 °C, 1 h; ii, NH_4Cl.

Here, initial lithiation of **9** may or may not be stereoselective but this is irrelevant as the configurationally unstable lithium derivative **30** equilibrates to a thermodynamic 93:7 mixture of *syn*- and *anti*-**30**. Provided that the rate of reaction of each of *syn*- and *anti*-**30** with Me_3SiCl is faster than their rate of interconversion, stereospecific reaction with Me_3SiCl will trap out the thermodynamic mixture to give the observed 93:7 mixture of *syn*- and *anti*-**24**. Such a mechanism was used by McDougal *et al.* to explain stereoselective reactions of chiral sulfides.[24] However, we can rule out this mechanism since our reactions are electrophile-dependent and McDougal's mechanism required that the *same* degrees of stereoselectivity would be observed with a range of electrophiles. In addition, essentially the same stereoselectivity is observed when we carry out silylation of phosphine oxide **9** using premixed LDA and Me_3SiCl (Corey's internal quench conditions[25]) which indicates that the rates of silylation of *syn*- and *anti*-**30** are slower than their interconversion.‖

We believe that the dynamic kinetic diastereoselection[27] mechanism shown in Scheme 7 is the only one which can accommodate all of the observed results described in this paper. Indeed, we suggest that stereoselective reactions of related systems (*e.g.* amino sulfones,[28] hydroxy sulfones[29] and sulfoxides[30]) may also occur *via* a similar process. When phosphine oxide **9** is lithiated, a rapidly equilibrating mixture of diastereomeric organolithiums *syn*- and *anti*-**30** is formed. Since silyl

¶ Additionally, with such a mechanism, we would not expect the ratio of diastereomeric addition products to be electrophile-dependent which they clearly are (see Table 3).

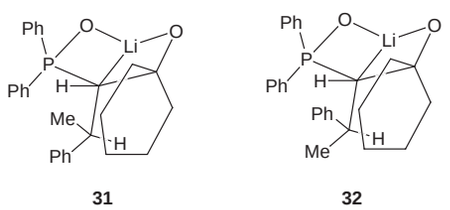
‖ We have also verified this result using our own recently developed internal quench reaction with cyclobutanone:[26] LDA was added to a solution of phosphine oxide **9** and cyclobutanone to give an 85:15 mixture of hydroxy phosphine oxides *syn*- and *anti*-**18**. Under the usual external quench conditions, an 80:20 mixture of *syn*- and *anti*-**18** was obtained (see Entry 4; Table 1).



Scheme 7 *Reagents and conditions*: (a) BuLi, THF, −78 °C, 30 min; (b) i, Me_3SiCl, −78 °C, 1 h; ii, NH_4Cl.

phosphine oxide *syn*-**24** is the major product, the rate of silylation of *syn*-**30** (k_{syn}) must be faster than that of *anti*-**30** (k_{anti}); for high β′ stereoselectivity both rates of silylation (k_{syn} and k_{anti}) must also be slower than the rate of interconversion of *syn*- and *anti*-**30** (k_{inv}). This second condition will only be met if we have "slow" reacting electrophiles such as ketones, esters and Me_3SiCl (Entries 1–4; Table 3). However, if we have a more reactive electrophile such as an aldehyde then the rate of reactions (k_{syn} and k_{anti}) will become competitive with the rate of interconversion (k_{inv}) which will lead to an erosion of the β′ selectivity (Entry 5; Table 3). Crucially, the dynamic kinetic diastereoselection mechanism can account for the electrophile-dependence of our reactions.**

The source of the observed *syn* β′ stereoselectivity is harder to explain and tentative suggestions are put forward here. Thus, the structures of the putative intermediates **31** and **32**†† are shown for the reaction of lithiated **9** with cyclohexanone; *syn*-**30** reacts *via* **31** and *anti*-**30** reacts *via* **32**. These intermediates have been constructed based on *ab initio* calculations carried out on a simpler reaction[6] and two assumptions were made: firstly we believe that the branched alkyl chain will adopt the less sterically hindered "outside" position of the butterfly structure and, secondly, we suggest that the hydrogen substituent at the chiral centre in both **31** and **32** will point towards the cyclo-

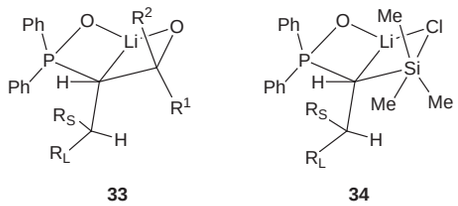


hexyl group as this is the most crowded of the possible orientations. As can be seen from the diagram, it is better to have the sterically smaller substituent pointing towards one of the phenyl rings of the diphenylphosphinoyl group and so reaction *via* **31** will be preferred and the *syn* β′ stereoselectivity can be rationalised.

** At present, we are unable to provide an explanation for the weakly *anti*-selective reactions with methyl iodide (Entry 6; Table 3).

†† For convenience and ease of comparison, complex **32** actually incorporates the enantiomeric lithiated phosphine oxide *anti*-**30**.

Extension of these ideas to the reactions of all of the chiral phosphine oxides with carbonyl electrophiles and Me_3SiCl leads to the generalised models **33** and **34**. Here, we assume that



General models for predicting stereoselectivity of reaction of chiral phosphine oxides with carbonyl electrophiles **33** and Me_3SiCl **34**.

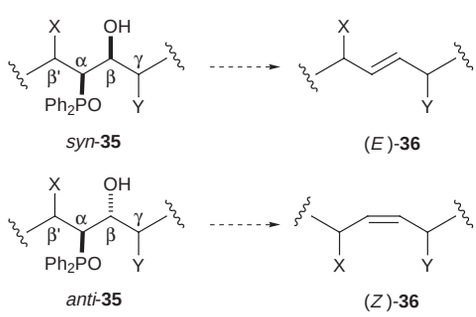
precoordination of the Me_3SiCl through the chlorine occurs. In all cases, *syn* β′ stereoselectivity is explained by the preferred orientation of the R_S and R_L groups as shown. Lower levels of *syn*-selectivity result if R_S and R_L are similar in size (*e.g.* in **4**; Entry 1, Table 2) or if a more reactive electrophile is used (*e.g.* benzaldehyde or cyclobutanone; Entries 1 and 4, Table 1) for the reasons outlined previously.

Synthetic application—preparation of an alkene with 1,4-related chiral centres across the double bond

Having carried out an extensive study on the scope and limitations of the reactions of lithium derivatives of chiral phosphine oxides, we were keen to demonstrate the usefulness of the reactions in stereocontrolled synthesis. In this section, we describe one such application in synthesis.[26]

For some time now, we have been exploring methods (based on both our diphenylphosphinoyl[10,11,31] and phenylsulfanyl[32] chemistry) for the stereocontrolled construction of molecules which possess 1,4-related chiral centres across a double bond of defined geometry. Such a structural motif is found in a variety of natural products (*e.g.* prostaglandins,[33] macbecins,[34] herbimycins,[35] leukotrienes[36] and others[37]) and has also attracted considerable interest as a novel peptide isostere.[38]

Previously, using the diphenylphosphinoyl group as a stereocontrol element,[1] we have described three different synthetic approaches to alkenes (*e.g.* **36**) with remotely related chiral centres flanking the double bond.[10,11,31] Each one of these methods relied on the synthesis of β-hydroxy phosphine oxides like *syn*- and *anti*-**35** with four contiguous chiral centres (Scheme 8). However, only one (quite long) route[31] really

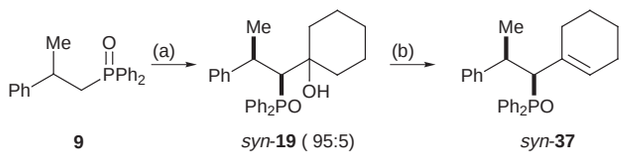


Scheme 8

addressed the issue of controlling the relative stereochemistry between the α and β′ chiral centres; the other routes required HPLC separation of diastereomers at the start of the synthetic sequences.[10,11] Here, we describe a stereocontrolled and concise synthesis of an alkene with 1,4-related chiral centres which does not require purification of any intermediates by HPLC.

Our synthesis began with phosphine oxide **9** which was lithiated and added to cyclohexanone to give a 44% isolated yield of hydroxy phosphine oxide *syn*-**19** (Entry 5; Table 1). Conversion of *syn*-**19** into allylic phosphine oxide *syn*-**37** was

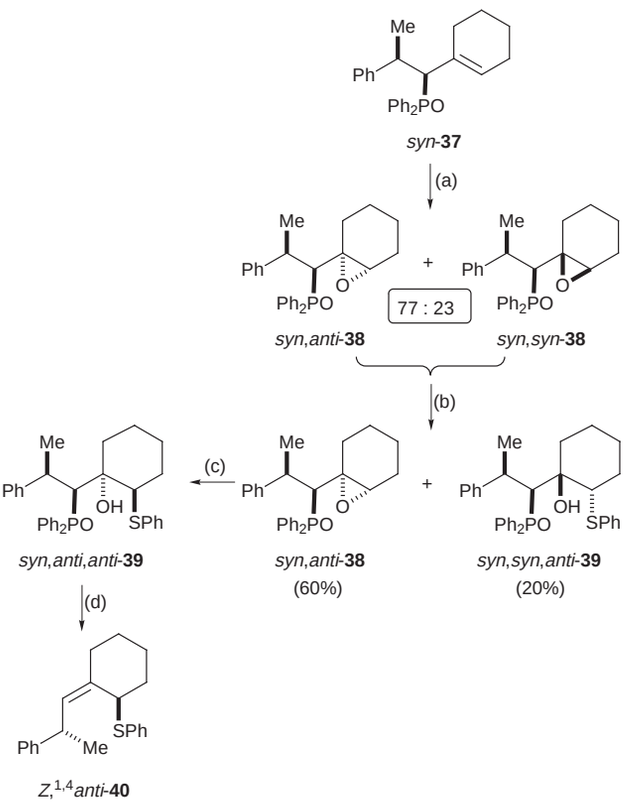
accomplished by refluxing for 30 minutes in trifluoroacetic acid[39] (Scheme 9). Allylic phosphine oxide *syn*-**37** is a particularly useful compound: significant quantities of it can easily be synthesised as a single diastereomer (*via* the highly stereoselective hydroxyalkylation reaction) and it contains a prochiral alkene unit suitable for further elaboration.



