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Phospho-transfer catalysis On the asymmetric hydrophosphonylation of aldehydes [1]

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Abstract

We report here a precise, in situ $^{31}P\{^1H\}$-NMR method of assaying enantiopurity of α-hydroxyphosphonate esters, the products of the carbonyl hydrophosphonylation (Pudovik) reaction. This method is based upon a diazaphospholidine chiral derivatising agent (CDA) which satisfies all of the criteria for a precise assay; (i) derivatisation of α-hydroxyphosphonate esters is both rapid and clean, (ii) kinetic resolution is absent and (iii) $^{31}P\{^1H\}$ chemical shift dispersions are excellent (> 5ppm). Calibration of this assay has been achieved by cross-referencing the $^{31}P\{^1H\}$-NMR signals obtained for the CDA-derivatised ester of $(MeO)_2P(=O)CHPh(OH)$ to optical rotation measurements from scalemic material obtained upon lipase catalysed hydrolysis (F–AP 15, *Rhizopus oryzae*) of $(MeO)_2P(=O)CHPh(OAc)$. Analysis of NMR chemical shift and coupling parameters for a closely related series of derivatised α-hydroxyphosphonate esters support further configuration assignments on the basis of inference. We report also on the configurational stability of α-hydroxyphosphonate esters in the presence of acids, organonitrogen bases and metal salts. ^2H-labelling and carbonyl crossover experiments reveal that low levels of epimerisation (< 2%) at the alpha-carbon atom (C_α) of α-hydroxyphosphonate esters is possible under certain conditions of catalysis and within certain limits. A design strategy for the construction of catalyst systems in the Pudovik reaction is outlined based upon a combination of Lewis acidic (*E*) and Lewis basic (*N*) sites. Four types of catalyst are outlined, members of two distinct Classes I and II according to the nature of the acid and base sites, along with our investigations of representative examples of each Class. A variety of Class I.1 systems based on β-amino alcohols (one hydrogen bonding *E* site and one organonitrogen *N* site), have been assayed in the model reaction between $(MeO)_2P(O)H$ and PhCHO. Results suggest that catalysis of the Pudovik reaction is clean and efficient in certain cases but that catalytic activity is strongly dependent upon the nature of the basic (*N*) nitrogen centre. Moreover, only low levels (< 10%) of enantioselectivity are afforded by all amino alcohols assayed. Achiral variants of Class I.2 catalysts (multiple hydrogen bonding *E* and/or *N* sites) have been examined to model carbonyl and H-phosphonate binding; an amphoteric receptor based on a pyridine dicarboxamide scaffold has been synthesised and shown to bind benzaldehyde > 50% more strongly (K_{11} 0.53 mol^{-1} dm^3) than dimethyl-H-phosphonate (K_{11} 0.34 mol^{-1} dm^3, 298 K) and to catalyse the hydrophosphonylation reaction between these two substrates with a second order rate constant comparable to that of triethylamine (both k_2 5.9×10^{-2} mol^{-1} dm^3 h^{-1}, 293 K). However, one of the major limitations of this model is that competitive product inhibition dominates after some 15 turnovers (75% completion). Model studies reveal that hydrophosphonylation catalysis via a nitrogen Lewis base is accelerated up to 10-fold upon the introduction of $[Zn(OSO_2CF_3)_2]$ as co-catalyst. Consequently, Class II.1 systems employ metal salts $[Zn(OSO_2CF_3)_2]$ as Lewis acidic *E* sites and chiral co-catalysts capable of binding to the metal and also acting as Lewis basic *N* sites. Such systems catalyse the addition of $(MeO)_2P(O)H$ to PhCHO cleanly with modest turnover numbers (< 10 turnovers; 50% completion) but with enhanced enantioselectivity over Class I catalysts (< 40% e.e.). However, competitive product inhibition is still problematic. Class II.2 systems are related to Class II.1 but possess directly coordinated *E* and *N* sites with more basic *N* functions and consequently are far more active as catalysts than the other classes. This increased catalytic activity is exemplified by one of the simplest achiral members, diethylzinc which catalyses the 100% chemo- and regioselective addition of $(MeO)_2P(O)H$ to PhCHO to afford $(MeO)_2P(O)CHPh(OH)$ with an average

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[1] It is a great pleasure to dedicate this article to Professor Ken Wade on the occasion of his 65th birthday in recognition of his many outstanding contributions to main group chemistry. One of the authors considers himself honoured to have been taught, guided and deeply influenced by Kens' approach to science. Long may that approach continue.

turnover rate (over a 1 h reaction time at 298 K) of 115 h^{-1} compared to ca. 1 h^{-1} for NEt_3 under analogous conditions. Chiral variants are proposed. © 1998 Elsevier Science S.A.

