Tetrahedron Vol 46 Nos 13/14 pp 4877 4886 1990
Printed in Great Britain

0040-4020/90 $3 00+ 00

THE NUCLEOPHILIC DISPLACEMENT ROUTE TO HOMOCHIRAL ARYLPHOSPHINE OXIDES

By John M. Brown , Joseph V. Carey and Michael J.H. Russell[a]

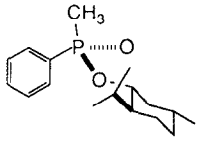
(Dyson Perrins Laboratory, South Parks Rd. OXFORD OX1 3QY and [a]Johnson-Matthey Chemicals, ROYSTON, Herts, SG8 5HE)

(*Received in UK* 13 *March* 1990)

Abstract. The stereoisomerically pure oxazaphospholidine formed by reaction of (1R, 2S)-ephedrine with $PhPCl_2$ is oxidised by Bu^tOOH to the corresponding P-oxide, shown to have R-stereochemistry at phosphorus by X-ray analysis The product reacts regio- and stereospecifically with o-anisylmagnesium bromide to give the product formed by P-O fission with retention of configuration, which was also characterised by X-ray diffraction The ephedrine residue was replaced by O-methyl under acid catalysis with inversion of configuration. Attempts to incorporate p-fluorophenyl using similar conditions led to isolation of the pyrophosphinate in low yield The OMe residue in the methoxyphosphinate was readily displaced by aliphatic or aromatic Grignard reagents giving the corresponding phosphine oxides with inversion of configuration This procedure constitutes a simple route to di- and triarylphosphine oxides in ca 95% e.e ; optical purities were estimated by NMR methods

Since the pioneering work of Mislow and co-workers[1] , the synthesis of optically pure phosphines and phosphine oxides with a stereogenic centre at phosphorus has attracted much attention. This early approach was based on a simple observation - that the diastereomeric O-menthylphosphinates (**1R$_P$**) and (**1S$_P$**) can be separated by fractional crystallisation. Displacement of menthol by arylmagnesium halides occurs with inversion of configuration under somewhat forcing conditions, giving (**2**) and its analogues. The starting menthylphosphinates can be prepared from $PhPCl_2$ by successive methanolysis, Arbusov reaction of the product with a catalytic quantity of MeI and finally displacement of OMe by O-menthyl via the corresponding phosphoryl chloride

Several attempts have been made to improve this route in the last twenty years, and to develop alternative approaches to homochiral phosphines and related compounds The basic chemistry of Mislow was developed by Horner and co-workers who synthesised a variety of monophosphine oxides with differing aryl-groups in optically active form by this method, for example (**3**) and (**4**)[2] .



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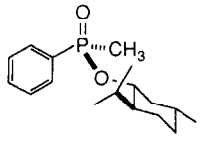

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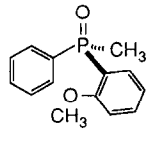

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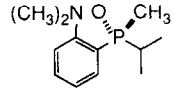

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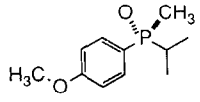

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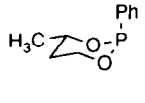
To mark the 65th birthday of David Ollis and his retirement from the Chair of Organic Chemistry at Sheffield University

The Arbusov approach has been adopted by other authors, using a range of chiral auxiliaries. Suga and co-workers[3] have reacted the cyclic phenylphosphonite (**5**), prepared from S-1,3-butanediol with alkyl halides and demonstrated a regioselective ring opening by cleavage of the primary P-O bond. After chromatographic separation and reaction with an alkylmagnesium halide, the corresponding aryldialkylphosphine oxide is formed in 76-100% e.e. The same group has utilised cyclic phosphonites (**6**) and (**7**) in a similar sequence, but here the enantiomeric purity of the resulting phosphine oxides is uniformly low. In this area the most successful development is due to Juge[4] , who has developed an approach based on the previously observed diastereoselectivity observed in formation of the oxazaphospholidine (**8**) from ephedrine[5]. Thus (**8**) undergoes an efficient reaction with MeI, EtI or PrI to give an average 9:1 ratio of (**9**) to its distereomer, separable by fractional crystallisation. The product can be converted into diarylalkylphosphine oxides by successive acid-catalysed methanolysis and Grignard displacement; in this way (**2**) and (**10**) were prepared in 95 and 92% E.e respectively.