9 *syn*-**19** (95:5) *syn*-**37**

Scheme 9 *Reagents and conditions*: (a) i, BuLi, THF, −78 °C; ii, cyclohexanone (44%); (b) TFA, reflux, 30 min (74%).

The conversion of allylic phosphine oxide *syn*-**37** into alkene (*Z*)-**40** is shown in Scheme 10. First of all, *syn*-**37** was epoxidised with *m*-CPBA to give a 77 : 23 mixture of epoxides *syn*,*anti*- and *syn*,*syn*-**38**. The *anti*-selectivity of the epoxidation results from preferential attack on the face of the alkene opposite to the diphenylphosphinoyl group in a Houk conformation.[40,41] Because we were unable to separate the two epoxides by conventional methods, we treated the mixture with lithium phenolthiolate in THF[42] at room temperature: interestingly, only the minor epoxide *syn*,*syn*-**38** reacted to give alcohol *syn*,*syn*,*anti*-**39** in 20% yield (87% based on epoxide *syn*,*syn*-**38**). The major epoxide *syn*,*anti*-**38** was completely inert to these conditions and could be recovered in 60% yield. Effectively then, this remarkable difference in the rates of reaction of epoxides *syn*,*anti*- and *syn*,*syn*-**38** with lithium benzenethiolate allowed us to "separate" the two "inseparable" epoxides. The relative stereochemistry of alcohol *syn*,*syn*,*anti*-**39** was determined using X-ray crystallography (Fig. 1) and allowed unambiguous assignment of the relative stereochemistry of the other compounds described in Schemes 9 and 10. It proved quite difficult to ring open the less reactive epoxide *syn*,*anti*-**38**. However, after attempting the reaction in the presence of a range of Lewis acids, we discovered that the epoxide could be opened using lithium benzenethiolate and trimethylaluminium in CH_2Cl_2. In this way, alcohol *syn*,*anti*,*anti*-**39** was obtained in 64% yield and Horner–Wittig elimination proceeded uneventfully to give alkene *Z*,[1,4]*anti*-**40**.



Scheme 10 *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2, Na_2HPO_4 (62%); (b) PhSLi, THF, rt, 24 h; (c) PhSLi, Me_3Al, CH_2Cl_2, rt, 24 h (64%); (d) KOH, DMSO, 50 °C, 45 min (58%).

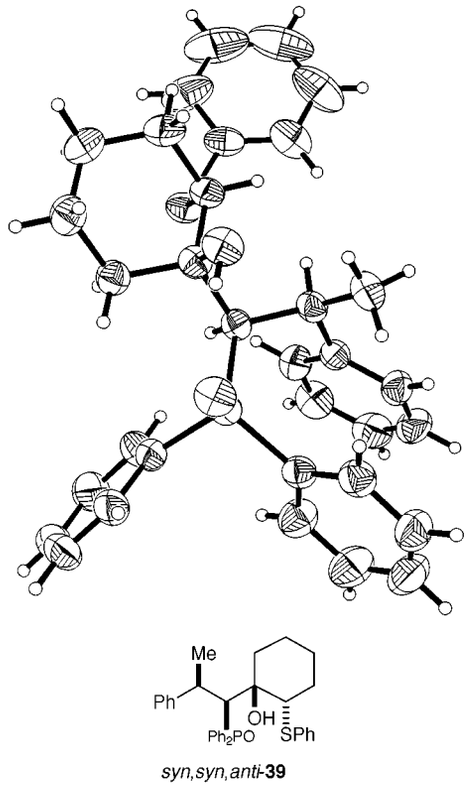


Fig. 1 X-Ray crystal structure of phosphine oxide *syn*,*syn*,*anti*-**39**.

Experimental

General

All solvents were distilled before use. THF was freshly distilled from lithium aluminium hydride whilst CH_2Cl_2 was freshly distilled from calcium hydride. Triphenylmethane was used as indicator for THF. Butyllithium was titrated against diphenylacetic acid before use. All non-aqueous reactions were carried out under argon using oven-dried glassware.

Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) according to the method of Still, Kahn and Mitra.[43] Thin layer chromatography was carried out on commercially available pre-coated plates (Merck Kieselgel $60F_{254}$). Proton and carbon NMR spectra were recorded on a Bruker WM 200, WM 250 or WM 400 Fourier transform spectrometer 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. 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 Reichert hot stage microscope or a Buchi 510 melting point apparatus and are uncorrected. Infra-red 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.

The synthesis of phosphine oxide **10** has been described previously.[8] Phosphine oxide **4** was available from the group store and was prepared in the standard way[44] from triphenylphosphine and the corresponding alkyl iodide.

2-Phenyl-1-bromopropane 14

Alcohol **13** (7.0 cm^3, 50 mmol) was added dropwise to a stirred solution of toluene-*p*-sulfonyl chloride (10.0 g, 52 mmol) and pyridine (12 cm^3, 150 mmol) in CH_2Cl_2 (50 cm^3) under argon at room temperature. The resulting solution was stirred for 8 h and then hydrochloric acid (3 M; 30 cm^3) was added. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Recrystallisation from hexane afforded 2-phenylpropan-1-yl toluene-*p*-sulfonate (14.0 g, 96%) as a white solid. This toluene-*p*-sulfonate (tosylate) (14.0 g, 48 mmol) was added in one portion to a stirred solution of lithium bromide (9.0 g, 96 mmol) in acetone (100 cm^3). The resulting mixture was heated at reflux for 8 h and, after being allowed to cool to room temperature, the solids were removed by filtration. The filtrate was evaporated under reduced pressure and the residue was dissolved in Et_2O–water (1:1; 200 cm^3). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the known[15] bromide **14** (8.2 g, 86%) as a colourless oil, δ_H(200 MHz, $CDCl_3$) 7.45–7.25 (5 H, m, Ph), 3.5–3.4 (2 H, m, CH_2Br), 3.2 (1 H, sextet, *J* 7.0, C*H*Me) and 1.5 (3 H, d, *J* 7.0, CH*Me*).

1-Diphenylphosphinoyl-2-phenylpropane 9

A solution of lithium diphenylphosphinide in THF was prepared according to the method of Ashby *et al.*:[16] butyllithium (1.6 M solution in hexane; 21.0 cm^3, 31.5 mmol) was added dropwise to a stirred solution of diphenylphosphine (5.0 cm^3, 28.6 mmol) in THF (100 cm^3) under argon at −30 °C to give a deep orange solution. After 4 h, a solution of bromide **14** (6.3 g, 34.3 mmol) in THF (20 cm^3) was added dropwise and the resulting bright red solution was allowed to warm to 0 °C. After 1 h at 0 °C, hydrogen peroxide (100 vol; 30 cm^3) was added dropwise (**CARE**—vigorous reaction) to give a colourless solution. Then, saturated aqueous ammonium chloride (20 cm^3) was added. The THF was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2–water (1:1; 300 cm^3) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 cm^3) and the combined organic extracts were washed with saturated brine (100 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Trituration with hexane afforded *phosphine oxide* **9** (8.5 g, 93%) as plates, mp 116–118 °C (from hexane); R_f(EtOAc) 0.4; ν_{max}($CHCl_3$)/cm^{-1} 1454 (P–Ph) and 1182 (P=O); δ_H(250 MHz, $CDCl_3$) 7.8–7.1 (4 H, m, Ph_2PO and Ph), 3.4–3.2 (1 H, m, C*H*Me), 2.65–2.55 (2 H, m, PCH_2) and 1.4 (3 H, d, *J* 6.9, CH*Me*); δ_C(63 MHz, $CDCl_3$) 147.0–126.0 (Ph_2PO and Ph), 38.4^- (d, *J* 69.0, PCH_2), 34.2^+ (d, *J* 3, *C*HMe) and 23.3^+ (d, *J* 5, CH*Me*); *m*/*z* 320 (45%, M^+), 215 (70, M − PhCHMe) and 202 (100, Ph_2POH) (Found: M^+, 320.1333. $C_{21}H_{21}OP$ requires *M*, 320.1330).

