On the Stereoselectivity of Nitrone Addition to α-Diphenylphosphinoylalkenes

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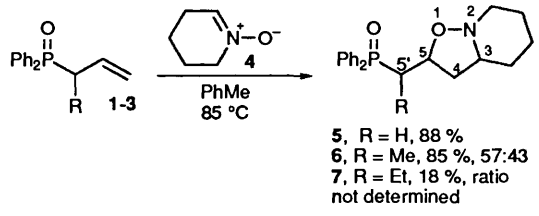
The title reaction was investigated for both achiral and α-chiral alkenes **1–3**, and for cyclic and acyclic nitrones **4** and **8**. In each case, addition to allyldiphenylphosphine oxide **1** gave a single isoxazolidine product. The configurations of these isoxazolidines (**5** and **9**) were investigated by NMR methods, and found to be consistent with reaction *via exo* transition states. Nitrone additions to α-chiral α-diphenylphosphinoyl alkenes **2** and **3** gave two diastereoisomeric products in all cases studied. The configurations of these isoxazolidines (**6**, **7**, **10**, **11**) were assigned by analogy with the achiral cases, and also by analogy with the addition of nitrile oxides to the same alkenes. In one case (**6a**) this was confirmed by chemical conversion. This conversion also demonstrated the potential of this method for the synthesis of 2-(alk-2′-enyl)piperidines, *e.g.* **17**, having defined double-bond geometry.

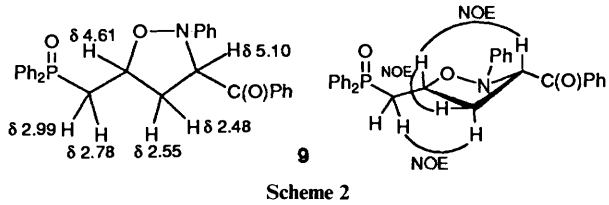
The stereoselectivity of nitrile oxide additions to α-chiral alkenes has received considerable attention over the last 10 years from Houk and others.[1] By contrast, the related addition of nitrones to α-chiral alkenes has received almost no systematic attention.[2] In earlier papers,[3,4] we have discussed the application of the transition state models of Houk and co-workers to the reaction between nitrile oxides and α-chiral α-diphenylphosphinoyl alkenes **2**, **3** *etc.* This paper will discuss the addition of two nitrones, **4** and **8**, to the same alkenes and the extent to which the same transition state models can be applied.

The α-diphenylphosphinoyl alkenes **1–3** used in this work are readily synthesised from allylic alcohols $RCH{=}CHCH_2OH$ by a Michaelis–Arbusov rearrangement. Earlier,[3] we found them to be comparatively unreactive towards nitrile oxides, possibly for steric reasons. For this study, therefore, we chose two readily available and comparatively reactive[5] nitrones **4** and **8**. The cyclic nitrone **4** was made from piperidine in a one-pot procedure,[6] involving H_2O_2 oxidation and SeO_2-catalysed dehydrogenation, and was used in solution to avoid dimerisation. The acyclic nitrone **8** was prepared by the method of Huisgen *et al.*[7] from phenacylpyridinium bromide and nitrosobenzene. Both nitrones reacted with all the alkenes used in the expected regiochemical sense[8] to give 2,3,5-trisubstituted isoxazolidines **5–7** (from the nitrone **4**) and **9–11** (from the nitrone **8**) (Scheme 1).

Addition of nitrones to the achiral alkene **1** (R = H) creates two new chiral centres. In each case, a single isoxazolidine **5** or **9** was produced: the reactions were totally stereoselective. The relative configurations of the chiral centres in **5** and **9** were investigated using NMR techniques, since the isoxazolidines did not readily form crystals suitable for X-ray analysis. The isoxazolidine **9** gave a sharp, well-resolved ^1H NMR spectrum at room temperature, with six distinct, assignable aromatic multiplets and six clearly separated non-aromatic protons (Scheme 2). By careful choice of irradiation frequency and power, it was possible to irradiate each aliphatic proton separately in a series of NOE experiments. The results of some of these are shown in Scheme 2, and demonstrate conclusively the *cis* relationship of three adjacent ring hydrogens. In the isoxazolidine **9**, therefore, the C-3 and C-5 substituents are *cis*-related.



Scheme 1



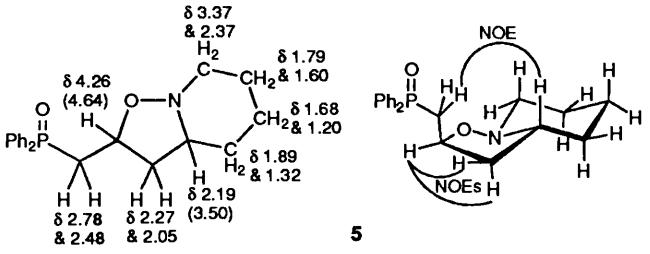
Scheme 2

The isoxazolidine **5** proved more difficult to analyse, since at room temperature it existed in two conformations with approximately a 2:1 population ratio. The rate of interconversion of these two isomers was comparable with the chemical shift difference between them, so that signals in the ^1H NMR spectrum at room temperature were not sharp, appearing as very broad, indistinct multiplets. A sample when heated in $[^2H_6]$DMSO to 385 K gave a sharp, well-resolved spectrum of a time-averaged conformer at 250 MHz; the multiplets collapsed back to broad humps when the sample was returned to ambient temperature. It was not practical to carry out NOE difference experiments at 385 K, but the broad peaks in the room temperature spectrum could be assigned (Scheme 3), using a combination of ^1H–^1H and ^1H–^{13}C correlation spectroscopy (COSY).

Subsequent NOE analysis was also complicated by the interconversion of the two conformers, as large exchange NOEs were seen. For example, irradiation of 3-H in the minor conformer at δ 3.50 caused a large enhancement, by exchange, of

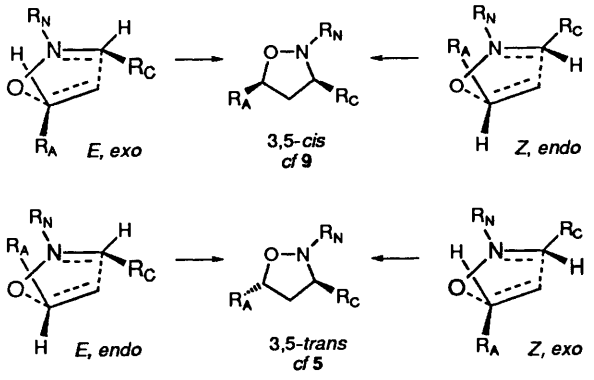
† Although the term isoxazolines has been used throughout the Discussion section for convenience, such compounds have been named in the Experimental section according to the IUPAC rules of nomenclature for organic compounds as 4,5-dihydroisoxazoles.

3-H in the major conformer at δ 2.19. This, unfortunately, swamped any enhancements of ring protons 4-H_2, at δ 2.05 and 2.27 in the major form (not assigned in the minor form). It did, however, enhance one of the diastereotopic protons 5'-H_2 next to phosphorus. 5-H in both forms was well removed from ring protons 4-H_2 but, unfortunately, irradiation of 5-H (at δ 4.26, major form) enhanced both of these protons. There was no connection in the NOE between 3-H and 5-H directly. Taken together, these data suggest that 3-H is on the same side of the ring as the $CH_2P(O)Ph_2$ group: that the isoxazolidine ring in **5** is 3,5-*trans*-disubstituted (Scheme 3).