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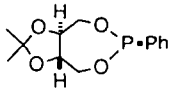

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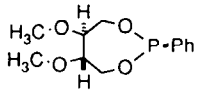

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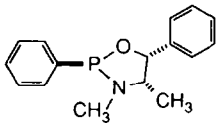

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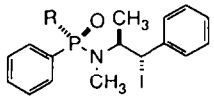

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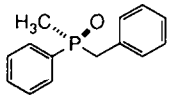

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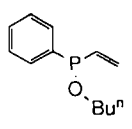
Menthoxycarbonylalkylmethyl side-chains have been utilised for homochiral phosphine oxide synthesis by two groups. Pietrusiewicz and co-workers[6] demonstrated that the vinylphosphonite (**11**) reacted with (-)-menthyl bromoacetate giving a diastereomeric mixture of the Arbusov products, in which one diastereomer (**12**) crystallised from the crude reaction mixture. This could be elaborated in various ways since it was subsequently shown that the CH_2 adjacent to P=O could be alkylated under basic conditions and also that the menthoxycarbonyl group could be readily removed. In a related approach, Johnson and Imamoto[7] demonstrated that (**13**) could be readily separated into its diastereomers which were separately subjected to hydrolysis and decarboxylation, giving (**14**) or its enantiomer. This approach was successfully used to prepare a variety of phosphine oxides such as (**15**).



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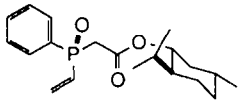

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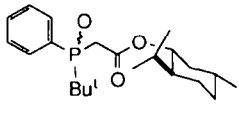

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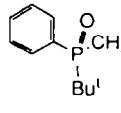

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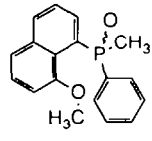

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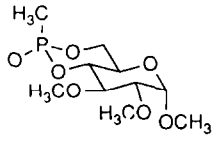
Surprisingly little work has been done on the direct preparation of homochiral phosphine oxides by sequential nucleophilic displacement routes. The first successful demonstration was due to Inch and co-workers who showed that the phosphonate (**16**) or its diastereomer with reversed configuration at phosphorus, derived simply from the corresponding pyranoside with methylphosphonic difluoride , reacted stereospecifically in a two step displacement sequence with different Grignard reagents giving optically pure phosphine oxide in ca. 10% overall yield[8]. Koizumi and co-workers[9] have taken the diastereomerically pure oxazaphospholidine oxide (**17a**) and sulphide (**17b**) and demonstrated that they react with Grignard reagents. The optical purities were only established for reaction with MeMgI, giving (**18**) (E.e.73-99%) and the second displacement necessary to complete the phosphine oxide synthesis was not carried out. Chodkiewicz[10] has completed a synthesis of the homochiral phosphine oxide (**2**) in which the chirality is derived from cinchonine and all steps conducted at the P(III) oxidation level. Details of this route have not been published and since it relies on kinetic discrimination between the two diastereomeric forms of (**19**) in the subsequent nucleophilic displacement step, it may lack generality .



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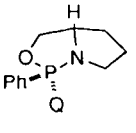
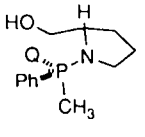


17 a Q=O
17 b Q=S



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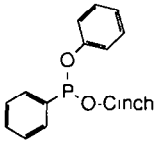

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Discussion

Our approach is based on the use of (1R,2S)-ephedrine as a chiral auxiliary, following on from the early pioneering observations of Inch and co-workers[11] in this field. Juge has already demonstrated the effectiveness of this basic direction through the Arbusov approach[4] , but from the outset our intention was to introduce the two alkyl groups by sequential nucleophilic displacement of the P-O and P-N bonds in an oxazaphospholidine, rather than rely on Arbusov chemistry.

Juge and Genet[4] had prepared the oxazaphospholidine (**8**) from $PhP(NEt_2)_2$ and (-)-ephedrine by heating in toluene at 100^0C, when one pure diastereomer is formed, presumably through thermodynamic control. We found that despite the caveat expressed by Richter[5] it is more convenient to react commercially available $PhPCl_2$ with (-)-ephedrine in the presence of two equivalents of N-methylmorpholine in toluene at 0^0C and monitor the supernatant liquid by ^{31}P NMR. Initially there is evidence for two diastereomeric compounds in the reaction mixture in ca. 50 : 50 ratio [δP = 152.9,139.3 ppm] but after stirring for a day at ambient temperature the low-field one essentially disappears. At that stage the reaction product is separated from the precipitated amine hydrochloride and oxidised with an equivalent of t-butyl hydroperoxide in CH_2Cl_2 without further purification. This step proceeds smoothly and diastereomerically pure oxide (**20**) [δP = 29.7 ppm] is obtained. The compound obtained in this way is identical to the major diastereomer formed in the reaction of (-)-ephedrine with $POCl_3$. Alternatively, the crude oxazaphospholidine was reacted with BH_3;$(CH_3)_2S$ to produce a crystalline borane complex[12] [δP = 129.0 ppm], which was stable to air and moisture.