3-Diphenylphosphinoyl-2-methyl-1-triphenylmethoxypropane 11

A solution of triethylamine (530 µl, 3.8 mmol), alcohol **12**[8] (516 mg, 1.9 mmol), triphenylmethyl chloride (788 mg, 2.8 mmol) and DMAP (52 mg, 0.5 mmol) in CH_2Cl_2 (10 cm^3) were stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica with EtOAc as eluent to give the *tritylated alcohol* **11** (940 mg, 97%) as plates, mp 164–166 °C (from EtOAc); R_f(EtOAc) 0.4 (Found: C, 81.2; H, 6.6; P, 6.0. $C_{35}H_{33}O_2P$ requires C, 81.4; H, 6.4; P, 6.0%); ν_{max}($CHCl_3$)/cm^{-1} 1594 (Ph), 1438 (P–Ph) and 1171 (P=O); δ_H(200 MHz, $CDCl_3$) 7.83–7.67 (4 H, m, *o*-Ph_2PO), 7.56–7.19 (21 H, m, *m*- and *p*-Ph_2PO and $OCPh_3$), 3.04 (1 H, ddd, *J* 1.0, 6.0 and 9.0, $CH_AH_BOCPh_3$), 2.96 (1 H, dd, *J* 7.5 and 9.0, $CH_AH_BOCPh_3$), 2.58 (1 H, ddd, *J* 3.0, 9.5 and 12.5, PCH_AH_B), 2.36–2.24 (1 H, br m, C*H*Me), 1.96 (1 H, ddd, *J* 9.5, 12.5 and 15.0, PCH_AH_B) and 1.06 (3 H, d, *J* 6.5, CH*Me*); δ_C(50 MHz, $CDCl_3$) 144.0^- (*ipso*-$OCPh_3$), 135.4–126.8 (Ph_2PO and $OCPh_3$), 86.4^- ($OCPh_3$), 69.0^- (d, *J* 13.5, CH_2O), 33.2^- (d, *J* 72.5, PCH_2), 29.2^+ (d, *J* 2.5, *C*HMe) and 18.5^+ (CHMe); *m*/*z* 314 (40%, M − Ph_2POH), 243 (100, CPh_3), 202 (20, Ph_2POH), 201 (20, Ph_2PO) and 77 (40, Ph).

2-Diphenylphosphinoyl-1,3-diphenylbutan-1-ol 15

LDA (0.3 M solution in THF; 2.2 cm^3, 0.66 mmol) was added dropwise to a stirred solution of phosphine oxide **9** (186 mg, 0.6 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 benzaldehyde (65 µl, 0.6 mmol) was added dropwise. After 30 min at −78 °C, saturated aqueous ammonium chloride (0.5 cm^3) was added and the colourless solution 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 an oil which contained a 24:26:17:33 ratio of alcohols **15** (by ^1H NMR spectroscopy). Purification by chromatography on silica with EtOAc–hexane (2:1) and then EtOAc as eluent gave the same ratio (by ^1H NMR spectroscopy) of alcohols **15** (250 mg, 100%) as a white solid, R_f(EtOAc) 0.35 and 0.6. The ratio of diastereomers was determined from the methyl signals of the alcohols **15** in the ^1H NMR spectrum: δ_H(400 MHz, $CDCl_3$) 1.74 (3 H, d, *J* 7.0, CH*Me*), 1.68 (3 H, d, *J* 7.5, CH*Me*), 1.28 (3 H, d, *J* 7.0, CH*Me*) and 1.22 (3 H, d, *J* 7.5, CH*Me*).

Dess–Martin periodinane oxidation of alcohols 15

A 24:26:17:33 mixture of alcohols **15** (235 mg, 0.55 mmol) in CH_2Cl_2 (5 cm^3) was added dropwise by means of a cannula to a stirred solution of Dess–Martin periodinane (333 mg, 0.9 mmol) in CH_2Cl_2 (5 cm^3) under argon at 0 °C. After 1 h at 0 °C, the mixture was diluted with CH_2Cl_2 (10 cm^3) and carefully poured into a solution of sodium thiosulfate (8 equiv. with respect to the periodinane) in saturated sodium hydrogen carbonate solution (20 cm^3). After stirring for 30 min, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed with saturated sodium hydrogen carbonate solution (20 cm^3) and then saturated brine (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by chromatography on silica with EtOAc as eluent gave a 55:45 ratio of ketones *anti*- and *syn*-**17** (195 mg, 84%) as plates, mp 170–175 °C (from EtOAc), R_f(EtOAc) 0.5 (Found: C, 79.4; H, 5.9; P, 7.5%; M^+, 424.1584. $C_{28}H_{25}O_2P$ requires C, 79.2; H, 5.9; P, 7.3%; *M*, 424.1592); ν_{max}($CHCl_3$)/cm^{-1} 1673 (C=O), 1597 (Ph), 1580 (Ph), 1438 (P–Ph) and 1196 (P=O); δ_H(400 MHz, $CDCl_3$) 8.21–6.98 (40 H, m, Ph_2PO, PhCO and Ph), 4.86 (1 H, dd, *J* 11.0 and 16.0, PCH^{syn}), 4.78 (1 H, dd, *J* 9.0 and 11.0, PCH^{anti}), 3.94 (1 H, qd, *J* 7.0 and 9.0, C*H*Me^{anti}), 3.85 (1 H, qd, *J* 7.0 and 11.0, C*H*Me^{syn}), 1.41 (3 H, d, *J* 7.0, CHMe^{syn}) and 1.30 (3 H, d, *J* 7.0, CHMe^{anti}); δ_C(100 MHz, $CDCl_3$) 198.85^- ($C{=}O^{syn}$), 198.2^- ($C{=}O^{anti}$), 144.3^- (d, *J* 13.0, *ipso*-Ph^{syn}), 142.7^- (d, *J* 4.5, *ipso*-Ph^{anti}), 138.4–126.7 (Ph_2PO, PhCO and Ph), 60.0^+ (d, *J* 54.5, PCH^{syn}), 58.8^+ (d, *J* 59.0, PCH^{anti}), 41.2^+ (*C*HMe^{syn}), 40.2^+ (*C*HMe^{anti}), 21.3^+ (CHMe^{syn}) and 21.2^+ (d, *J* 8.5, CHMe^{anti}); *m*/*z* 424 (70%, M^+), 319 (30,

M − PhCO), 219 (80), 202 (100, Ph_2POH), 201 (80, Ph_2PO), 105 (60, PhCO) and 77 (70, Ph).

General procedure for the reaction of chiral phosphine oxides with electrophiles (Tables 1 and 2)

Butyllithium (1.5 M solution in hexane; 0.4 mmol) was added dropwise to a stirred solution of the chiral phosphine oxide (0.4 mmol) in THF (10 cm^3) under argon at −78 °C. The resulting orange–red solution was stirred at −78 °C for 30 min and then the electrophile (0.6 mmol) was added dropwise. After 1 h at −78 °C, saturated aqueous ammonium chloride (1 cm^3) was added and the 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) 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 or crystalline solid.

(2*R**,3*S**,4*R**)-2,4-Diphenyl-3-diphenylphosphinoyloctan-4-ol *syn*,*anti*-16

Using the general procedure, phosphine oxide **9** (2.0 g, 6.2 mmol) and valerophenone (2.0 cm^3, 12 mmol) gave a crude product which contained only starting material and alcohol *syn*,*anti*-**16** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc–hexane (1:1) as eluent gave *alcohol syn*,*anti*-**16** (1.37 g, 46%) as plates, mp 182–183 °C (from EtOAc); R_f(EtOAc) 0.64 (Found: C, 79.7; H, 7.3; P, 6.5%; M^+ − Bu, 425.1699. $C_{32}H_{35}O_2P$ requires C, 79.6; H, 7.3; P, 6.4%; *M* − Bu, 425.1670); ν_{max}(Nujol)/cm^{-1} 3342 (OH), 1438 (P–Ph) and 1159 (P=O); δ_H(400 MHz, $CDCl_3$) 7.9–6.4 (20 H, m, Ph_2PO and Ph), 5.6 (1 H, br s, OH), 3.4 (1 H, d, *J* 5.5, PCH), 3.1 (1 H, qd, *J* 7.0 and 31.0, C*H*Me), 1.55 (3 H, d, *J* 7.0, CH*Me*), 2.0–0.7 (6 H, m, 3 × CH_2) and 0.5 (3 H, t, *J* 7.0, CH_2*Me*); δ_C(100 MHz, $CDCl_3$) 145.6$^-$ (*ipso*-Ph), 145.1$^-$ (d, *J* 10.0, *ipso*-Ph), 139.0–125.0 (Ph_2PO and Ph), 82.7$^-$ (d, *J* 2.5, COH), 53.7$^+$ (d, *J* 63.0, PCH), 45.1$^-$ (CH_2), 35.9$^+$ (*C*HMe), 22.6$^-$ (CH_2), 25.9$^-$ (CH_2), 14.5$^+$ (d, *J* 6.0, CH*Me*) and 13.5$^+$ (CH_2*Me*); *m*/*z* 425 (60%, M^+ − Bu), 320 (30), 305 (35), 202 (100, Ph_2POH), 105 (45, PhCHMe) and 77 (35, Ph).