Scheme 3 ^{1}H Chemical shifts for major (minor) conformer

These apparently opposite results are readily rationalised by considering the possible transition states for the cycloadditions. Nitrone cycloadditions may proceed through either *exo* or *endo* transition states, and acyclic nitrones may react in either the *Z* or the more stable *E* configuration (Scheme 4), which may be

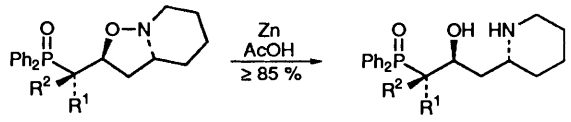


Scheme 4

interconvertible under the reaction conditions.[9] Steric factors favour the *exo* transition states, especially with large alkene substituents, whereas *endo* transition states may be stabilised by secondary orbital interactions between the nitrone and a suitable alkene substituent.[10] The diphenylphosphinoyl group in the alkene **1** is likely to be badly positioned for secondary orbital interactions (see below), and its size will strongly disfavour *endo* transition states. The opposite stereochemistry of the isoxazolidines **5** and **9** is, therefore, consistent with *exo* transition state geometries in both cycloadditions, provided that the acyclic nitrone **6** reacts in the sterically favoured *E* configuration.

We reasoned that the chiral centre in the alkenes **2** and **3** was unlikely to affect the geometry of these transition states significantly, since the new alkyl group cannot take part in secondary orbital interactions, but increases the steric bulk of the alkene, thus favouring an *exo* transition state. Addition of the nitrones **4** and **8** to alkenes **2** and **3** gave two diastereoisomeric isoxazolidine products in each case. We did not attempt to apply the extensive series of NMR experiments used on isoxazolidine **5** to compounds **6** and **7**, which also existed as mixtures of two conformers. In the major isomer of the isoxazolidine **10**, the ring protons 4-CH_2 appeared as a single triplet in the ^{1}H NMR, and NOE experiments were inconclusive (see Experimental section). By analogy with compounds **5** and **9**, therefore, we assumed that bicyclic isoxazolidines **6** and **7** were 3,5-*trans*-disubstituted, whereas the monocyclic isoxazolidines **10** and **11** were 3,5-*cis*-disubstituted. These four diastereoisomeric pairs of isoxazolidines (**6**, **7**, **10** and **11**) therefore differed only in the configuration of the third, exocyclic, chiral centre relative to the other two. We investigated the stereochemistry of this centre by chemical conversion.

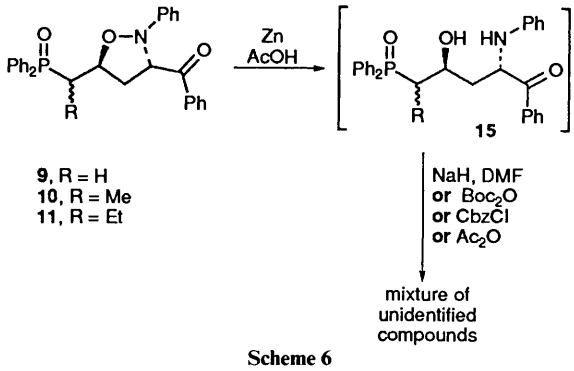
The isoxazolidines **5**, **6a** and **6b** were readily reduced using acetic acid and activated zinc dust, giving the amino alcohols **12**–**14** in good yields (Scheme 5). The isoxazolidines **9** and **10**



5, 12, $R^1 = R^2 = H$
6a, 13, R^1 = Me, $R^2 = H$
6b, 14, $R^1 = H$, R^2 = Me

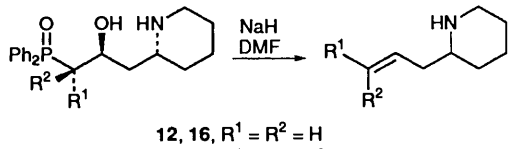
Scheme 5

were apparently also reduced under these conditions, but the product amino alcohols **15** were unstable and impossible to isolate. Attempted *in situ* protection and elimination also failed (Scheme 6). The products of cycloaddition with the acyclic nitrone **8** were, therefore, useless to us for synthetic purposes.



Scheme 6

Treatment of a β-hydroxy alkyldiphenylphosphine oxide with NaH in *N*,*N*-dimethylformamide at room temperature results in the stereospecific elimination of sodium diphenylphosphinate, giving an alkene of defined double bond geometry. This method was applied to the amino alcohols **12** and **13** (see below), but in all cases the reactions were incomplete, and the yields rather low. Thus, the terminal alkene **16**, identified from its ^{1}H NMR spectrum, was obtained in low yield from the amino alcohol **12** (Scheme 7). The two diastereoisomers of



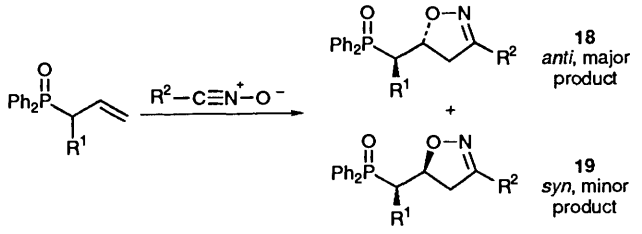
12, 16, $R^1 = R^2 = H$
13, 17, R^1 = Me, $R^2 = H$
14, $R^1 = H$, R^2 = Me

Scheme 7

6 were differentiated by their chromatographic behaviour (normal phase elution using ethyl acetate–hexane mixtures): **6a** was the faster-running on silica, and **6b** the slower. The amino alcohol **13**, derived from reduction of **6a**, gave the alkene **17**. This showed a vicinal vinylic coupling constant $^3J_{HH}$ of 14.6 Hz in the ^{1}H NMR spectrum, indicating a *trans* alkene. This must

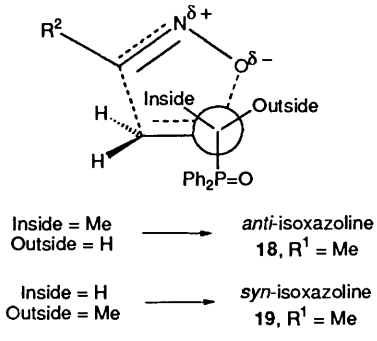
arise from an amino alcohol **13** having an *anti* relationship between the diphenylphosphinoyl and hydroxy groups (Scheme 7). The isomer **6b** was the minor isomer, and although reduction to the amino alcohol **14** was straightforward, the low yield in the elimination step precluded isolation of the product. By analogy with our earlier work (see below), and assuming that the cycloaddition proceeds through an *exo* transition state (see above), the amino alcohol **14** and the isoxazolidine **6b** are expected to have a *syn* relationship between the diphenylphosphinoyl and hydroxy groups. This would give rise to a *cis* alkene on stereospecific elimination (Scheme 7).

In the related series of reactions between α-chiral α-diphenylphosphinoyl alkenes **2**, **3** *etc.* and nitrile oxides, described in our earlier work, the isoxazolines **18** and **19** having only two chiral centres are formed (Scheme 8). The two possible



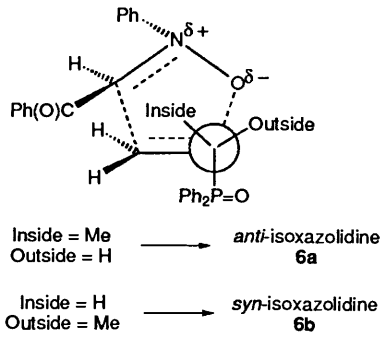
Scheme 8

diastereoisomers are formed in ratios ranging from 65:35 to 91:9, and the *anti* isomer **18** always predominates over the *syn* isomer **19**. These cycloadditions were explained in terms of Houk's transition state model[1] for α-chiral alkenes, in which the three groups on the α-centre occupy 'inside', 'outside' and 'opposite' * positions relative to the developing isoxazoline ring. In our alkenes, we believe that the diphenylphosphinoyl group is too bulky to occupy any but the 'opposite' position. In the transition state leading to the favoured *anti* product **18**, the alkyl group takes the 'inside' position, and the hydrogen the most sterically demanding 'outside' position. In the transition state leading to the minor *syn* isoxazoline **19**, these two groups are reversed (Scheme 9).