A preliminary survey was made of the reaction of oxazaphospholidine, its P-oxide and the borane adduct with Grignard and organolithium reagents . The cleanest results obtained (^{31}P monitoring of the reaction mixtures) were with the P-oxide and Grignard reagents in diethyl ether or thf, and this was the approach followed in the larger-scale procedures described. We were pleased to discover that the reaction of (**20**) with o-anisylmagnesium bromide produced a single diastereomeric product (**21**) in 70% yield, by selective cleavage of the P-O bond. This observation has precedents in the work of Inch[13] on the reaction of the oxazaphospholidinethione analogue of (**19**) with PhLi, which occurs with retention of configuration, and Koziumi's work on the reaction of the bicyclic oxazaphospholidinone (**16**) which is reported to proceed with inversion of configuration; the corresponding thione reacts similarly.

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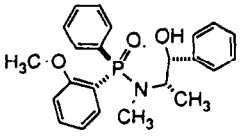

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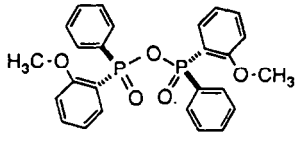

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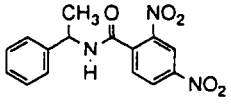

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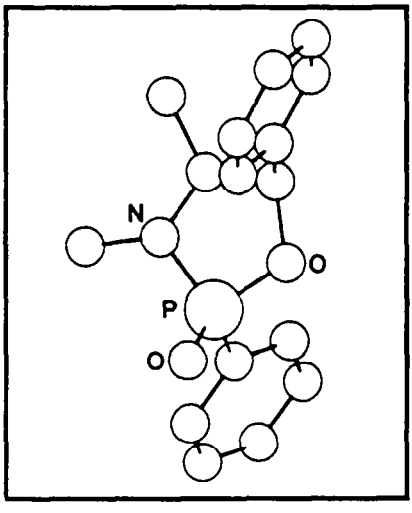

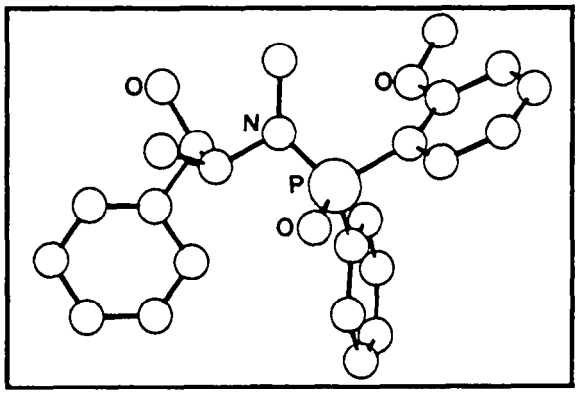

Figure1 X-Ray crystal structures of compounds (20) and (21), demonstrating the retention of configuration in the first nucleophilic displacement step.

In view of these contrasting results, the X-ray crystal structures of both (**20**) and (**21**) were obtained[14] . The former confirms that the assignment specified in the literature based on NMR assignments and stereochemical considerations is correct. This is because the P-Ph and Ph,CH_3 substituents of the ephedrine backbone are disposed on opposite sides of the 5-membered ring in the preferred diastereomer , and oxidation occurs with retention of configuration (Figure 1). Inspection of the X-ray structure of the ring-opened product (**21**) makes it clear that in this case the Grignard reaction occurs with retention of configuration, unlike the example claimed by Koizumi but in accord with Inch's work. Thus the cyclic ephedrine derivatives react with organomagnesium

reagents in opposite stereochemical sense to the open-chain examples of Mislow. The reasons for this stereochemical divergence are not well understood, but must require that there are 5-coordinate intermediates in an associative pathway with the opportunity for pseudorotation, as indicated in Figure 2 .

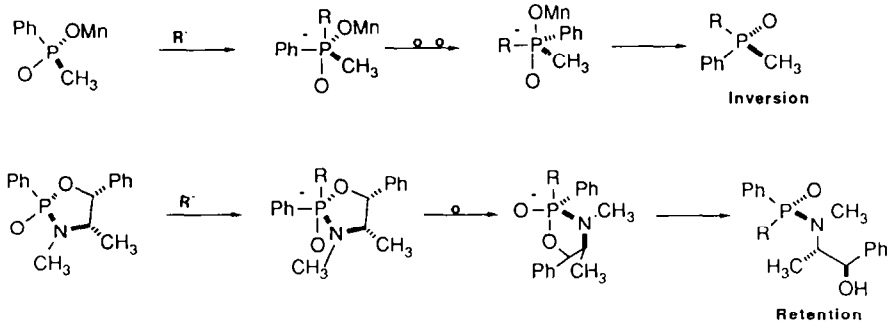

Figure 2. Pseudorotation-controlled stereochemistry of nucleophilic displacement by Grignard reagents.