(2*S**,3*R**)-1,3-Diphenyl-2-diphenylphosphinoylbutan-1-one *syn*-17

Using the general procedure, phosphine oxide **9** (500 mg, 1.6 mmol) and ethyl benzoate (0.45 cm^3, 3.1 mmol) gave a crude product which contained a 92:8 ratio of ketones *syn*- and *anti*-**17** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc–hexane (4:1) as eluent gave *ketone syn*-**17** (250 mg, 38%) as plates, mp 221–222 °C (from EtOAc); R_f(EtOAc) 0.4 (Found: C, 78.8; H, 6.0; P, 7.6%; M^+, 424.1591. $C_{28}H_{25}O_2P$ requires C, 79.2; H, 5.9; P, 7.3%; *M*, 424.1592); ν_{max}(Nujol)/cm^{-1} 1660 (C=O), 1559 (P–Ph) and 1180 (P=O); δ_H(400 MHz, $CDCl_3$) 8.21–6.98 (20 H, m, Ph_2PO, PhCO and Ph), 4.86 (1 H, dd, *J* 11.0 and 16.0, PCH), 3.85 (1 H, qd, *J* 7.0 and 11.0, C*H*Me) and 1.41 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz, $CDCl_3$) 198.9$^-$ (C=O), 144.3$^-$ (d, *J* 13.0, *ipso*-Ph), 138.4–126.7 (Ph_2PO, PhCO and Ph), 60.0$^+$ (d, *J* 54.5, PCH), 41.2$^+$ (*C*HMe) and 21.3$^+$ (CH*Me*); *m*/*z* 424 (85%, M^+), 319 (25, M − PhCO), 219 (75), 202 (100, Ph_2POH), 105 (80, PhCO) and 77 (70, Ph).

(1′*S**,2′*R**)-1-(1′-Diphenylphosphinoyl-2′-phenylpropyl)cyclobutan-1-ol *syn*-18

Using the general procedure, phosphine oxide **9** (2.0 g, 6.2 mmol) and cyclobutanone (1.1 cm^3, 15.0 mmol) gave a crude product which contained an 80:20 ratio of alcohols *syn*- and *anti*-**18** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc–hexane (3:2) as eluent followed by recrystallisation from Et_2O gave *alcohol syn*-**18** (960 mg, 40%) as plates, mp 120–121 °C (from Et_2O); R_f(EtOAc) 0.6; ν_{max}(Nujol)/cm^{-1} 3361 (OH), 1438 (P–Ph) and 1161 (P=O); δ_H(400 MHz, $CDCl_3$) 7.9–6.7 (15 H, m, Ph_2PO and Ph), 5.45 (1 H, br s, OH), 3.5 (1 H, qd, *J* 7.0 and 26.0, C*H*Me), 3.0 (1 H, dd, *J* 2.0 and 8.0, PCH), 2.2–1.4 (6 H, m, 3 × CH_2) and 1.6 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz, $CDCl_3$) 145.7$^-$ (*ipso*-Ph), 136.0–125.0 (Ph_2PO and Ph), 81.1$^-$ (d, *J* 5.0, COH), 54.0$^+$ (d, *J* 64.0, PCH), 38.0$^-$ (d, *J* 3.5, CH_2), 36.8$^-$ (d, *J* 11.5, CH_2), 36.0$^+$ (*C*HMe), 16.5 (d, *J* 6.5, CH*Me*) and 15.7$^-$ (CH_2); *m*/*z* 390 (20%, M^+), 319 (30), 305 (20), 202 (100, Ph_2POH) and 77 (20, Ph) (Found: M^+, 390.1747. $C_{25}H_{27}O_2P$ requires *M*, 390.1748).

(1′*S**,2′*R**)-1-(1′-Diphenylphosphinoyl-2′-phenylpropyl)cyclohexan-1-ol *syn*-19

Using the general procedure, phosphine oxide **9** (2.0 g, 6.2 mmol) and cyclohexanone (1.5 cm^3, 15.0 mmol) gave a crude product which contained a ≥95:5 ratio of alcohols *syn*- and *anti*-**19** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc–hexane (3:2) as eluent followed by recrystallisation from Et_2O gave *alcohol syn*-**19** (1.15 g, 44%) as plates, mp 180–182 °C (from Et_2O); R_f(EtOAc) 0.55 (Found: C, 77.3; H, 7.6; P, 7.5%; M^+, 418.2059. $C_{27}H_{31}O_2P$ requires C, 77.5; H, 7.5; P, 7.4%; *M*, 418.2062); ν_{max}(Nujol)/cm^{-1} 3361 (OH), 1438 (P–Ph) and 1161 (P=O); δ_H(400 MHz, $CDCl_3$) 7.8–6.7 (15 H, m, Ph_2PO and Ph), 5.2 (1 H, br s, OH), 3.8 (1 H, qd, *J* 7.0 and 32.5, C*H*Me), 3.1 (1 H, dd, *J* 1.5 and 10.0, PCH), 2.2–1.1 (10 H, m, 5 × CH_2) and 1.7 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz, $CDCl_3$) 145.0–125.0 (Ph_2PO and Ph), 77.2$^-$ (d, *J* 2.0, COH), 52.2$^+$ (d, *J* 65.0, PCH), 40.7$^-$ (d, *J* 4.0, *C*H_2COH), 37.2$^-$ (d, *J* 7.0, *C*H_2COH), 34.3$^+$ (*C*HMe), 30.9$^-$ (CH_2), 25.6$^-$ (CH_2), 22.2$^-$ (d, *J* 8.0, CH_2) and 14.7 (d, *J* 6.0, CH*Me*); *m*/*z* 418 (30%, M^+), 320 (80), 305 (90), 202 (100, Ph_2POH) and 77 (65, Ph).

(1′*S**,2′*R**)-1-[3′-(1,1-Dimethylethyl)dimethylsiloxy-1′-diphenylphosphinoyl-2′-methylpropyl]cyclohexan-1-ol *syn*-20 and (1′*R**,2′*R**)-1-[3′-(1,1-dimethylethyl)dimethylsiloxy-1′-diphenylphosphinoyl-2′-methylpropyl]cyclohexan-1-ol *anti*-20

Using the general procedure, phosphine oxide **10** (194 mg, 0.5 mmol) and cyclohexanone (80 μl, 0.8 mmol) gave a crude product which contained an 80:20 ratio of alcohols *syn*- and *anti*-**20** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc–hexane (1:1) as eluent gave *alcohol anti*-**20** (31 mg, 13%) as plates, mp 170–172 °C (from EtOAc); R_f(EtOAc) 0.65; ν_{max}($CHCl_3$)/cm^{-1} 3361 (OH), 1591 (Ph), 1438 (P–Ph), 1258 (Si^{t}BuMe_2), 1214 (P=O) and 838 (Si^{t}BuMe_2); δ_H(400 MHz, $CDCl_3$) 7.91–7.86 (2 H, m, *o*-Ph_2PO), 7.73–7.67 (2 H, m, *o*-Ph_2PO), 7.46–7.36 (6 H, m, *m*- and *p*-Ph_2PO), 5.22 (1 H, br s, OH), 3.69 (1 H, t, *J* 10.0, C$H_A$$H_B$OSi), 3.42 (1 H, ddd, *J* 1.0, 6.5 and 10.0, C$H_A$$H_B$OSi), 3.27 (1 H, d, *J* 14.0, PCH), 2.03–1.94 (1 H, m, C*H*Me), 1.84–1.06 (10 H, m, 5 × CH_2), 0.97 (3 H, d, *J* 7.5, CH*Me*), 0.95 (9 H, s, CMe_3), 0.04 (3 H, s, Si*Me*$_A$$Me_B$) and 0.035 (3 H, s, Si$Me_A$*Me*$_B$); δ_C(50 MHz, $CDCl_3$) 137.3–128.1 (Ph_2PO), 76.7$^-$ (d, *J* 2.5, COH), 67.7$^-$ (d, *J* 15.0, CH_2OSi), 44.2$^+$ (d, *J* 66.0, PCH), 40.6$^-$ (d, *J* 5.5, *C*H_2COH), 37.6$^-$ (d, *J* 11.5, *C*H_2COH), 36.3$^+$ (*C*HMe), 25.9$^+$ (C*Me*$_3$), 25.5$^-$ (CH_2), 21.9$^-$ (CH_2), 21.8$^-$ (CH_2), 18.2$^-$ (*C*Me_3), 14.1$^+$ (CH*Me*), −5.4$^+$ (Si*Me*$_A$$Me_B$) and −5.45$^+$ (SiMe_A*Me*$_B$); *m*/*z* 486 (20%, M^+), 471 (10, M − Me), 429 (40, M − CMe_3), 243 (100), 202 (40, Ph_2POH) and 201 (50, Ph_2PO) (Found: M^+, 486.2726. $C_{28}H_{43}O_3PSi$ requires *M*, 486.2719), *alcohol syn*-**20** (154 mg, 63%) as a non-crystallisable foam; R_f(EtOAc) 0.6; ν_{max}($CHCl_3$)/cm^{-1} 3361 (OH), 1591 (Ph), 1438 (P–Ph), 1258 (Si^{t}BuMe_2), 1214 (P=O) and 838 (Si^{t}BuMe_2); δ_H(400 MHz, $CDCl_3$) 7.90–7.85 (2 H, m, *o*-Ph_2PO), 7.81–7.76 (2 H, m, *o*-Ph_2PO), 7.46–7.33 (6 H, m, *m*- and *p*-Ph_2PO), 4.69 (1 H, br s, OH), 3.33 (1 H, dd, *J* 6.0 and 10.0, C$H_A$$H_B$OSi), 3.09