Scheme 9

Our nitrone cycloadditions, reported in this paper, can be interpreted using a very similar transition state model (Scheme 10). In particular, placing the bulky diphenylphosphinoyl group away from the developing ring means that secondary orbital interactions with the nitrone are impossible, rendering an *endo* transition state unlikely (*cf.* above). As before, placing the alkyl group in the 'inside' position and the hydrogen in the more sterically hindered 'outside' position gives the observed major, *anti*, isoxazolidine **6a**, while reversing these two groups gives the



Scheme 10

minor, *syn*, isoxazolidine **6b**. Other nitrone cycloadditions have similarly been interpreted in terms of Houk's nitrile oxide transition state models.[11]

In conclusion, we have investigated the mode of attack of nitrones on α-diphenylphosphinoyl alkenes **1**–**3**. With the achiral alkene **1**, an *exo* transition state is believed to lead to the single observed product **7a** or **8a** in each case. With α-chiral alkenes **2** and **3**, attack is still believed to involve *exo* transition states. Two diastereoisomeric products are formed, of which the major (*e.g.* **6a**) has *anti* stereochemistry across the 5,5′ chiral centres, while the minor (*e.g.* **6b**) is presumed to have *syn* stereochemistry across these two centres. This is in accordance with a modified Houk transition state (Scheme 10). In addition, it has been demonstrated that the isoxazolidines resulting from nitrone addition to these alkenes can be used in a novel synthesis of unprotected 2-(alk-2′-enyl)piperidines such as **17**. This synthetic route could in future be extended to the synthesis of various unprotected secondary homoallylic amines.

Experimental

Column chromatography was carried out at slightly greater than atmospheric pressure using Merck Kieselgel 60 (230–400 mesh). High performance liquid chromatography was performed using a Dynamax pre-packed silica column (21.4 mm i.d. × 25 cm), with a Gilson model 303 pump operating at 10 cm^3 min^{-1} and a Cecil Instruments CE 212A UV detection system measuring the absorbance at 254 nm. Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck silica Kieselgel $60F_{254}$). All solvents were distilled before use. Tetrahydrofuran (THF) was freshly distilled from potassium using benzophenone radical as an indicator. Diethyl ether (Et_2O) was dried by distillation from calcium hydride. Dimethylformamide (DMF) was dried with and stored over activated molecular sieves (4 Å). RT stands for room temperature.

Melting points were measured on a Reichart hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 grating spectrophotometer. ^1H NMR spectra were recorded on Bruker WP 80 (80 MHz), WM 250 (250 MHz) and WM 400 (400 MHz) Fourier transform spectrometers. ^1H NMR spectra were recorded at 250 MHz unless otherwise stated. ^{13}C NMR were recorded on a Bruker WM 400 (100 MHz) spectrometer. Chemical shifts are quoted in parts per million relative to chloroform, δ 7.27 ppm for ^1H spectra, and δ 77.0 ppm for ^{13}C spectra; J values are given in Hz. Mass spectra were recorded on an AEI Kratos MS30 machine using a DS503 data system for high resolution analysis. Microanalysis was carried out using a Carlo Erba 1106 automatic analyser.

3,4,5,6-*Tetrahydropyridine* N-*Oxide* **4**.—*By a one-pot method.*[6] H_2O_2 (30% solution; 12 cm^3) was added slowly dropwise to a stirred solution of piperidine (5 cm^3, 51.8 mmol)

* Houk[1] terms this position *anti*. We prefer to call it *opposite* which still describes its position relative to the developing ring and avoids confusion with *syn* and *anti* relationships in the isoxazoline products.

and SeO_2 (52 mg) in acetone (100 cm^3), the temperature being maintained in the range 0–6 °C with an ice-bath. The ice-bath was removed and the mixture stirred at RT. for 3 h. The following day the acetone was removed under reduced pressure and toluene (100 cm^3) was added to the residue. The resulting solution[8] of the nitrone **4** was used for the cycloadditions below.

trans-2-*Diphenylphosphinoylmethylhexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* **5**.—A solution of the *N*-oxide **4** in toluene (4 cm^3 of solution, *ca.* 4 mmol) was added to 3-diphenylphosphinoylprop-1-ene **1** (235 mg, 1 mmol) and the mixture stirred at 85 °C for 24 h and then allowed to cool. The supernatant was decanted from a deep red viscous oil and evaporated. The residue from the supernatant was purified by column chromatography on SiO_2, eluting with 10% MeOH in EtOAc. The first compound isolated was 3-diphenylphosphinoylprop-1-ene **1** (16 mg, 7%). The second fraction eluted contained the *isoxazolidine* **5** (290.5 mg, 88% as a 2:1 mixture of two conformers **A** and **B**, respectively, as white needles, m.p. (MeOAc–hexane) 148–150 °C (Found: M^+ + H, 342.1625. $C_{20}H_{24}NO_2P$ requires *M* + H, 342.1623); R_F (10% MeOH) in EtOAc) 0.21; ν_{max}/cm^{-1} (CH_2Cl_2) 3000–2760 (CH), 1480–1440 (P–Ph), 1200–1140 (P=O) and 1110 (C–O); $\delta_H(CDCl_3)$ 1.14–2.35 (10 H**A** and **B**, m, ring CH_2s), 2.46 (1 H**A**, dt, *J* 9.7 and 14.2, PCH_AH_B), 2.60–2.63 (1 H**B**, br m, PCH_AH_B), 2.76 (1 H**A**, ddd, *J* 3.8, 10.2 and 14.2, PCH_AH_B), 2.93 (1 H**B**, br m, PCH_AH_B), 3.32–3.36 (1 H**A**, br m, NCH), 3.48 (1 H**B**, br s, NCH), 4.22 (1 H**A**, br s, OCH), 4.62 (1 H**B**, br s, OCH), 7.40–7.53 (6 H**A** and **B**, m, Ph_2PO) and 7.72–7.75 (4 H**A** and **B**, m, Ph_2PO); $\delta_C(CDCl_3$, 63 MHz), 19.1 (CH_2**B**), 23.5 (CH_2**B**), 23.7 (CH_2**A**), 24.7 (CH_2**A**), 25.3 (CH_2**B**), 29.2 (CH_2**A**), 35.7 (d, *J* 69, PC**H**A), 36.3 (d, *J* 76, PC**H**B), 40.5 (CH_2**A**), 45 (CH_2**B**), 50.0 (NCH_2**B**), 55.0 (NCH_2**A**), 59.7 (NC**H**B), 66.4 (NC**H**A), 70.8 (OC**H**A), 71.8 (OC**H**B), 128.6, 128.8, 130.5, 130.6, 130.8, 131.0, 131.8, 132.2 (d, *J* 101, *ipso* C) and 133.7 (d, *J* 95, *ipso* C); *m/z* 342 (M^+ + H, 0.26%), 258 [$Ph_2P(O)C_3H_5O$, 1], 245 [$Ph_2P(O)C_2H_4O$, 7], 242 [$Ph_2P(O)C_3H_5$, 5], 215 [$Ph_2P(O)CH_2$, 21], 202 (Ph_2PHO, 22), 201 (Ph_2PO, 83), 140 ($M^+ - Ph_2PO$, 26), 126 ($M^+ - Ph_2POCH_2$, 23), 97 ($M^+ - Ph_2POC_2H_3O$, 100), 84 ($C_5H_{10}N$, 61) and 77 (Ph, 33). For further NMR experiments on the isoxazolidine **5**, see text.