Up to this point the procedure has provided a precursor to a homochiral phosphine oxide with two of the three P-C bonds in place and stereochemically defined. In order to make the third replacement, a better nucleofugal leaving group than the P-N moiety is required. There is precedent for acid-catalysed cleavage of P-N bonds with inversion of configuration in the presence of alcohols[4,8,10], and initial efforts centred on applying this route to the introduction of p-fluorophenolate and other phenolic groups. Reaction of compound (**21**) with p-F-phenol under a variety of conditions failed to give a clean product, and the product (**22**) isolated was the consequence of dimerisation. Presumably the desired product (**23**) is formed and p-fluorophenoxide is displaced by the P-O of another molecule. More success was obtained with acid-catalysed methanolysis, and the desired methoxy-compound was isolated in good yield as an oil. The enantiomer excess was established to be better than 96% using the NMR chiral-shift reagent (**24**) introduced by Kagan[15].

From this point the route to homochiral phosphines follows the displacement chemistry used by Mislow, although OMe is replaced by alkyl or aryl groups under much milder conditions than is O-menthyl. Initial experiments were carried out with MeMgCl in thf, monitoring by ^{31}P NMR; it was found that reaction was complete after several hours at ambient temperature. Work-up gave the well-known (R)-o-anisylmethylphenylphosphine oxide (**2**), in high yield. This was reduced by $HSiCl_3$ to give the phosphine[16] which was reoxidised by Bu^tOOH to give the (S)- enantiomer. NMR analysis of the initially obtained (R) - enantiomer demonstrates that the unpurified reaction product has an e.e. of 94%. This was confirmed by spiking the NMR shift assay solution with the (S)- enantiomer.

The displacement reaction was equally successful with ethylmagnesium chloride again giving the chiral phosphine oxide (**25**)[17] in 94% e.e., although attempts to carry out the related reaction with vinylmagnesium

bromide were unsuccessful, giving rise to a complex mixture. In order to demonstrate that the chemistry can be effective with aromatic Grignard reagents, the addition of p-methoxyphenylmagnesium bromide was carried out to give the triarylphosphine oxide (**26**) as a colourless oil, albeit in lower yield after chromatographic purification. The overall transformations involved in this work are summarised in Figure 3.

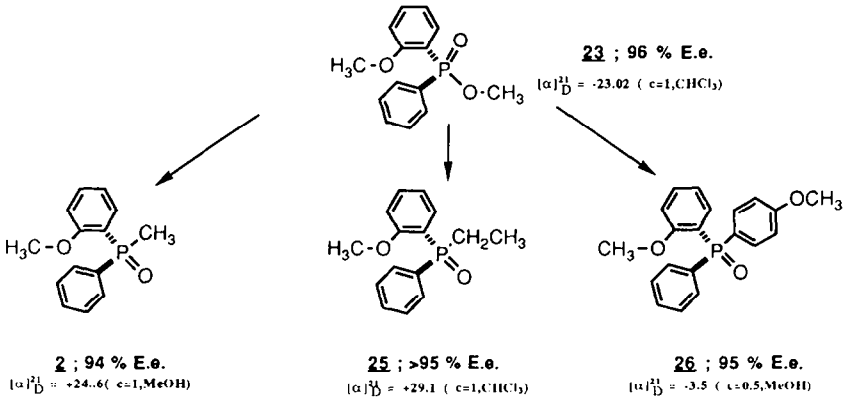

Figure 3. Preparation of phosphine oxides in the Grignard displacement step

Summary and Conclusions

These experiments demonstrate that it is possible to prepare homochiral di- and triarylphosphine oxides by two sequential nucleophilic displacements on a derivative of $PhPCl_2$ utilising (-)-ephedrine as a chiral auxiliary. The basic ideas behind this approach were pioneered by Inch and co-workers, who demonstrated diastereoselectivity in formation of ephedrine-derived oxazaphospholidine derivatives, by Knowles and co-workers[18] who utilised the selective nucleophilic displacement of P-N rather than P-O in their ephedrine-based synthesis of isotopically chiral phosphates, and by Juge's homochiral phosphine oxide synthesis. The optical integrity of the initial product is very much greater than that obtained by Koizumi who used the related chiral auxiliary derived from proline and carried out the displacement step *inter alia* with o-anisylMgBr, with some loss of stereochemical integrity. It was not clear why this occurred. In the more recent work of Juge, the cleavage of the oxazaphospholidine is carried out through an Arbuzov reaction with CH_3I, which gives a 92:8 mixture of the two diastereomers, although the minor contaminant is readily removed by chromatography.

We suspect that the reasons for the success of our approach lie in the order of the different stages, with the ring-opening of (**20**) by an arylmagnesium halide being of critical importance. Whatever the detailed explanation, this represents a simple and versatile route to a class of molecules of considerable general interest.