(1 H, dd, *J* 1.0 and 9.5, PCH), 2.88 (1 H, t, *J* 10.0, CH_AH_BOSi), 2.42 (1 H, sextet d, *J* 6.5 and 30.5, C*H*Me), 1.88–1.02 (10 H, m, 5 × CH_2), 1.13 (3 H, d, *J* 6.5, CH*Me*), 0.93 (9 H, s, CMe_3), 0.03 (3 H, s, $SiMe_AMe_B$) and 0.01 (3 H, s, $SiMe_AMe_B$); δ_C(50 MHz, $CDCl_3$) 138.3–127.9 (Ph_2PO), 76.2$^-$ (d, *J* 3.0, COH), 65.6$^-$ (CH_2OSi), 46.0$^+$ (d, *J* 66.5, PCH), 39.6$^-$ (d, *J* 4.0, CH_2COH), 37.1$^-$ (d, *J* 6.0, CH_2COH), 34.3$^+$ (*C*HMe), 25.8$^+$ (CMe_3), 25.4$^-$ (CH_2), 22.0$^-$ (CH_2), 21.9$^-$ (CH_2), 18.1$^-$ (CMe_3), 15.5$^+$ (d, *J* 8.0, CH*Me*), −5.4$^+$ ($SiMe_AMe_B$) and −5.5$^+$ ($SiMe_AMe_B$); *m*/*z* 486 (20%, M$^+$), 429 (40, M − CMe_3), 243 (90), 202 (30, Ph_2POH), 201 (40, Ph_2PO) and 75 (100) (Found: M$^+$, 486.2718. $C_{28}H_{43}O_3PSi$ requires *M*, 486.2719) and recovered phosphine oxide **10** (33 mg, 17%).

(1′*S**,2′*R**)-1-[1′-Diphenylphosphinoyl-2′-methyl-3′-(triphenylmethoxy)propyl]cyclohexan-1-ol *syn*-21

Using the general procedure, phosphine oxide **11** (197 mg, 0.4 mmol) and cyclohexanone (60 µl, 0.6 mmol) gave a crude product which contained a 96:4 ratio of alcohols *syn*- and *anti*-**21** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc as eluent gave *alcohol syn*-**21** (152 mg, 65%) as plates, mp 228–230 °C (from EtOAc), R_f(EtOAc) 0.6 (Found: C, 79.5; H, 7.1; P, 4.9%; M$^+$, 614.2943. $C_{41}H_{43}O_3P$ requires C, 80.1; H, 7.05; P, 5.0%; *M*, 614.2950); ν_{max}($CHCl_3$)/cm^{-1} 3670 (OH), 1597 (Ph), 1438 (P–Ph) and 1211 (P=O); δ_H(400 MHz, $CDCl_3$) 7.80–7.76 (2 H, m, *o*-Ph_2PO), 7.50–7.02 (23 H, m, Ph_2PO and $OCPh_3$), 4.53 (1 H, br s, OH), 3.21 (1 H, d, *J* 9.0, PCH), 2.99–2.94 (1 H, m, $CH_AH_BOCPh_3$), 2.73–2.62 (2 H, m, $CH_AH_BOCPh_3$ and C*H*Me), 2.16–1.18 (10 H, m, 5 × CH_2) and 0.99 (3 H, d, *J* 7.0, CH*Me*); δ_C(50 MHz, $CDCl_3$) 144.2$^-$ (*ipso*-$OCPh_3$), 138.3–127.1 (Ph_2PO and $OCPh_3$), 86.8$^-$ (O*C*Ph_3), 77.2$^-$ (COH), 67.2$^-$ (CH_2O), 47.0$^+$ (d, *J* 68.0, PCH), 40.0$^-$ (CH_2COH), 36.7$^-$ (CH_2COH), 32.45$^+$ (*C*HMe), 25.6$^-$ (CH_2), 22.2$^-$ (CH_2), 22.0$^-$ (CH_2) and 15.6$^+$ (d, *J* 8.0, CH*Me*); *m*/*z* 614 (10%, M$^+$), 515 (5, M − $C_6H_{12}OH$), 371 (20, M − CPh_3), 297 (60), 273 (20, CH_2OCPh_3), 243 (100, CPh_3), 202 (25, Ph_2POH), 201 (20, Ph_2PO) and 77 (20, Ph) and recovered phosphine oxide **11** (43 mg, 22%). Diagnostic signal for alcohol *anti*-**21**: δ_H(400 MHz, $CDCl_3$) 5.13 (1 H, br s, OH).

(1*S**,2*R**)-1-Diphenylphosphinoyl-2-methyl-1-trimethylsilylbutane *syn*-23 and (1*S**,2*S**)-1-diphenylphosphinoyl-2-methyl-1-trimethylsilylbutane *anti*-23

Using the general procedure, phosphine oxide **4** (287 mg, 1.1 mmol) and trimethylsilyl chloride (300 µl, 2.4 mmol) gave a crude product which contained a 56:44 ratio of silyl phosphine oxides *syn*- and *anti*-**23** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc as eluent gave a 56:44 ratio (by ^{1}H NMR spectroscopy) of *silyl phosphine oxides syn*- and *anti*-**23** (310 mg, 85%) as fine needles, mp 132–140 °C (from EtOAc); R_f(EtOAc) 0.5 (Found: C, 69.8; H, 8.7; P, 9.2%; M$^+$, 344.1720. $C_{20}H_{29}OPSi$ requires C, 69.7; H, 8.5; P, 9.0%; *M*, 344.1725); ν_{max}($CHCl_3$)/cm^{-1} 1591 (Ph), 1438 (P–Ph), 1252 ($SiMe_3$), 1182 (P=O) and 843 ($SiMe_3$); δ_H(400 MHz, $CDCl_3$) 7.83–7.77 (8 H, m, 2 × *o*-Ph_2PO), 7.45–7.40 (6 H, m, 2 × *m*- and *p*-Ph_2PO), 1.92–1.87 (3 H, m), 1.67–1.64 (1 H, m), 1.55–1.50 (1 H, m), 1.47–1.35 (1 H, m), 1.28–1.15 (2 H, m), 1.11 (3 H, d, *J* 6.5, CHMe^{anti}), 1.09 (3 H, d, *J* 6.5, CHMe^{syn}), 0.80 (3 H, t, *J* 7.5, CH_2Me^{syn}), 0.67 (3 H, t, *J* 7.5, CH_2Me^{anti}), 0.0 (9 H, s, $SiMe_3^{syn}$) and −0.01 (9 H, s, $SiMe_3^{anti}$); δ_C(100 MHz, $CDCl_3$) 137.4–128.2 (Ph_2PO), 35.2$^+$ (2 × *C*HMe), 34.3$^+$ (d, *J* 58.0, PCH^{syn}), 33.35$^+$ (d, *J* 56.0, PCH^{anti}), 31.15$^-$ (d, *J* 14.0, CH_2Me^{anti}), 29.5$^-$ (CH_2Me^{syn}), 20.35$^+$ (d, *J* 13.5, CHMe^{syn}), 19.6$^+$ (CHMe^{anti}), 12.8$^+$ (CH_2Me^{syn}), 12.75$^+$ (CH_2Me^{anti}), 1.7$^+$ (d, *J* 1.5, $SiMe_3^{syn}$) and 2.2$^+$ (d, *J* 2.0, $SiMe_3^{anti}$); *m*/*z* 344 (70%, M$^+$), 343 (80, M − H), 329 (50, M − Me), 315 (100, M − Et), 215 (50) and 201 (20, Ph_2PO).

(1*S**,2*R**)-1-Diphenylphosphinoyl-2-phenyl-1-trimethylsilylpropane *syn*-24

Using the general procedure, phosphine oxide **9** (104 mg, 0.33 mmol) and trimethylsilyl chloride (75 µl, 0.6 mmol) gave a crude product which contained a 93:7 ratio of silyl phosphine oxides *syn*- and *anti*-**24** (by ^{1}H NMR spectroscopy). Recrystallisation from EtOAc gave *silyl phosphine oxide syn*-**24** (73 mg, 57%) as fine needles, mp 145–146 °C (from EtOAc); R_f(EtOAc) 0.55 (Found: C, 73.65; H, 7.45; P, 8.1%; M$^+$, 392.1712. $C_{24}H_{29}OPSi$ requires C, 73.4; H, 7.5; P, 7.9%; *M*, 392.1725); ν_{max}($CHCl_3$)/cm^{-1} 1436 (P–Ph), 1251 ($SiMe_3$), 1172 (P=O) and 843 ($SiMe_3$); δ_H(400 MHz, $CDCl_3$) 7.79–7.74 (2 H, m, *o*-Ph_2PO), 7.45–7.40 (2 H, m, *o*-Ph_2PO), 7.39–6.93 (11 H, m, *m*- and *p*-Ph_2PO and Ph), 3.53 (1 H, qd, *J* 7.5 and 28.5, C*H*Me), 2.31 (1 H, dd, *J* 1.5 and 12.0, PCH), 1.56 (3 H, d, *J* 7.5, CH*Me*) and −0.01 (9 H, s, $SiMe_3$); δ_C(50 MHz, $CDCl_3$) 146.0$^-$ (*ipso*-Ph), 138.1–125.5 (Ph_2PO and Ph), 36.2$^+$ (d, *J* 59.0, PCH), 35.8$^+$ (d, *J* 3.0, *C*HMe), 18.0$^+$ (d, *J* 7.5, CH*Me*) and 0.4$^+$ ($SiMe_3$); *m*/*z* 392 (10%, M$^+$), 377 (60, M − Me), 320 (40), 274 (50), 215 (30), 202 (10, Ph_2POH) and 77 (30, Ph).