anti,trans- *and* syn,trans-2-(1′-*Diphenylphosphinoylethyl*)-*hexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* **6**.—A solution of the *N*-oxide **4** in toluene (25 cm^3, *ca.* 10 mmol) was added to 3-diphenylphosphinoylbut-1-ene **2** (505 mg, 2 mmol) and the mixture stirred at 85 °C for 24 h. The supernatant was decanted from a deep red viscous oil, and the solvent removed under reduced pressure. The residue from the supernatant was purified by column chromatography on SiO_2, eluting with 10% MeOH in EtOAc. The first fraction isolated contained 3-diphenylphosphinoylbut-1-ene **2** (80 mg, 15%). The second fraction isolated contained the major product *isoxazolidine* **6a** (271.5 mg, 39%) in a 3.0:1 ratio of conformers **A** and **B** respectively as white plates, m.p. 168–172 °C (Found: M^+ + H, 356.1786. $C_{21}H_{26}NO_2P$ requires *M* + H, 356.1779); R_F (30% Pr^iOH in hexane) 0.31; ν_{max}/cm^{-1} ($CDCl_3$) 3120–3050 (aryl C–H), 3030–2800 (CH), 1600 (Ph), 1440 (P–Ph), 1210–1170 (P=O) and 1120 (C–O); $\delta_H(CDCl_3)$ 1.18 (3 H**A**, dd, *J* 7.0 and 15.7, Me), 1.10–2.49 (10 H**A** and 13 H**B**, m, ring CH_2s**A** and **B**, and Me**B**), 2.75–3.00 (1 H**A** and **B**, m, PCH), 3.30–3.40 (1 H**A**, m, NCH), 3.40–3.50 (1 H**B**, m, NCH), 4.18–4.19 (1 H**A**, m, OCH), 4.57 (1 H**B**, br s, OCH), 7.35–7.52 (6 H**A** and **B**, m, Ph_2PO) and 7.72–7.90 (4 H**A** and **B**, m, Ph_2PO); *m/z* 356 (M^+ + H, 0.75%), 259 [$Ph_2P(O)C_3H_6O$, 18], 230 [$Ph_2P(O)Et$, 48], 202 (Ph_2PHO, 57), 201 (Ph_2PO, 97), 154 ($M^+ - Ph_2PO$, 47), 126 [$M^+ - Ph_2P(O)C_2H_4$, 82], 97 ($C_6H_{11}N$, 100) and 77 (Ph, 31). The third fraction isolated contained both isoxazolidines **6a** and **6b** (204 mg, 29%). This fraction was further separated by HPLC, eluting with 40% Pr^iOH in hexane to give the major tetrahydroisoxazole **6a** (as above) (48 mg, 7%) in a 3.3:1 ratio of conformers, a mixture of both isoxazolidines **6a** and **6b** (21 mg, 3%), and the minor tetrahydroisoxazole **6b** (as below) (128 mg, 18%) in a 3.0:1 ratio of conformers **C** and **D**, respectively. The fourth fraction isolated from the column contained the minor isoxazolines **6b** (116 mg, 17%) in a 2.7:1 ratio of conformers **C** and **D**, respectively, as white prisms, m.p. 160–164 °C (Found: M^+ + H, 356.1773. $C_{21}H_{26}NO_2P$ requires *M* + H, 356.1780); R_F (30% Pr^iOH in hexane) 0.27; ν_{max}/cm^{-1} ($CDCl_3$) 3110–3050 (aryl CH), 3020–2800 (CH), 1600 (Ph), 1440 (P–Ph), 1210–1170 (P=O) and 1115 (C–O); $\delta_H(CDCl_3)$ 1.19 (3 H**C**, dd, *J* 7.1 and 16.1, Me), 1.27–2.35 (10 H**C** and 13 H**D**, m, ring CH_2s**C** and **D**, and Me**D**), 2.60–2.70 (1 H**C**, m, PCH), 2.92–3.04 (1 H**D**, m, PCH), 3.20–3.30 (1 H**C**, m, NCH), 3.33–3.47 (1 H**D**, m, NCH), 4.15–4.32 (1 H**C**, m, OCH), 4.61 (1 H**D**, br s, OCH), 7.36–7.60 (6 H**C** and **D**, m, Ph_2PO), 7.70–7.88 (4 H**C** and **D**, m, Ph_2PO); *m/z* 356 (M^+ + H, 0.33%), 259 [$Ph_2P(O)C_3H_6O$, 14], 230 [$Ph_2P(O)Et$, 40], 229 [$Ph_2P(O)C_2H_4$, 23], 202 (Ph_2PHO, 43), 201 (Ph_2PO, 78), 154 ($M^+ - Ph_2PO$, 45), 126 [$M^+ - Ph_2P(O)C_2H_4$, 76], 97 ($C_6H_{11}N$, 100) and 77 (Ph, 26).

anti,trans- *and* syn,trans-2-(1′-*Diphenylphosphinoylpropyl*)-*hexahydro*-2H-*isoxazolo*[2,3-a]*pyridine* **7**.—A solution of the *N*-oxide **4** in toluene (25 cm^3 of solution, *ca.* 10 mmol) was added to 3-diphenylphosphinoylpent-1-ene **3** (542 mg, 2 mmol) and the mixture heated to reflux for 24 h. The supernatant was decanted from the oily red residue and evaporated under reduced pressure. This crude mixture was purified by column chromatography on SiO_2, eluting with 10% MeOH in EtOAc to give recovered 3-diphenylphosphinoylpent-1-ene **3** (*ca.* 400 mg, *ca.* 75%) and a mixture of the isoxazolidines **7** which was purified by HPLC eluting with 30% Pr^iOH in hexane. The first compound isolated was the faster-running minor product isoxazolidine **7** as two nitrogen invertomers **A** and **B** in a 3.5:1 ratio (45.5 mg, 6%) as white prisms, m.p. 161–166 °C (Found: M^+ + H, 370.1939. $C_{22}H_{28}NO_2P$ requires *M* + H, 370.1936); R_F (30% Pr^iOH in hexane) 0.36; ν_{max}/cm^{-1} 2980–2760 (CH), 1590 (Ph), 1460–1430 (P–Ph), 1185 (P=O) and 1115 (C–O); $\delta_H(CDCl_3)$ 0.87 (3 H**A** and **B**, t, *J* 7.5, Me), 1.54–1.36 (2 H**A** and **B**, m), 1.56–1.93 (7 H**A** and 8 H**B**, m), 2.04–2.20 (1 H**A**, m), 2.35–2.52 (2 H**A** and **B**, m), 2.66 (1 H**A**, dtd, *J* 3.7, 5.5 and 9.5, probably NCH), 2.89 (1 H**B**, br s), 3.34 (1 H**A**, m), 3.47 (1 H**B**, br s), 4.19 (1 H, dtd, *J* 4.0, 4.7 and 8.7, OCH), 4.60 (1 H**B**, br s, OCH), 7.44–7.49 (6 H**A** and **B**, m, Ph_2PO) and 7.75–7.86 (4 H**A** and **B**, m, Ph_2PO); $\delta_C(CDCl_3)$ (only **A** reported) 15.1 (d, *J* 7, Me), 16.7 (d, *J* 22, CH_2), 23.7 (CH_2), 24.8 (CH_2), 29.5 (CH_2), 36.4 (CH_2), 42.1 (d, *J* 69, PCH), 54.9 (NCH_2), 67.8 (NCH), 75.0 (OCH), 128.5, 128.6, 128.7, 130.7, 130.8, 130.8, 131.6 and 133.1 (d, *J ca.* 100, *ipso*-C); *m/z* 370 (M^+ + H, 0.2%), 273 [$Ph_2P(O)C_4H_8O$, 39], 229 [$Ph_2P(O)C_2H_4$, 84], 202 (Ph_2PHO, 31), 201 (Ph_2PO, 93), 168 ($M^+ - Ph_2PO$, 48), 126 [$M^+ - Ph_2P(O)Pr$, 90], 97 ($C_6H_{11}N$, 100) and 77 (Ph, 28). The second compound isolated was the slower-running major product the *isoxazolidine* **7** as two nitrogen invertomers **C** and **D** in a 4:1 ratio (92 mg, 12%) as white needles, m.p. 124–128 °C (Found: $M^+ - H_2O$, 351.1747. $C_{22}H_{28}NO_2P$ requires *M* − H_2O, 351.1752); R_F (30% Pr^iOH in hexane) 0.36; ν_{max}/cm^{-1} 2990–2770 (CH), 1610, 1590 (Ph), 1190 (P=O) and 1110 (C–O); $\delta_H(CDCl_3)$ 0.95 (3 H**C** and **D**, t, *J* 7.5, Me), 1.20–1.24 (1 H**C**, m), 1.50–2.02 (10 H**C** and 11 H**D**, m), 2.59–2.68 (2 H**C** and **D**, m), 2.94 (1 H**D**, br s), 3.11 (1 H**C**, m, probably NCH), 3.37 (1 H **D**, br s), 4.40 (1 H**C**, tdd, *J* 4.5, 9.0 and 21, OCH), 4.72 (1 H**D**, br s, OCH), 7.35–7.50 (6 H**C** and **D**, m, Ph_2PO) and 7.75–7.89 (4 H**C** and **D**, m, Ph_2PO); $\delta_C(CDCl_3)$ (only **C** reported) 13.6 (d, *J* 10, Me), 19.7 (d, *J* 42, CH_2), 23.7 (CH_2), 24.6