Acknowledgments

We thank Mrs. E. McGuinness for determination of optical purity by NMR methods with characteristic care, Mrs V. Lambourn for prompt determination of combustion analyses, and Johnson Matthey for support of a Studentship (to JVC). Dr. Kevin Matthews made a very useful early suggestion.

Experimental

^{1}H Nuclear magnetic resonance (n.m.r) spectra were recorded on a Varian Gemini 200 (200 MHz) or a Bruker AM 500 (500 MHz) spectrometer as indicated. Heteronuclear n.m.r spectra were recorded on a Bruker AM 250 spectrometer. Chemical shifts (δ) are given in p.p.m relative to tetramethylsilane (^{1}H, ^{13}C), 85% phosphoric acid (^{31}P) or BF_3 (^{11}B). Solvents and references are as indicated. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet). I.r. spectra were determined on a Perkin-Elmer 781 spectrometer with absorption maxima given in cm^{-1} with the following abbreviations: strong (s), medium (m) and weak (w). Samples were prepared as Nujol mulls or neat as indicated. Mass spectra were recorded on a Varian MAT CH7, V.G Micromass 16F or ZAB-1F/16F spectrometers; *m/z* values followed by the percentage abundance in parentheses, are given for the molecular ion peaks in Daltons. Optical rotations were measured on a thermostatted Perkin-Elmer 241 polarimeter using the 589.3 nm D line of sodium. Melting-points are uncorrected.

Silica gel for flash chromatography was 60 'Merck' 230-300 mesh supplied by B.D.H. When appropriate, components were identified by t.l.c in suitable solvents on Merck Kiesegel 60F 254 plastic plates coated with 0.2 mm of silica visualised by u.v light. Toluene, triethylamine and N-methylmorpholine were freshly distilled from CaH_2. Methanol was freshly distilled from magnesium, dichloromethane from P_2O_5; tetrahydrofuran (thf), diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl under nitrogen prior to use. All solvents were obtained from either B.D.H or Aldrich Chemical Co. Dichlorophenylphosphine, [(1*R*, 2*S*)-(-)-α-(1-methylaminoethyl)benzyl alcohol], (*S*)-(+) or (*R*)-(-)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine, , *tert*-butylhydroperoxide (3.0 M in toluene), methylmagnesium chloride (1.0 M in thf) and ethylmagnesium chloride (1.0 M in thf), borane-methyl sulfide complex (10 M in BH_3), 4-methylmorpholine, triethylamine, 4-fluorophenol, $CDCl_3$ and methylsulphonic acid were obtained from the Aldrich Chemical Co and used without further purification. $CDCl_3$ was dried over 4-Å molecular sieves.

^{1}H n.m.r chemical shift experiments were performed as follows: an aliquot of (*R*)-(-) or (*S*)-(+)-*N*-(3,5-dinitrobenzoyl)-α-methylbenzylamine (0.064 M) in $CDCl_3$ was added to the phosphine oxide (0.50 ml, 0.019 M) in $CDCl_3$ contained in a 5 mm n.m.r tube. Its ^{1}H n.m.r spectrum (500 MHz) was then recorded and the procedure repeated for the opposite antipode of the chiral shift reagent.

(-)-(2*R*,4*R*,5*S*)-2-Phenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-oxide(**20**) Dichlorophenyl phosphine (32.84 ml, 0.24 mol) was added dropwise *via* cannula over 30min to a cooled (0 °C) and vigorously stirred solution of (1*R*, 2*S*)-(-)- ephedrine (40.0 g, 0.24 mol) and N-methylmorpholine (53.4 ml, 0.484 mol) in dry toluene (500 ml) under an argon atmosphere. Stirring was continued at this temperature for 1h after which the mixture was left to stir at ambient temperature for 18h. A portion (2 ml) was removed and its ^{31}P nmr spectrum recorded. δ_P (101 MHz; toluene; external standard $CDCl_3$) 139.31 (1P, s) which confirmed the presence of only one diastereoisomer. The solid N-methylmopholine hydrochloride was removed by standard Schlenk filtration and washed with dry toluene (3 x 30 ml). A portion was removed (2 ml) and the solvent removed *in vacuo* to yield a white solid. δ_H (200 MHz; $CDCl_3$): 0.65 (3H, d), 2.6 (3H, d), 3.25 (1H, m), 5.55 (1H, d), 7.1-7.7 (10H, m). The solution was then used in the next step without further purification.
The combined filtrate was cooled to -10 °C and *tert*-butylhydroperoxide (80.66 ml, 0.24 mol, 3.0 M in toluene)