(2*R**,3*S**)-1-[(1,1-Dimethylethyl)dimethylsiloxy]-3-diphenylphosphinoyl-2-methyl-3-trimethylsilylpropane *syn*-25 and (2*R**,3*R**)-1-[(1,1-dimethylethyl)dimethylsiloxy]-3-diphenylphosphinoyl-2-methyl-3-trimethylsilylpropane *anti*-25

Using the general procedure, phosphine oxide **10** (204 mg, 0.5 mmol) and trimethylsilyl chloride (140 µl, 1.1 mmol) gave a crude product which contained an 85:15 ratio of silyl phosphine oxides *syn*- and *anti*-**25** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc as eluent gave an 85:15 ratio (by ^{1}H NMR spectroscopy) of *silyl phosphine oxides syn*-**25** and *anti*-**25** (192 mg, 79%) as plates, mp 92–94 °C (from EtOAc); R_f(EtOAc) 0.55 (Found: C, 65.5; H, 9.1; P, 6.9%; M$^+$, 460.2376. $C_{25}H_{41}O_2PSi_2$ requires C, 65.2; H, 9.0; P, 6.7%; *M*, 460.2374); ν_{max}($CHCl_3$)/cm^{-1} 1592 (Ph), 1438 (P–Ph), 1223 ($SiMe_3$ and Si^tBuMe_2), 1182 (P=O) and 841 ($SiMe_3$ and Si^tBuMe_2); δ_H(400 MHz, $CDCl_3$) for *syn*-**25**: 7.87–7.75 (4 H, m, *o*-Ph_2PO), 7.40–7.31 (6 H, m, *m*- and *p*-Ph_2PO), 3.19 (1 H, dd, *J* 7.0 and 9.5, CH_AH_BOSi), 3.05 (1 H, t, *J* 9.5, CH_AH_BOSi), 2.42 (1 H, d, *J* 11.0, PCH), 2.22 (1 H, sextet d, *J* 7.0 and 30.0, C*H*Me), 1.09 (3 H, d, *J* 7.0, CH*Me*), 0.90 (9 H, s, CMe_3), −0.02 (3 H, s, $SiMe_AMe_B$), −0.03 (3 H, s, $SiMe_AMe_B$) and −0.04 (9 H, s, $SiMe_3$); δ_C(100 MHz, $CDCl_3$) for *syn*-**25**: 138.0–128.1 (Ph_2PO), 66.75$^-$ (CH_2OSi), 35.2$^+$ (d, *J* 3.5, *C*HMe), 28.0$^+$ (d, *J* 62.0, PCH), 26.0$^+$ (CMe_3), 18.2$^-$ (CMe_3), 15.9$^+$ (d, *J* 9.0, CH*Me*), 0.5$^+$ ($SiMe_3$), −5.3$^+$ ($SiMe_AMe_B$) and −5.4$^+$ ($SiMe_AMe_B$); *m*/*z* 460 (5%, M$^+$), 459 (5, M − H), 445 (60, M − Me), 403 (40, M − CMe_3), 331 (100), 315 (40, M − OSi^tBuMe_2) and 201 (10, Ph_2PO).

(2*R**,3*S**)-3-Diphenylphosphinoyl-2-methyl-3-trimethylsilyl-1-triphenylmethoxypropane *syn*-26

Using the general procedure, phosphine oxide **11** (203 mg, 0.4 mmol) and trimethylsilyl chloride (100 µl, 0.8 mmol) gave a crude product which contained a 96:4 ratio of silyl phosphine oxides *syn*- and *anti*-**26** (by ^{1}H NMR spectroscopy). Purification by chromatography on silica with EtOAc as eluent gave *silyl phosphine oxide syn*-**26** (204 mg, 89%) as a non-crystallisable foam, R_f(EtOAc) 0.6 (Found: C, 77.2; H, 7.0; P, 5.2. $C_{38}H_{41}O_2PSi$ requires C, 77.5; H, 7.0; P, 5.3%); ν_{max}($CHCl_3$)/cm^{-1} 1597 (Ph), 1438 (P–Ph), 1218 (P=O) and 851 ($SiMe_3$); δ_H(400 MHz, $CDCl_3$) 7.81–7.76 (2 H, m, *o*-Ph_2PO), 7.57–7.52 (2 H, m, *o*-Ph_2PO), 7.41–7.13 (21 H, m, *m*- and *p*-Ph_2PO and $OCPh_3$), 2.88 (1 H, dd, *J* 5.5 and 9.0, $CH_AH_BOCPh_3$), 2.87 (1 H, dd, *J* 5.0 and 9.0, $CH_AH_BOCPh_3$), 2.50 (1 H, br m, C*H*Me), 2.33 (1 H, d, *J* 11.0, PCH), 1.08 (3 H, d, *J* 7.5, CH*Me*) and −0.03 (9 H, s, $SiMe_3$); δ_C(50 MHz, $CDCl_3$) 144.3$^-$ (*ipso*-$OCPh_3$), 137.9–127.0 (Ph_2PO and $OCPh_3$), 86.5$^-$ ($OCPh_3$),

68.2$^-$ (CH_2O), 33.4$^+$ (d, *J* 3.5, *C*HMe), 30.0$^+$ (d, *J* 61.0, PCH), 16.9$^+$ (d, *J* 10.0, CH*Me*) and 0.6$^+$ ($SiMe_3$).

(2*R**,3*S**)-2-Diphenylphosphinoyl-3-phenylbutane *anti*-27 and (2*S**,3*S**)-2-diphenylphosphinoyl-3-phenylbutane *syn*-27

Using the general procedure, phosphine oxide **9** (102 mg, 0.3 mmol) and methyl iodide (20 μl, 0.4 mmol) gave a crude product which contained a 62:38 ratio (by ^{1}H NMR spectroscopy) of phosphine oxides *anti*- and *syn*-**27** (110 mg, 100%), R_f(EtOAc) 0.4; ν_{max}($CHCl_3$)/cm^{-1} 1602 (Ph), 1592 (Ph), 1494 (Ph), 1438 (P–Ph) and 1174 (P=O); *m*/*z* 334 (80%, M$^+$), 319 (10, M − Me), 229 (60, M − PhCHMe), 202 (100, Ph_2POH), 201 (40, Ph_2PO) and 77 (30, Ph) (Found: M$^+$, 334.1484. $C_{22}H_{23}OP$ requires *M*, 334.1487). Diagnostic signals for phosphine oxide *anti*-**27**: δ_H(400 MHz, $CDCl_3$) 1.41 (3 H, d, *J* 7.0, CH*Me*) and 1.10 (3 H, dd, *J* 5.5 and 13.0, PCH*Me*); δ_C(100 MHz, $CDCl_3$) 145.75$^-$ (d, *J* 14.5, *ipso*-Ph), 135.3–126.4 (Ph_2PO and Ph), 38.8$^+$ (d, *J* 69.0, PCH), 37.0$^+$ (*C*HMe), 14.3$^+$ (CH*Me*) and 6.7$^+$ (PCH*Me*). Diagnostic signals for phosphine oxide *syn*-**27**: δ_H(400 MHz, $CDCl_3$) 1.18 (3 H, d, *J* 7.0, CH*Me*) and 0.86 (3 H, dd, *J* 7.0 and 17.0, PCH*Me*); δ_C(100 MHz, $CDCl_3$) 145.0$^-$ (d, *J* 9.9, *ipso*-Ph), 135.3–126.4 (Ph_2PO and Ph), 41.1$^+$ (*C*HMe), 38.5$^+$ (d, *J* 70.0, PCH), 22.6$^+$ (d, *J* 4.5, CH*Me*) and 13.8$^+$ (PCH*Me*).

(2*R**,3*S**)-2,3-Dimethyl-1-[(1,1-dimethylethyl)dimethylsiloxy]-3-diphenylphosphinoylpropane *anti*-28 and (2*R**,3*R**)-2,3-dimethyl-1-[(1,1-dimethylethyl)dimethylsiloxy]-3-diphenylphosphinoylpropane *syn*-28

Using the general procedure, phosphine oxide **10** (406 mg, 1.05 mmol) and methyl iodide (60 μl, 1.2 mmol) gave a crude product which contained a 55:45 ratio (by ^{1}H NMR spectroscopy) of phosphine oxides *anti*- and *syn*-**28** (444 mg, 100%). Purification by chromatography on silica with EtOAc as eluent gave phosphine oxide *syn*-**28** (156 mg, 37%) and phosphine oxide *anti*-**28** (181 mg, 43%). The full details have been reported elsewhere.[8]

(2*R**,3*S**)-2,3-Dimethyl-3-diphenylphosphinoyl-1-triphenylmethoxypropane *anti*-29 and (2*R**,3*R**)-2,3-dimethyl-3-diphenylphosphinoyl-1-triphenylmethoxypropane *syn*-29