(CH_2), 29.3 (CH_2), 37.4 (CH_2), 42.6 (d, *J* 70, PCH), 54.3 (NCH_2), 66.2 (NCH), 75.2 (OCH), 128.0, 128.1, 128.5, 128.6, 130.6, 130.7, 131.1, 131.3, 133.6 (d, *J* 96, *ipso*-C) and 134.1 (d, *J* 95, *ipso*-C); *m/z* 351 ($M^+ - H_2O$, 1.3%), 273 [$Ph_2P(O)C_4H_8O$, 21], 244 [$Ph_2P(O)C_2H_3O$, 40], 229 [$Ph_2P(O)C_2H_4$, 91], 202 (Ph_2PHO, 35), 201 (Ph_2PO, 100), 168 ($M^+ - Ph_2PO$, 52), 126 [$M^+ - Ph_2P(O)Pr$, 83], 97 ($C_6H_{11}N$, 97) and 77 (Ph, 29).

C-Benzoyl-N-phenylnitrone **8**.—Phenacylpyridinium bromide (8.988 g, 32 mmol) in water (30 cm^3) was added at 0 °C to a stirred solution of nitrosobenzene (3.439 g, 32 mmol) in EtOH (150 cm^3), The resulting green solution was cooled to −8 °C, and NaOH (1.0 mol dm^{-3} solution *ca.* 30 cm^3; *ca.* 30 mmol) was added dropwise to it over 20 min until its pH reached 6.5. The resulting orange mixture was stirred at −5 to 0 °C for 30 min and then filtered with suction, washed with water and dried *in vacuo* over $CaCl_2$ to give the nitrone **8** as small yellow plates (6.272 g, 87%), m.p. 105–106.5 °C (lit.,[7] 109–110 °C). The nitrone was stored in a freezer and used without further purification.

cis-3-*Benzoyl*-5-*diphenylphosphinoylmethyl*-2-*phenylisoxazolidine* **9**.—3-Diphenylphosphinoylprop-1-ene **1** (131 mg, 0.54 mmol) and the nitrone **8** (135 mg, 0.6 mmol) were stirred together in CH_2Cl_2 (5 cm^3) for 24 d at RT. More nitrone was added to the mixture after 7, 14 and 17 d. The solvent was removed under reduced pressure from the mixture and the residue purified by column chromatography on SiO_2, eluting with EtOAc. The first fraction isolated contained the *isoxazolidine* **9** (193 mg, 76%) as white plates, m.p. 135.5–137.5 °C (Found: C, 74.4; H, 5.6; N, 3.15; P, 6.6%; $M^+ - H_2O$, 449.1539. $C_{29}H_{26}NO_3P$ requires C, 74.5; H, 5.6; N, 3.0; P, 6.6; $M - H_2O$, 449.1544); R_F (EtOAc) 0.34; ν_{max}/cm^{-1} (CH_2Cl_2) 2980–2820 (CH), 1690 (C=O), 1595 (Ph), 1490 (P=O), 1185 (P=O) and 1120 (C–O); $\delta_H(CDCl_3)$, 2.42–2.60 [2 H, 2° m (see below for decoupling experiment), 4-H_AH_B], 2.78 (1 H, ddd, J_{HH} 7.8 and 14.9, J_{PH} 12.1, PCH_AH_B), 2.99 (1 H, ddd, J_{HH} 4.9 and 15.0, J_{PH} 10.4, PCH_AH_B), 4.61 (1 H, d quintet, J_{HH} 5.1 and 7.3, J_{PH} 7.3, OCH), 5.10 (1 H, dd, *J* 4.6 and 8.0, NCH), 6.87–6.98 (3 H, m, Hs *o* and *p* to N), 7.21 (2 H, dd, *J* 8.5 and 9.5, Hs *m* to N), 7.42–7.60 (9 H, m, Hs *m* and *p* to C=O and P=O), 7.74–7.85 (4 H, m, Hs *o* to P) and 8.02–8.06 (2 H, m, Hs *o* to C=O); $\delta_C(CDCl_3)$ 34.0 (d, *J* 70, PCH), 37.3 (d, *J* 4, C-4), 70.3 and 72.8 (OCH and NCH), 114.3 (*o* to N), 122.4 (*p* to N), 128.7, 128.8, 129.0, 129.2, 130.7, 130.8, 130.9, 131.0, 131.9, 132.0, 132.8 (d, *J* 53, *ipso* to P), 133.4, 135.0 (*ipso* to C=O), 150.0 (*ipso* to N) and 196.2 (C=O); *m/z* 449 ($M^+ - H_2O$, 2.8%), 362 ($M^+ - PhCO$, 1.2), 344 ($M^+ - H_2O - PhCO$, 4.3), 215 [$Ph_2P(O)CH_2$, 10], 202 (Ph_2PHO, 5), 201 (Ph_2PO, 17), 151 ($PhC_2H_4O_2N$, 100), 118 (PhCOCH, 69), 109 ($PhNOH_2$, 41), 105 (PhCO, 20) and 77 (Ph, 80). The second fraction isolated contained 3-diphenylphosphinoylprop-1-ene **1** (13 mg, 10%).

Decoupling Experiments on cis-3-*Benzoyl*-5-*diphenylphosphinoylmethyl*-2-*phenylisoxazolidine* **9**.—Irradiation at δ 5.1 and 4.6 shows that the second order multiplet at δ 2.5 consists of: δ 2.55 (1 H, ddd, *J* 7.7, 8.0 and 12.5, 4-H_AH_B) and δ 2.48 (1 H, ddd, *J* 4.4, 7.0 and 12.8, 4-H_AH_B).

NOE Difference Experiments on cis-3-*Benzoyl*-5-*diphenylphosphinoylmethyl*-2-*phenylisoxazolidine* **9**.—Irradiation at δ 8.05 (*o* to C) gave enhancements at 7.8 (negative NOE), 7.6 (negative NOE), 7.5, 6.9 (*o* to N), 5.1 (NCH), and 2.48 (4-H_AH_B, small NOE). Irradiation at 6.9 (*o* to N) gave enhancements at δ 8.05 (*o* to C, small NOE), 7.2 (*m* to N), 6.95 (*p* to N, negative NOE), 5.1 (NCH) and 4.6 (OCH). Irradiation at δ 5.1 (NCH) gave enhancements at 8.05 (*o* to C), 7.5 (very small negative NOE), 7.2 (*m* to N, negative NOE), 6.9 (*o* to N) and 2.55 (4-H_AH_B). Irradiation at δ 4.6 (OCH) gave enhancements at 6.9 (*o* to N), 3.0 (PCH_AH_B), 2.8 (PCH_AH_B, small NOE) and 2.55 (4-H_AH_B). Irradiation at δ 3.0 (PCH_AH_B) gave enhancements at 7.8, 4.6 (OCH) and 2.8 (PCH_AH_B). Irradiation at δ 2.8 (PCH_AH_B) gave enhancements at 7.8, 4.6 (OCH), 3.0 (PCH_AH_B), and 2.48 (4-H_AH_B). Irradiation at δ 2.55 (4-H_AH_B) gave enhancements at 5.1 (NCH), 4.6 (OCH) and 2.48 (4-H_AH_B). Irradiation at δ 2.48 (4-H_AH_B) gave enhancements at 8.05 (*o* to C, small NOE), 4.6 (OCH, very small NOE), 2.8 (PCH_AH_B, small NOE) and 2.55 (4-H_AH_B).