was added with vigorous stirring at such a rate as to keep the temperature below 0 °C. After being stirred for 1h the solution was left to stir at ambient temperature for 18h. White crystals were deposited which were collected by filtration and dried *in vacuo*. Concentration of the filtrate yielded a second crop which was treated similarly. Crystallization from dry thf gave compound (**20**) (25.6 g, 39.3%) as white crystals, m.p. 169-70 °C. (Found: C, 67.13; H, 6.30; N, 4.73; P, 10.83. $C_{16}H_{18}NO_2P$ requires C, 66.87; H, 6.31; N, 4.86; P, 10.87%); $[\alpha]_D^{22}$ -31.2 (c= 1, MeOH) ; ν_{max} (Nujol) 1 438 (s, P-Ph), 1 295 (s, P=O), 1 040 cm^{-1} (s, P-C-alkyl); δ_H (500 MHz, $CDCl_3$) 0.92 (3 H, d, *J* 6.54Hz, 4-Me), 2.63 (3 H, d, *J* 10.1Hz, P-N-Me), 3.87 (1 H, m, 4-H), 5.62 (1 H, m, 5-H), 7.2-7.6 (8 H, m), 7.8-7.9 (2 H, m); δ_C (63 MHz, $CDCl_3$) 14.50 (s, 4-Me), 28.55 (d, Me, *J* 6 Hz, P-N-Me), 59.22 (s, C-4), 82.56 (d, C-5, *J* 9.6, P-O-C), 126-136 (m, aromatics); δ_P (101 MHz, $CDCl_3$) 29.7 (1 P, s); *m/z* 287 (M^+, 45), 272 (50), 196 (12), 181 (55), 146 (15), 104 (27), 77 (34).

(2*R*, 4*R*, 5*S*)-2-Phenyl-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine-2-borane - To the filtrate from the condensation step above carried out on a 30.5 mmolar scale was added borane-methyl sulfide complex (3.9 ml, 10 M, 39.05 mmol,) with constant stirring under argon. After 18 h the solution was concentrated under vacuum to yield a white solid which was collected by filtration and washed with cold toluene (10 ml). Crystallization from toluene gave the product (3.0 g, 34%) as a white crystalline solid, m.p. 105 °C. $[\alpha]_D^{21}$ -45.5 (c=2, $CHCl_3$) ; (Found: C, 67.46; H, 7.57; N, 4.71. $C_{16}H_{21}POBN$ requires C, 67.40; H, 7.42; N, 4.91%); δ_H (500 MHz; $CDCl_3$) 0.84 (3 H, d, *J* 6.5Hz, 4-Me), 2.69 (3 H, d, *J* 10.94 Hz, P-N-Me), 3.68 (1 H, m, 4-H), 5.6 (1 H, m, 5-H), 7.3-7.6 (8 H, m, aromatics), 7.8 (2 H, m). δ_C (63 Hz; $CDCl_3$) 13.56 (s, 4-Me), 29.45 (d, Me, *J* 8 Hz, P-N-Me), 59.16 (s, 4-C), 84.01 (d, 5-C, *J* 7.5 Hz, P-O-C), 126-132 (m, aromatics); δ_P (101 Hz; $CDCl_3$) 129 (q, *J* 74 Hz, P-B); δ_B (80.18 Hz; $CDCl_3$) -40.5 (d, *J* 74 Hz, B-P); *m/z* 284 (M^+, 284), 272 (100), 165 (35).

(*S*)-(-)-*N*-methyl-*N*-(methyl-1-hydroxy-2-phenyl-2)-ethyl-(1*S*, 2*S*)-*P*-methyl-*P*-phenyl phosphinamide (**21**) - To a cooled (-30 °C) and stirred solution of (-)-(2*R*, 4*R*, 5*S*)-2-phenyl-3,4-dimethyl-5-phenyl-1,3,2-oxzaphospholidine-2-oxide (10.0 g, 34.8 mmol) in dry thf (150 ml) was added via cannula, under argon, a solution of 2-methoxyphenylmagnesium bromide (100 ml, 50 mmol, 0.5 M in thf). Stirring was continued at this temperature for 1h after which the solution was left to stir for 18h at ambient temperature. The excess Grignard reagent was destroyed by quenching with water (100 ml) and the mixture extracted with dichloromethane (3 x 100 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated to yield a white solid. Crystallization from toluene (two crops, white needles) gave compound (**21**) (9.6 g, 70%), m.p. 195-7°C (Found: C, 69.92; H, 6.81; N, 3.54; P, 7.56. $C_{23}H_{26}NO_3P$ requires C, 69.86; H, 6.63; N, 3.54; P, 7.82%); $[\alpha]_D^{21}$ -14..8(c=1.0, $CHCl_3$) ; ν_{max} (Nujol) 3 250 (br, OH), 1 462 (s, P-Ph), 1 245 (m, P=O), 1035 cm^{-1} (s, P-O-Alkyl); δ_H (500 MHz; $CDCl_3$) 1.17 (3 H, d, *J* 7.1 Hz, Me), 2.27 (3 H, d, *J* 10.7 Hz, P-N-Me), 3.7-3.8 (1 H, m), 3.77 (3 H, s, OMe), 4.8 (1 H, q), 6.9-7.8 (14 H, m); δ_C (63 MHz; $CDCl_3$) 13.46 (s, CH_3), 32.1 (d, Me *J* 5.4 Hz, P-N-Me), 55.28 (s, OCH_3), 55.48 (s, 5-C), 58.48 (s, 4-C), 110-160 (m, 18 aromatics); δ_P (101 MHz; $CDCl_3$) 30.98 (s); *m/z* : 396 (M^+, 100), 378 (10), 288 (35), 248 (10), 148 (20).