Using the general procedure, phosphine oxide **11** (108 mg, 0.2 mmol) and methyl iodide (15 μl, 0.3 mmol) gave a crude product which contained a 55:45 ratio (by ^{1}H NMR spectroscopy) of phosphine oxides *anti*- and *syn*-**29** (120 mg, 100%). Purification by chromatography on silica with EtOAc–hexane (2:1) as eluent gave *phosphine oxide syn*-**29** (40 mg, 36%) as a non-crystallisable foam, R_f(EtOAc) 0.55; ν_{max}($CHCl_3$)/cm^{-1} 1592 (Ph), 1438 (P–Ph) and 1174 (P=O); δ_H(400 MHz, $CDCl_3$) 7.74–7.67 (4 H, m, *o*-Ph_2PO), 7.47–7.19 (21 H, m, *m*- and *p*-Ph_2PO and $OCPh_3$), 3.46 (1 H, dd, *J* 4.5 and 8.5, C$H_A$$H_B$$OCPh_3$), 2.88 (1 H, t, *J* 8.5, CH$_A$$H_B$$OCPh_3$), 2.44 (1 H, dqd, *J* 4.5, 7.5 and 15.0, PCH), 2.37–2.14 (1 H, br m, C*H*Me), 1.14 (3 H, d, *J* 7.0, CH*Me*) and 0.93 (3 H, dd, *J* 7.0 and 16.5, PCH*Me*); δ_C(100 MHz, $CDCl_3$) 144.3$^-$ (*ipso*-$OCPh_3$), 137.9–126.8 (Ph_2PO and $OCPh_3$), 86.35$^-$ ($OCPh_3$), 65.0$^-$ (CH_2O), 35.9$^+$ (d, *J* 71.0, PCH), 34.2$^+$ (*C*HMe), 17.85$^+$ (d, *J* 10.5, CH*Me*) and 9.5$^+$ (PCH*Me*); *m*/*z* 530 (5%, M$^+$), 287 (100, M − CPh_3), 243 (80, CPh_3), 201 (60, Ph_2PO), 165 (90) and 77 (40, Ph) (Found: M$^+$, 530.2385. $C_{36}H_{35}O_2P$ requires *M*, 530.2375) and *phosphine oxide anti*-**29** (58 mg, 52%) as a non-crystallisable foam, R_f(EtOAc) 0.45; ν_{max}($CHCl_3$)/cm^{-1} 1592 (Ph), 1438 (P–Ph) and 1174 (P=O); δ_H(400 MHz, $CDCl_3$) 8.05–7.95 (2 H, m, *o*-Ph_2PO), 7.80–7.75 (2 H, m, *o*-Ph_2PO), 7.52–7.22 (21 H, m, *m*- and *p*-Ph_2PO and $OCPh_3$), 2.96–2.85 (2 H, m, CH_2OCPh_3), 2.58–2.36 (2 H, m, PCH and C*H*Me), 0.90 (3 H, d, *J* 7.0, CH*Me*) and 0.77 (3 H, dd, *J* 7.0 and 17.0, PCH*Me*); δ_C(100 MHz, $CDCl_3$) 144.2$^-$ (*ipso*-$OCPh_3$), 134.0–126.9 (Ph_2PO and $OCPh_3$), 86.8$^-$ ($OCPh_3$), 65.9$^-$ (d, *J* 13.5, CH_2O), 32.3$^+$ (*C*HMe), 30.9$^+$ (d, *J* 73.0, PCH), 12.3$^+$ (CH*Me*) and 5.6$^+$ (PCH*Me*); *m*/*z* 287 (90%, M − CPh_3), 243 (80, CPh_3), 201 (70, Ph_2PO), 165 (100) and 77 (40, Ph).

(*Z*)-2,4-Diphenyloct-3-ene 22

Potassium hydroxide (30 mg, 0.5 mmol) was added to a stirred solution of alcohol *syn*,*anti*-**16** (120 mg, 0.25 mmol) in DMSO (10 cm^3) and the resulting suspension was heated at 50 °C for 45 min. After being allowed to cool to room temperature, the reaction mixture was poured into water (20 cm^3) and extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were washed with water (3 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an oil. Purification by chromatography on silica with EtOAc–hexane (1:4) as eluent gave *alcohol* (*Z*)-**22** (62 mg, 94%) as an oil, R_f(EtOAc) 0.7; δ_H(400 MHz, $CDCl_3$) 7.4–7.1 (10 H, m, Ph), 5.6 (1 H, d, *J* 10.2, C=CH), 3.5 (1 H, qd, *J* 7.0 and 10.0, C*H*Me), 2.3 (2 H, t, *J* 6.0, CH_2C=), 1.3 (3 H, d, *J* 7.0, CH*Me*), 1.3–1.2 (4 H, m, CH_2CH_2) and 0.9 (3 H, t, *J* 7.0, CH_2*Me*); δ_C(100 MHz, $CDCl_3$) 146.9$^-$ (*C*=CH), 141.5$^+$ (*C*=CH), 140.0–126.0 (2 × Ph), 39.2$^-$ (CH_2), 38.5$^+$ (*C*HMe), 30.2$^-$ (CH_2), 22.7$^+$ (CH*Me*), 22.3$^-$ (CH_2) and 14.0$^+$ (CH_2*Me*); *m*/*z* 264 (90%, M$^+$), 249 (35, M − Me), 207 (65, M − ^{n}Bu) and 77 (50, Ph) (Found: M$^+$, 264.1877. $C_{20}H_{24}$ requires *M*, 264.1878).

(1′*S**,2′*R**)-1-(1′-Diphenylphosphinoyl-2′-phenylpropyl)cyclohexene *syn*-37

A solution of phosphine oxide *syn*-**19** (1.0 g, 2.4 mmol) in trifluoroacetic acid (10 cm^3) was heated under reflux for 30 min. After being allowed to cool to room temperature, the reaction mixture was poured into water (20 cm^3) and extracted with chloroform (3 × 10 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (2 × 10 cm^3) and then water (2 × 10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a white solid. Recrystallisation from hexane gave *alkene syn*-**37** (700 mg, 74%) as plates, mp 203–205 °C (from hexane); R_f(EtOAc) 0.5 (Found: C, 80.7; H, 7.2; P, 7.9%; M$^+$, 400.1951. $C_{27}H_{29}OP$ requires C, 81.0; H, 7.3; P, 7.7%; *M*, 400.1956); ν_{max}(Nujol)/cm^{-1} 1460 (P–Ph) and 1176 (P=O); δ_H(400 MHz, $CDCl_3$) 8.1–7.0 (15 H, m, Ph_2PO and Ph), 5.1 (1 H, br s, C=CH), 3.6 (1 H, qd, *J* 7.0 and 14.0, CH*Me*), 3.1 (1 H, m, PCH), 1.7–0.8 (8 H, m, 4 × CH_2) and 1.1 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz, $CDCl_3$) 150.7$^+$ (d, *J* 5.0, C=*C*H), 144.7$^-$ (d, *J* 6.0, *ipso*-Ph), 134.0–121.0 (Ph_2PO, Ph and *C*=CH), 57.3$^+$ (d, *J* 66.0, PCH), 51.7$^-$ (CH_2), 40.5$^+$ (*C*HMe), 40.1$^-$ (d, *J* 7.5, CH_2), 32.5$^-$ (d, *J* 8.5, CH_2), 23.0$^+$ (d, *J* 7.0, CH*Me*) and 16.5$^-$ (CH_2); *m*/*z* 400 (20%, M$^+$), 320 (10), 295 (95), 202 (100, Ph_2POH) and 77 (25, Ph).

(1*S**,2*S**,1′*S**,2′*R**)-1-(1′-Diphenylphosphinoyl-2′-phenylpropyl)-1,2-epoxycyclohexane *syn*,*anti*-38 and (1*R**,2*R**,1′*S**,2′*R**)-1-(1′-diphenylphosphinoyl-2′-phenylpropyl)-1,2-epoxycyclohexane *syn*,*syn*-38

Disodium hydrogen phosphate (1.0 g, 7.0 mmol) and *m*-CPBA (600 mg, 3.5 mmol) were added in one portion to a stirred solution of alkene *syn*-**37** (700 mg, 1.7 mmol) in CH_2Cl_2 (20 cm^3) under argon at room temperature. After 24 h, the solid residues were removed by filtration and the filtrate was washed with 10% aqueous sodium hydroxide solution (2 × 10 cm^3) and then water (2 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a white solid which contained a 77:23 ratio of *epoxides syn*,*anti*- and *syn*,*syn*-**38** (by ^{1}H NMR spectroscopy). Recrystallisation from EtOAc gave the same 77:23 ratio of epoxides *syn*,*anti*- and *syn*,*syn*-**38** (400 mg, 62%) as plates, mp 240–245 °C (from EtOAc), R_f(EtOAc) 0.4 (Found: C, 77.7; H, 7.0; P, 7.5%; M$^+$,

416.1882. $C_{27}H_{29}OP$ requires C, 77.8; H, 7.0; P, 7.4%; *M*, 416.1905); ν_{max}(Nujol)/cm^{-1} 1438 (P–Ph) and 1198 (P=O); δ_H(400 MHz, $CDCl_3$) 8.1–7.1 (30 H, m, Ph_2PO and Ph), 3.7 (1 H, m, CHMe^{syn,anti}), 3.6 (1 H, m, C*H*Me^{syn,syn}), 2.5 (2 H, m, CHO$^{syn,anti+syn,syn}$), 2.45 (2 H, m, PCH$^{syn,anti+syn,syn}$), 2.4–0.3 (16 H, m, 4 × $CH_2$$^{syn,anti+syn,syn}$), 1.2 (3 H, d, *J* 7.0, CH*Me*^{syn,anti}) and 1.1 (3 H, d, *J* 7.0, CH*Me*^{syn,syn}); δ_C(100 MHz, $CDCl_3$) for *syn*,*anti*-**38**: 145.0–126.0 (Ph_2PO and Ph), 60.0$^+$ (CHO), 59.7$^-$ (CO), 53.5$^+$ (d, *J* 64.0, PCH), 38.4$^+$ (*C*HMe), 26.6$^-$ (CH_2), 23.7$^-$ (CH_2), 19.7$^-$ (CH_2), 17.8$^-$ (CH_2) and 23.2 (CH*Me*); *m*/*z* 416 (40%, M$^+$), 400 (75), 311 (45, M − PhCHMe), 202 (100, Ph_2POH) and 77 (20, Ph).