These experiments demonstrated conclusively that the three protons with δ 5.1, 4.6 and 2.55 were all on the same side of the ring, which was thus *cis*-substituted.

3-*Benzoyl*-5-(1′-*diphenylphosphinoylethyl*)-2-*phenylisoxazolidine* **10**.—3-Diphenylphosphinoylbut-1-ene **2** (100 mg, 0.39 mmol) and the nitrone **8** were stirred together in CH_2Cl_2 (5 cm^3) for 8 d at RT., more nitrone being added after 5 d. The solvent was removed under reduced pressure from the mixture and the residue combined with that from a separate small-scale reaction. The mixture was purified by column chromatography on SiO_2, eluting with EtOAc–hexane (3:1). The first fraction isolated contained the major product *isoxazolidine* **10** (46 mg) as a yellow oil (Found: $M^+ - PhCO$, 376.1467. $C_{30}H_{28}NO_3P$ requires $M - PhCO$, 376.1466); R_F (EtOAc–hexane, 3:1) 0.38; ν_{max}/cm^{-1} (CH_2Cl_2) 3000–2800 (C–H), 1695 (C=O), 1600, 1575 and 1490 (Ph), 1185 (P=O) and 1120 (C–O); $\delta_H(CDCl_3)$ 1.36 (3 H, dd, *J* 7.1 and 16.8, Me), 2.24 (2 H, t, *J* 7.1, 4-H_2), 2.93 (1 H, sextet, *J* 7.8, PCH), 4.44 (1 H, dq, *J* 5.4 and 7.9, OCH), 5.01 (1 H, t, *J* 6.6, NCH), 6.93–6.99 (3 H, m, *o* and *p* to N), 7.25 (2 H, dd, *J* 7.0 and 8.7, *m* to N), 7.38–7.59 (9 H, m, *m* and *p* to C and P), 7.79–7.90 (4 H, m, *o* to P), and 8.00 (2 H, d, *J* 7.2, *o* to C); $\delta_C(CDCl_3)$ 11.4 (Me), 36.1 (CH_2), 36.9 (d, *J* 69, PCH), 70.5 (NCH), 77.3 (OCH), 114.3 (*o* to N), 122.3 (*p* to N), 128.6, 128.7, 128.8, 129.0, 129.2, 130.9 (half a C *ipso* to P), 131.0, 131.1, 131.2, 131.9, 131.9, 132.5 (d, *J* 95, *ipso* to P), 133.4, 134.8 (*ipso* to C), 150.2 (*ipso* to N) and 196.4 (C=O); *m/z* 463 ($M^+ - H_2O$, 4%), 376 ($M^+ - PhCO$, 2), 358 ($M^+ - PhCO - H_2O$, 6), 262 ($M^+ - Ph_2PO - H_2O$, 30), 202 (Ph_2PHO, 18), 201 (Ph_2PO, 37), 118 (PhCOCH, 100) and 77 (Ph, 72). The second fraction isolated was a 2.8:1 mixture of the major isomer **A** (above) and one other isomer **B**, respectively, of the *isoxazolidine* **10** (162 mg) as a yellow oil (Found: $M^+ - PhCO$, 376.1446. $C_{30}H_{28}NO_3P$ requires $M - PhCO$, 376.1466); R_F (EtOAc–hexane, 3:1) 0.38 and 0.34; ν_{max}/cm^{-1} (CH_2Cl_2) 2980–2820 (CH), 1695 (C=O), 1600 (Ph), 1490 (P–Ph), 1185 (P=O) and 1115 (C–O); $\delta_H(CDCl_3)$ 1.18 (3 H**B**, dd, *J* 7.2 and 16.0, Me), 1.36 (3 H**A**, dd, *J* 7.1 and 16.7, Me), 2.23 (2 H**A**, t, *J* 7.1, 4-H_2), 2.66 (2 H**B**, t, *J* 7.4, 4-H_2), 2.93 (1 H**A**, sextet, *J* 7.6, PCH), 3.09 (1 H**B**, sextet, *J* 6.7, PCH), 4.38–4.50 (1 H**A** and **B**, m, OCH), 5.01 (1 H**A**, t, *J* 6.6, NCH), 5.05 (1 H**B**, t, *J* 7.2, NCH), 6.74 (2 H**B**, d, *J* 7.7, *o* to N), 6.86–6.99 (1 H**B** and 3 H**A**, m, *p* to N**A** and **B** and *o* to N**A**), 7.16 (2 H**B**, t, *J* 7.9, *m* to N), 7.25 (2 H**A**, dd, *J* 7.0 and 9.0, *m* to N), 7.40–7.61 (9 H**A** and **B**, m, *m* and *p* to C and P), 7.74–7.89 (4 H**A** and **B**, m, *o* to P) and 7.98–8.06 (2 H**A** and **B**, *o* to C); $\delta_C(CDCl_3)$ 8.9 (**B**Me), 11.4 (**A**Me), 34.4 (d, *J* 73, **B**PCH), 35.6 (**B**CH_2), 36.1 (**A**CH_2), 36.9 (d, *J* 69, **A**PCH), 70.5, (**A**NCH), 70.8 (**B**NCH), 77.3 (**A** and **B**OCH), 114.1 (**B** *o* to N), 114.3 (**A** *o* to N), 122.0 (**B** *p* to N), 122.3 (**A** *p* to N), 128.6, 128.7, 128.7, 128.8, 129.0, 129.2, 130.8, 130.9, 131.0, 131.1, 131.2, 131.7, 131.8, 131.9, 132.6 (d, *J* 95, *ipso* to P), 133.4, 133.5, 134.8 (*ipso* to C), 150.2 (**A** *ipso* to N), 150.4 (**B** *ipso* to N), 196.4 (**A** *ipso* to C), and 196.6 (**B** *ipso* to C); *m/z* 463 ($M^+ - H_2O$, 0.15%), 376 ($M^+ - PhCO$, 0.08), 358 ($M^+ - PhCO - H_2O$, 4), 262 ($M^+ - Ph_2PO - H_2O$, 14), 202 (Ph_2PHO, 13), 201 (Ph_2PO, 30), 118 (PhCOCH, 100) and 77 (Ph, 58).

NOE Difference Experiments on the Major Isomer of 3-*Benzoyl*-5-(1′-*diphenylphosphinoylethyl*)-2-*phenylisoxazolidine* **10**.—Irradiation at δ 5.0 (NCH) gave enhancements at 8.0 (*o* to C), 6.9 (*o* to N) and 2.2 (4-H_2). Irradiation at δ 4.4 (OCH) gave enhancements at 6.9 (*o* to N), 2.9 (PCH, small NOE) and 2.2 (4-H_2).