Phenyl methyl-(2-methoxyphenyl)phosphonate (**23**) - A standardized methanol solution of dry HCl (17.0 ml, 31.2 mmol, 1.845 M in methanol) was added dropwise to a vigorously stirred solution of (*S*)-(-)-*N*-methyl-*N*-(methyl-1-hydroxy-2 phenyl-2)-ethyl-(1S, 2S)-*P*-methyl-*P*-phenyl phosphinamide (6.2 g, 15.6 mmol) in dry methanol (20 ml) at ambient temperature under argon. The reaction was left to stir for 18h after which it was poured into HCl (50 ml, 0.1 M) and extracted with dichloromethane (3 x 20 ml) aliquots. The organics were combined and washed with NaOH (50 ml, 0.1 M), they were then separated and the organics dried ($MgSO_4$) and concentrated to yield a yellow oil (3.8 g, 93%). $[\alpha]_D^{21}$ -23.02 (c =1, $CHCl_3$) ; ν_{max} (Neat) 1 435 (br, P-Ph), 1 245 (s, P=O), 1 035 cm^{-1} (br, P-OMe); δ_H (500 MHz, $CDCl_3$) 3.71 (3 H, s, OMe), 3.75 (3 H, d, *J* 11.4 Hz, POMe), 6.8-8.1 (9 H, m); δ_C (63 MHz, $CDCl_3$) 51.25 (d, *J* 5.9 Hz, P-OMe), 55.42 (s, OMe), 111-135 (m, 12 aromatics); δ_P (101 MHz; $CDCl_3$) 26.04 (1 P, s); *m/z* 262 (M^+ - 1, 100).

bis-(Phenyl, 2-methoxyphenyl)-pyrophosphinate (**22**) - To (-)-*N*-methyl-*N*-(methyl-1 hydroxy-2 phenyl-2)-ethyl-(1*S*, 2*S*)-*P*-methyl-*P*-phenyl phosphinamide (2.0 g, 5.06 mmol) in dry dichloromethane (50 ml) was added a solution of 4-fluorophenol (3.4 g, 30 mmol) in dry dichloromethane (10 ml) followed by methanesulfonic acid (0.65 ml, 10.12 mmol) under argon with constant stirring. Stirring was continued at this temperature for 48 h after which the mixture was quenched with HCl (50 ml, 0.1 M) and the organic phase was decanted off. The organic phase was washed with NaOH (50 ml, 0.1 M) and separated. The organics were dried ($MgSO_4$) and concentrated under vacuum to yield a white solid. Recrystallization (dichlormethane/hexane) yielded (**22**) (0.2 g, 8.3 %) as white crystals, m.p. 195 °C (decomp.) (Found: C, 64.92; H, 5.06; P, 12.76.

$C_{26}H_{24}P_2O_5$ requires; C, 65.27; H, 5.06; P, 12.95%); ν_{max} (Nujol) 1 440 (br, P-Ph), 1 240 (br, P=O), 960-979 (br, P-O-P); δ_H (500 MHz; $CDCl_3$) 3.56 (6H, s), 7.0-7.9 (18 H, m); δ_P (101 Hz; $CDCl_3$) 21.40 (1 P, s), 22.04 (1 P, s); *m/z* 479 (M^+ - 1, 100), 249 (35).

(*R*)-(2-Methoxyphenyl)methylphenylphosphine oxide **R-(2)** - To a stirred solution of phenyl methyl-(2-methoxyphenyl)phosphinate (1.00 g, 3.81 mmol) in dry thf (50 ml) was added dropwise, under argon, methylmagnesium chloride (3.05 ml, 7.62 mmol, 2.5 M in thf) at ambient temperature. After 7h. the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. A colourless oil was obtained, which after evacuation (0.01 mmHg) for 4 days yielded the product (0.90 g, 97%) as a white solid,m.p. 80-1°C (Lit[16] m.p.=75-80°C) $[\alpha]_D^{21}$+24.6 (c=1.0,MeOH); Lit[16] +25.9 (c=1, MeOH); δ_H (200 MHz; $CDCl_3$) 2.1 (3 H, d, *J* 14 Hz, P-Me), 3.74 (3 H, s, OMe), 6.8-8.1 (9 H, m); δ_P (101 MHz; $CDCl_3$) 25.48 (1 P, s).