(1*R**,2*S**,1′*S**,2′*R**)-1-(1′-Diphenylphosphinoyl-2′-phenylpropyl)-2-phenylsulfanylcyclohexan-1-ol *syn*,*syn*,*anti*-39

Butyllithium (1.4 cm^3 of a 1.6 M solution in hexane, 2.3 mmol) was added dropwise to a stirred solution of thiophenol (0.64 cm^3, 3.8 mmol) in THF (10 cm^3) at room temperature under nitrogen. Then, a solution of a 77:23 mixture of epoxides *syn*,*anti*- and *syn*,*syn*-**38** (800 mg, 1.9 mmol) in THF (2 cm^3) was added and the resulting mixture was stirred for 24 h. Aqueous ammonium chloride (5 cm^3) was added, the layers were separated and the organic layer was extracted with CH_2Cl_2 (3 × 10 cm^3). The combined organic extracts were washed with 10% aqueous sodium hydroxide (2 × 10 cm^3) and then water (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a white solid. The unreacted epoxide *syn*,*anti*-**38** (500 mg, 60%) was precipitated by adding hexane and the filtrate was evaporated under reduced pressure to give a crude product as an oil. Purification by flash chromatography on silica with EtOAc–hexane (6:4) as eluent followed by crystallisation from Et_2O gave *alcohol syn*,*syn*,*anti*-**39** (250 mg, 20%) as colourless crystals, mp 217–218 °C (from Et_2O); R_f(EtOAc) 0.64 (Found: C, 75.4; H, 6.7; P, 6.0%; M$^+$, 526.2100. $C_{33}H_{35}O_2P$ requires C, 75.3; H, 6.7; P, 5.9%; *M*, 526.2095); ν_{max}(Nujol)/cm^{-1} 3314 (OH), 1437 (P–Ph) and 1216 (P=O); δ_H(400 MHz; $CDCl_3$) 7.8–6.8 (20 H, m, Ph_2PO and Ph), 5.9 (1 H, s, OH), 4.0 (1H, qd, *J* 7.0 and 34.0, C*H*Me), 3.7 (1 H, br s, C*H*SPh), 3.67 (1 H, d, *J* 2.0, PCH), 2.3–1.1 (8 H, m, 4 × CH_2), 1.85 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz; $CDCl_3$) 145.1$^-$ (*ipso*-Ph), 138.0–125.0 (Ph_2PO and Ph), 78.4$^-$ (COH), 52.4$^+$ (d, *J* 8.0, *C*HSPh), 49.8$^+$ (d, *J* 65.0, PCH), 37.0$^-$ (CH_2), 33.1$^+$ (*C*HMe), 25.5$^-$ (CH_2), 21.0$^-$ (CH_2), 19.4$^-$ (CH_2) and 14.6$^+$ (d, *J* 4.5, CH*Me*); *m*/*z* 526 (20%, M$^+$).

(1*S**,2*R**,1′*S**,2′*R**)-1-(1′-Diphenylphosphinoyl-2′-phenylpropyl)-2-phenylsulfanylcyclohexan-1-ol *syn*,*anti*,*anti*-39

Butyllithium (0.94 cm^3 of a 1.6 M solution in hexane, 1.5 mmol) was added dropwise to a stirred solution of thiophenol (0.5 cm^3, 3.0 mmol) in CH_2Cl_2 (10 cm^3) at room temperature under nitrogen. Then, trimethylaluminium (0.5 cm^3, 4.7 mmol) was added followed by the addition of a solution of epoxide *syn*,*anti*-**38** (500 mg, 1.2 mmol) in CH_2Cl_2 (5 cm^3) and the resulting mixture was stirred for 24 h. Aqueous ammonium chloride (10 cm^3) was added, the layers were separated and the organic layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were washed with 3% aqueous sodium hydroxide (2 × 10 cm^3) and then water (10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an oil. Purification by flash chromatography on silica with EtOAc–hexane (6:4) as eluent followed by crystallisation from Et_2O gave *alcohol syn*,*anti*,*anti*-**39** (400 mg, 64%) as a white solid, mp 185–187 °C (from Et_2O); R_f(EtOAc) 0.6 (Found: C, 74.6; H, 6.7; P, 5.9%; M$^+$, 526.2130. $C_{33}H_{35}O_2PS$ requires C, 75.3; H, 6.7; P, 5.9%; *M*, 526.2095); ν_{max}(Nujol)/cm^{-1} 3314 (OH), 1437 (P–Ph) and 1216 (P=O); δ_H(400 MHz; $CDCl_3$) 7.9–6.8 (20 H, m, Ph_2PO and Ph), 5.9 (1 H, s, OH), 4.0 (1 H, qd, *J* 7.0 and 34.0, C*H*Me), 3.72 (1 H, br s, C*H*SPh), 3.69 (1 H, d, *J* 2.0, PCH), 2.3–1.2 (8 H, m, 4 × CH_2), 1.85 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz; $CDCl_3$) 145.1$^-$ (*ipso*-Ph), 138–125 (Ph_2PO and Ph), 78.4$^-$ (d, *J* 3.0, COH), 52.5$^+$ (d, *J* 8.0, *C*HSPh), 49.8$^+$ (d, *J* 65.0, PCH), 37.0$^-$ (d, *J* 2.5, CH_2), 33.1$^+$ (*C*HMe), 25.5$^-$ (CH_2), 21.0$^-$ (CH_2), 19.7$^-$ (CH_2), 14.6$^+$ (d, *J* 4.5, CH*Me*); *m*/*z* 526 (10%, M$^+$).

Horner–Wittig elimination of phosphine oxide *syn*,*anti*, *anti*-39

Potassium hydroxide (30 mg, 0.5 mmol) was added to a stirred solution of phosphine oxide *syn*,*anti*,*anti*-**39** (120 mg, 0.25 mmol) in DMSO (10 cm^3) at room temperature under nitrogen. The resulting suspension was heated at 50 °C for 45 min. After being allowed to cool to room temperature, the reaction mixture was poured into water (20 cm^3) and extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were washed with water (3 × 10 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as an oil. Purification by flash chromatography on silica with EtOAc–hexane (1:4) as eluent gave *alkene Z*,[1,4]*anti*-**40** (44 mg, 58%) as an oil, R_f(EtOAc) 0.7; δ_H(400 MHz; $CDCl_3$) 7.4–7.0 (10 H, m, Ph), 5.3 (1 H, dd, *J* 9.5 and 1.5, C=CH), 4.5 (1 H, s, C*H*SPh), 3.5 (1 H, qd, *J* 7.0 and 9.5, C*H*Me), 2.6–1.3 (8 H, m, 4 × CH_2) and 1.25 (3 H, d, *J* 7.0, CH*Me*); δ_C(100 MHz; $CDCl_3$) 145.9$^-$ (*C*=CH), 136.6$^+$ (C=*C*H), 135.0–125.0 (Ph), 47.7$^+$ (*C*HSPh), 37.1$^+$ (*C*HMe), 32.7$^-$ (CH_2), 29.7$^-$ (CH_2), 21.4$^-$ (CH_2) and 22.5$^+$ (CH*Me*); *m*/*z* 308 (40%, M$^+$), 198 (100, M − PhS), 183 (25) and 105 (30) (Found: M$^+$, 308.1593. $C_{21}H_{24}S$ requires *M*, 308.1599).

X-Ray structure analysis of (1*R**,2*S**,1′*S**,2′*R**)-1-(1′-diphenylphosphinoyl-2′-phenylpropyl)-2-phenylsulfanylcyclohexan-1-ol *syn*,*syn*,*anti*-39

Molecular formula $C_{33}H_{35}O_2PS$ (M_r = 526.64), crystals grown by slow evaporation from EtOAc–MeOH as cubes, crystal size 0.20 × 0.15 × 0.15 mm^3, orthorhombic, space group $P2_12_12_1$, a = 13.3755(9), b = 22.060(2), c = 9.6380(9) Å, V = 2844(2) Å^3, Z = 4, D_x = 1.230 g cm^{-3}, μ(Cu-Kα) = 1.751 mm^{-1}, F(000) = 1120; 4197 unique reflections collected on a RIGAKU AFC7R sequential diffractometer, $2\theta_{max}$ = 119.8°, structure solved by direct methods and 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 335 parameters with SHELXL-93,[45] 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 = 0.076 on all data corresponding to R_1 = 0.027 for 4049 observed reflections with [|F| > 4σ(F)], $w = 1/[\sigma^2F_o^2 + (0.0583P)^2 + 0.2326P]$ where $P = (F_o^2 + 2F_c^2)/3$, Δ = 0.929, $\Delta\rho$ in final difference map within 0.187 and −0.113 e Å^{-3}. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/256.

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