3-*Benzoyl*-5-(1′-*diphenylphosphinoylpropyl*)-2-*phenylisoxazolidine* **11**.—3-Diphenylphosphinoylpent-1-ene **3** (132 mg, 0.5 mmol) and the nitrone **8** (135 mg, 0.6 mmol) in CH_2Cl_2 (8 cm^3) were stirred for 28 d, more nitrone being added after 7, 14 and 17 d. The solvent was removed under reduced pressure from the mixture and the residue purified by column chromatography on SiO_2, eluting with EtOAc–hexane (4:1). The first fraction isolated contained the major product isomer of the *isoxazolidine* **11** (46 mg, 19%) as a yellow oil (Found: M^+, 495.1971. $C_{31}H_{30}NO_3P$ requires *M*, 495.1964); R_F (EtOAc–hexane, 4:1) 0.38; ν_{max}/cm^{-1} (CH_2Cl_2) 2980–2760 (CH), 1680 (C=O), 1600 and 1570 (Ph), 1490 (P–Ph), 1175 (P=O) and 1110 (C–O); δ_H($CDCl_3$) 1.05 (3 H, t, *J* 7.5, Me), 1.75–2.01 (2 H, m, MeCH_2), 2.11–2.30 (2 H, 2° m, 4-H_2), 2.78 (1 H, tt, *J* 4.4 and 8.8, PCH), 4.57 (1 H, m, OCH), 5.00 (1 H, dd, *J* 5.2 and 8.0, NCH), 6.93–7.00 (3 H, m, *o* and *p* to N), 7.25 (2 H, t, *J* 8.0, *m* to N), 7.39–7.58 (9 H, m, *m* and *p* to C and P), 7.81–7.90 (4 H, m, *o* to P) and 7.98 (2 H, d, *J* 7.2, *o* to C); δ_C($CDCl_3$) 12.9 (d, *J* 6, Me), 20.5 (CH_2), 36.5 (CH_2), 43.0 (d, *J* 68, PCH), 70.4 (OCH), 76.9 (NCH), 114 (*o* to N), 122.3 (*p* to N), 128.6, 128.7, 129.0, 129.2, 130.9, 130.9, 131.0, 131.0, 131.7, 132.0 (d, *J* 97, *ipso* to P), 132.3 (d, *J* 94 *ipso* to P), 133.4, 134.8 (*ipso* to C), 150.3 (*ipso* to N) and 196.4 (C=O); *m/z* 495 (M^+, 0.4%), 477 ($M^+ - H_2O$, 17), 390 (M^+ – PhCO, 10), 372 ($M^+ - H_2O$ – PhCO, 30), 276 ($M^+ - Ph_2PO - H_2O$, 72), 244 [$Ph_2P(O)Pr$, 20], 229 [$Ph_2P(O)C_2H_4$, 17], 202 (Ph_2PHO, 19), 201 (Ph_2PO, 76), 118 (PhCOCH, 100), 105 (PhCO, 35) and 77 (Ph, 84). The second fraction isolated was a 2:1 mixture of the major isomer **A** (above) and one other isomer **B**, respectively, of the *isoxazolidine* **11** (46.5 mg, 19%) (Found: M^+, 495.1999. $C_{31}H_{30}NO_3P$ requires *M*, 495.1963); R_F (EtOAc–hexane, 4:1) 0.38 and 0.32; ν_{max}/cm^{-1} ($CDCl_3$) 3130–3030 (aryl CH), 3020–2800 (CH), 1695 (C=O), 1600, 1570 and 1490 (Ph), 1445 (P–Ph), 1200–1175 (P=O) and 1120 (C–O); δ_H($CDCl_3$) 0.88 (3 H**B**, t, *J* 7.5, Me), 1.05 (3 H**A**, t, *J* 7.5, Me), 1.66–2.04 (2 H**A** and 3 H**B**, m, MeCH_2**A** and **B**, and 4-$H_A$$H_B$**B**), 2.21 (2 H**A**, 2° m, 4-H_2), 2.65–2.73 (1 H**B**, m, 4-$H_A$$H_B$), 2.79 (1 H**A**, tt, *J* 4.5 and 9.0, PCH), 2.91 (1 H**B**, qd, *J* 5.5 and 8.0, PCH), 4.45–4.63 (1 H**A** and **B**, m, OCH), 5.00 (1 H**A**, dd, *J* 5.2 and 8.2, NCH), 5.04 (1 H**B**, dd, *J* 6.3 and 8.3, NCH), 6.77 (2 H**B**, d, *J* 8.2, *o* to N), 6.89 (1 H**B**, t, *J* 7.2, *p* to N), 6.93–7.00 (3 H**A**, m, *o* and *p* to N), 7.16 (2 H**B**, t, *J* 8.0, *m* to N), 7.25 (2 H**A**, t, *J* 8.0, *m* to N), 7.39–7.54 (9 H**A** and **B**, m, *m* and *p* to C and P), 7.77–7.89 (4 H**A** and **B**, m, *o* to P), and 7.96–8.05 (2 H**A** and **B**, m, *o* to C); δ_C($CDCl_3$) 12.9 (d, *J* 6, Me**A**), 14.0 (d, *J* 7, Me**B**), 18.1 (CH_2**B**), 20.6 (CH_2**A**), 35.9 (CH_2**B**), 36.6 (CH_2**A**), 41.0 (d, *J* 69, PCH**B**), 43.0 (d, *J* 68, PCH**A**), 70.5 (OCH**A**), 70.6 (NCH**B**), 70.9 (OCH**B**), 76.9 (NCH**A**), 114.1 (*o* to N**B**), 114.2 (*o* to N**A**), 121.9 (*p* to N**B**), 122.3 (*p* to N**A**), 128.2, 128.6, 128.7, 128.8, 129.0, 129.2, 130.7, 130.8, 130.9, 131.0, 131.4, 131.6, 131.7, 132.6 (C *ipso* to P), 132.9 (C *ipso* to P), 133.4, 133.5, 134.9 (*ipso* to C), 150.3 (*ipso* to N**A**), 150.4 (*ipso* to N**B**), 196.4 (C=O**A**) and 196.8 (C=O**B**); *m/z* 495 (M^+, 0.41%), 477 ($M^+ - H_2O$, 12), 390 (M^+ – PhCO, 11), 372 ($M^+ - H_2O$ – PhCO, 14), 276 ($M^+ - Ph_2PO$, 100), 202 (Ph_2PHO, 22), 201 (Ph_2PO, 79), 118 (PhCOCH, 34), 105 (PhCO, 28) and 77 (Ph, 46).

Method for the Reduction of Isoxazolidines.—Activated Zn (15 equiv.) was added to a *preheated* solution of the isoxazolidine in H_2O–HOAc (1:1) (75 cm^3 per mmol of isoxazolidine) under Ar at 60 °C, and the mixture stirred for 1 h at 60 °C. The mixture was cooled and filtered, and the filtrate basified to *ca.* pH 9 with conc. NH_3 (*d* 0.88) and extracted three times with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product.

2-(3′-*Diphenylphosphinoyl*-2′-*hydroxypropyl*)*piperidine* **12**.—By the above method, Zn (200 mg) was added to a solution of the isoxazolopyridine **5** (71.5 mg, 0.21 mmol) in H_2O–HOAc (16 cm^3) and the mixture stirred at 60 °C for 1 h. Work-up gave the *amino alcohol* **12** (66 mg, 92%) as white needles, m.p. 135–137 °C (Found: M^+, 343.1726. $C_{20}H_{26}NO_2P$ requires *M*, 343.1702); ν_{max}/cm^{-1} ($CDCl_3$) 3700 and 3610 (NH), 3500–3300 (OH), 3120–3050 (aryl CH), 3000–2800 (C–H), 1600 (Ph), 1440 (P–Ph), 1185 (P=O) and 1125 (C–O); δ_H($CDCl_3$) 1.07–1.42 (3 H, m), 1.43–1.59 (2 H, m), 1.60–1.68 (2 H, m) and 1.69–1.79 (1 H, m) (CH_2C[N]H–CH_2CH_2CH_2), 2.39 (1 H, ddd, *J* 4.8, 10.2 and 15.0, PC$H_A$$H_B$), 2.50–2.64 (2 H, m, PC$H_A$$H_B$ and NCH), 2.79–2.86 (1 H, m, NCH), 2.97 (1 H, br dd, *J ca.* 2 and 12.0, NCH), 4.29 (1 H, m, OCH), 7.42–7.54 (6 H, m, Ph_2PO) and 7.68–7.78 (4 H, m, Ph_2PO); *m/z* 343 (M^+, 1%), 260 ($Ph_2POC_3H_7O$, 12), 242 (Ph_2POC_2HO, 9), 216 (Ph_2POMe, 20), 215 (Ph_2POCH_2, 27), 202 (Ph_2PHO, 26), 201 (Ph_2PO, 33), 142 ($M^+ - Ph_2PO$, 26), 124 ($M^+ - Ph_2PO - H_2O$, 17), 98 ($C_6H_{12}N$, 22), 97 ($C_6H_{11}N$, 21), 84 ($C_5H_{10}N$, 100) and 77 (Ph, 13).