(*S*)-(2-Methoxyphenyl)methylphenylphosphine oxide **S-(2)** - To a stirred solution of (*R*)-(2-methoxyphenyl)methylphenylphosphine oxide (0.1 g, 0.41 mmol) and triethylamine (0.23 ml, 1.64 mmol) in dry benzene (8 ml) was added dropwise, under argon a solution of trichlorosilane (0.165 ml, 1.64 mmol) at ambient temperature under argon. After 18h the reaction was quenched with sodium hydroxide (25%) over a 5 min period and left to stirr for a further 30 min. The organic phase was separated and the aqueous layer extracted with dichloromethane (3 x 25 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. A colourless oil was obtained; δ_H (200 MHz; $CDCl_3$) 1.6 (3 H, d, *J* 3.9 Hz, P-Me), 3.8 (3 H, s, OMe), 6.8-7.5 (9 H, m); δ_P (101 MHz; $CDCl_3$) –39.7 (1 P, s). The liquid was redissolved in dichloromethane (10 ml) to which was added *tert*-butylhydroperoxide (0.55 ml, 1.64 mmol, 3.0 M in toluene) with constant stirring over 5 min. The mixture was quenched with water (10 ml) and the organic layer separated, dried ($MgSO_4$) and concentrated to yield a colourless liquid which after evacuation (0.01 mmHg) for 4 days yielded (**8**) (0.1 g) as a white solid, used directly in NMR shift experiments

(*R*)-(2-Methoxyphenyl)ethylphenylphosphine oxide (**25**) - To a stirred solution of phenyl methyl-(2-methoxyphenyl)phosphinate (0.65 g, 2.48 mmol) in dry thf (50 ml) was added dropwise, under argon, ethylmagnesium chloride (2.73 ml, 2.73 mmol, 1.0 M in thf) at ambient temperature. After 18h the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. A colourless oil was obtained, which after evacuation (0.01 mmHg) for 4 days yielded (**25**) (0.54 g, 84%) as a white solid, m.p. 85-7 °C (Found; C, 69.23; H, 6.72; P, 12.06. $C_{15}H_{17}PO_2$ requires; C, 69.22; H, 6.58; P, 11.98%); $[\alpha]_D^{21}$ +29.1 (c= 1.0, $CHCl_3$) ; ν_{max} (nujol) 1 445 (br, P-Ph), 1 245 cm^{-1} (br, P=O); δ_H (500 MHz; $CDCl_3$) 1.1 (3 H, dq, *J* 7.7 Hz, P-CH_2CH_3, *J* 25.8 Hz, P-CH_2CH_3), 2.35 (2 H, m, P-CH_2CH_3); 3.75 (3 H, s, OMe), 6.8-8.0 (9 H, m); δ_C (63 MHz; $CDCl_3$) 5.3 (d, Me), 21.5 (d, CH_2CH_3); 55.17 (s, OMe), 110-134 (m, aromatics); δ_P (101 Hz; $CDCl_3$) 30.32 (1 P, s); *m/z* 521 (20), 396 (25), 261 (M^+ + 1, 100).

2-Methoxyphenyl(4-methoxyphenyl)phenylphosphine oxide (**26**) - To a cooled (-20 °C) and stirred solution of phenyl methyl-(2-methoxyphenyl)phosphinate (0.86 g, 3.28 mmol) in dry thf (70 ml) was added dropwise, under argon, 4-methoxyphenylmagnesium bromide (14.9 ml, 3.28 mmol, 0.22 M in thf) at ambient temperature. After 18h the reaction was quenched with water (50 ml) and extracted with dichloromethane (3 x 50 ml) aliquots. The organics were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (Flash silica, Et_2O/CH_2Cl_2; 60:40) yielded a colourless viscous liquid (**26**) (0.4 g, 36%) (Found; C,70.75; H, 5.74. $C_{20}H_{19}PO_3$ requires; C, 71.00; H, 5.66%); $[\alpha]_D^{21}$ –3.5 (c = 0.5 , MeOH) ; ν_{max} (nujol) 1 440 (br, P-Ph), 1 240 cm^{-1} (br, P=O); δ_H (500 MHz; $CDCl_3$) 3.57 (3 H, s, 2-OMe), 3.85 (3 H, 4-OMe), 6.7-7.9 (13 H, m); δ_P (101 MHz; $CDCl_3$) 30.6 (1 P, s); *m/z* 339 (M^+ +1, 100).

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