2-(3′-*Diphenylphosphinoyl*-2′-*hydroxybutyl*)*piperidine* **13**.—By the above method, Zn (580 mg) was added to a solution of the isoxazolopyridine **6a** (211 mg, 0.59 mmol) in H_2O–HOAc (45 cm^3) and the mixture stirred at 60 °C for 1 h. Work-up gave the *amino alcohol* **13** (212 mg, 100%) as a white foam (Found: M^+, 357.1834. $C_{21}H_{28}NO_2P$ requires *M*, 357.1858); ν_{max}/cm^{-1} ($CDCl_3$) 3700 and 3620 (NH), 3460–3120 (O–H), 3210–3050 (aryl CH), 3000–2800 (CH), 1600 (Ph), 1440 (P–Ph), 1185 (P=O) and 1120 (C–O); δ_H($CDCl_3$) 1.10 (3 H, dd, *J* 7.3 and 16.8, Me), 1.18–1.51 [5 H, m, 5 H from CH_2C(N)HCH_2–CH_2CH_2], 1.61 [1 H, ddd, *J* 3.5, 10.8 and 14.0, C$H_A$$H_B$ from CH_2C(N)HCH_2CH_2CH_2], 1.66–1.74 [1 H, m, 1 H from CH_2C(N)HCH_2CH_2CH_2], 1.81 [1 H, ddd, *J* 2.7, 6.3 and 14.5, CH$_A$$H_B$ from CH_2C(N)HCH_2CH_2CH_2], 2.54 (1 H, dt, *J* 2.8 and 11.5, NCH), 2.70 (1 H, tqd, *J* 2.0, 7.4 and 14.8, PCH), 2.83–2.92 (1 H, m, NCH), 2.98 (1 H, br dd, *J ca.* 3 and 13.0, NCH), 4.14 (1 H, m, OCH), 7.42–7.54 (6 H, m, Ph_2PO) and 7.72–7.84 (4 H, m, Ph_2PO); *m/z* 357 (M^+, 0.34%), 274 ($M^+ - C_5H_{10}N$, 10), 259 ($M^+ - C_6H_{13}N$, 9), 230 [$Ph_2P(O)Et$, 33], 229 [$Ph_2P(O)C_2H_4$, 11], 202 (Ph_2PHO, 46), 201 (Ph_2PO, 40), 156 ($M^+ - Ph_2PO$, 42), 98 ($C_6H_{12}N$, 25), 97 ($C_6H_{11}N$, 27), 84 ($C_5H_{11}N$, 100) and 77 (Ph, 11).

2-(3′-*Diphenylphosphinoyl*-2′-*hydroxybutyl*)*piperidine* **14**.—By the above method, Zn (440 mg) was added to a solution of the isoxazolopyridine **6b** (122 mg, 0.34 mmol) in H_2O–HOAc (25 cm^3) and the mixture stirred at 60 °C for 1 h. Work-up gave the *amino alcohol* **14** (104 mg, 85%) as a white foam (Found: 357.1850. $C_{21}H_{28}NO_2P$ requires *M*, 357.1858); R_F (CH_2Cl_2–MeOH–NH_3, 100:10:2) 0.23; ν_{max}/cm^{-1} ($CDCl_3$) 3680 and 3600 (NH), 3500–3260 (OH), 3100–3040 (aryl CH), 3000–2780 (C–H), 1600 (Ph), 1435 (P–Ph), 1165 (P=O) and 1115 (C–O); δ_H($CDCl_3$) 1.16 (3 H, dd, *J* 7.2 and 17.0, Me), 1.26–1.37 [3 H, m, 3 H from CH_2C(N)HCH_2CH_2CH_2], 1.47–1.57 [2 H, m, 2 H, from CH_2C(N)HCH_2CH_2CH_2], 1.68–1.72 [1 H, m, 1 H from CH_2C(N)HCH_2CH_2CH_2], 1.77 [1 H, ddd, *J* 3.9, 9.8 and 13.7, C$H_A$$H_B$ from CH_2C(N)HCH_2CH_2CH_2], 2.37 (1 H, dq, *J* 1.5 and 7.3, PCH), 2.56 (1 H, dt, *J* 2.7 and 11.8, NCH), 2.64–2.73 (1 H, m, NCH), 2.96 (1 H, br dd, *J ca.* 2.5 and 12.7, NCH), 4.26 (1 H, ddt, *J ca.* 1.5, 4.0 and 10.1, OCH), 7.43–7.50 (6 H, m, Ph_2PO) and 7.69–7.86 (4 H, m, Ph_2PO); *m/z* 357 (M^+, 3%), 274 (M^+

– $C_5H_{10}N$, 10), 259 ($M^+ - C_6H_{13}N$, 11), 230 [$Ph_2P(O)Et$, 35], 229 [$Ph_2P(O)C_2H_4$, 10], 202 (Ph_2PHO, 35), 201 (Ph_2PO, 32), 156 ($M^+ - Ph_2PO$, 42), 138 ($M^+ - Ph_2PO - H_2O$, 16), 98 ($C_6H_{12}N$, 18), 97 ($C_6H_{11}N$, 21), 84 ($C_5H_{11}N$, 100) and 77 (Ph, 9).

trans-2-*But*-2′-*enylpiperidine Hydrochloride* **17**.—NaH (60% dispersion in oil; 25 mg, 0.6 mmol) was added to a stirred solution of 2-(3′-diphenylphosphinoyl-2′-hydroxybutyl)-piperidine **13** (0.29 mmol) in DMF (6 cm^3) under Ar, and the mixture stirred at RT for 18 h. Et_2O (30 cm^3) was added to the mixture which was then washed with NaOH (20% aqueous solution; 3 × 25 cm^3). The organic fraction was dried (Na_2SO_4) and evaporated under reduced pressure and the residue was purified by column chromatography on SiO_2, eluting with CH_2Cl_2–MeOH–NH_3 (80:10:2). The fractions containing the alkene **17** were washed with 20% aqueous NaOH, dried (Na_2SO_4) and treated with concentrated HCl (2 equiv.). The solvents were removed under reduced pressure, and the residual water was removed azeotropically using MeCN, to give the alkene **17** as a fine white powder (35 mg) identified by its NMR spectrum (Found: $M^+ + H$, 140.1442. $C_9H_{17}N$ requires M + H, 140.1439); R_F (CH_2Cl_2–MeOH–NH_3, 80:10:2) 0.48; ν_{max}/cm^{-1} (CH_2Cl_2) 3660 and 3430 (NH), 2980–2210 (CH), 1660 (C=C) and 970 (*trans* C=C); $\delta_H(CDCl_3)$ 1.2–2.0 (7 H, m, ring protons), 1.67 (3 H, d, *J* 6.0, Me), 2.40 (1 H, td, *J* 7.7 and 13.9, probably NCH_AH_B), 2.68–2.88 (3 H, m, probably $C{=}CCH_2$ and NCH), 3.45 (1 H, br d, *J* 11.7, NH), 5.36 (1 H, td, *J* 6.5 and 14.5, MeCH=C*H*), 5.61 (1 H, qd, *J* 6.3 and 15.1, MeC*H*); *m*/*z* 140 ($M^+ + H$, 0.4%) and 84 ($C_5H_{10}N$, 100).

2-*Allylpiperidine Hydrochloride* **16**.—In the same way NaH (60% dispersion in oil; 14 mg, 0.6 mmol) and the piperidine **13** (62 mg, 0.18 mmol) in DMF (3 cm^3) gave the alkene **16** (5 mg, 17%) identified by its NMR spectrum $\delta_H(CDCl_3)$ 1.2–2.1 (6 H, m, ring protons), 2.3–3.6 (5 H, m, CHN, CH_2N and $C{=}CHCH_2$), 5.18 (1 H, d, *J* 8, *cis* $CH{=}CH_AH_B$), 5.20 (1 H, d, *J* 16, *trans* $CH{=}CH_AH_B$), 5.75 (1 H, m, $CH{=}CH_AH_B$) and 9.1–9.6 (2 H, br m, NH_2^+).

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