Keywords: Enantiopurity assay; Chiral derivatising agent; Absolute configuration; Enantioselective; Pudovik reaction; Configurational stability; Amphoteric catalysts; Metal complexes

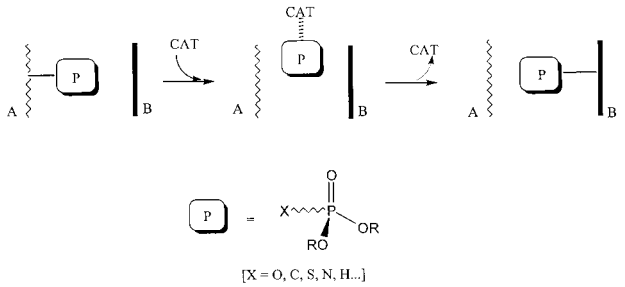
1. Introduction

Phospho-transfer catalysis refers to the process of transferring the phospho function [$(RO)_2P(O)$] or a derivative thereof, from one chemical site to another mediated by a distinct catalytic species (Scheme 1) [1].

One representative example of such a transformation is the kinase and phosphatase catalysed phosphorylation of proteins involving [P–O] bond formation [2], a fundamental process in the regulation of biological systems the significance of which was recently demonstrated by the award of the 1992 Nobel prize for medicine or physiology to Edmond Fisher and Edwin Krebs.

A somewhat less well investigated relative of phosphorylation is that of phosphonylation, where instead of forming a new [P–O] bond, the new linkage formed is a phosphorus–carbon [P–C] bond (X = C in Scheme 1). Whereas phosphorylation results in phosphate esters (X = O, Scheme 1), phosphonylation results in phosphonate esters (X = C, Scheme 1); both classes of which play profoundly important roles in biological and medicinal chemistry. Phosphate-diesters for example form the backbone of genetic materials DNA and RNA and control signal transduction through the central nervous system [3] whilst phosphonate esters, especially those with secondary functionality in the X group, find widespread application as mimics of phosphate esters [4].

The addition of a dialkyl-H-phosphonate ester to an aldehyde to afford an α-hydroxyphosphonate ester, the Pudovik reaction (Scheme 2), is a phosphonylation process which has been known for many years [5], but only relatively recently has interest been focused on the development of asymmetric variants. This in turn has grown from a need to access functionalised phosphonate esters and phosphonic acids readily, cleanly, efficiently and with close control over stereochemistry since functionalised phosphonate derivatives (especially those with functionality in the alpha position) have been shown to possess highly desirable physiological properties as, for example, substitutes for amino carboxylic acids, the design of phosphono-peptides [6], antibiotics [7], antiviral agents [8], enzyme inhibitors [6,9], agrochemicals



Scheme 1. Phospho-transfer catalysis.

and modified oligonucleotides [4,10]. In many of these applications stereochemistry plays a major role in determining the physiological properties of the system [10].

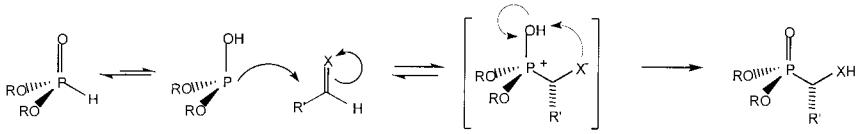
One of the main themes within our programme of phosphorus chemistry is the development of catalytic enantioselective variants of the Pudovik reaction. Our strategy towards this objective is based on addressing four distinct problems; (1) being able to assay enantiopurity of the product α-functionalised phosphonate esters readily, conveniently and precisely, (2) the determination of absolute configuration within α-functionalised phosphonate esters, (3) the establishment of configurational stability α-functionalised phosphonate esters under various conditions and (4) the development of a catalyst design strategy for the Pudovik reaction. In this paper we describe our solutions to problems 1–3 and the foundations of our strategy for hydrophosphonylation catalyst design in order to address problem 4. Portions of this work have been released in preliminary form [11].

2. Results and discussion

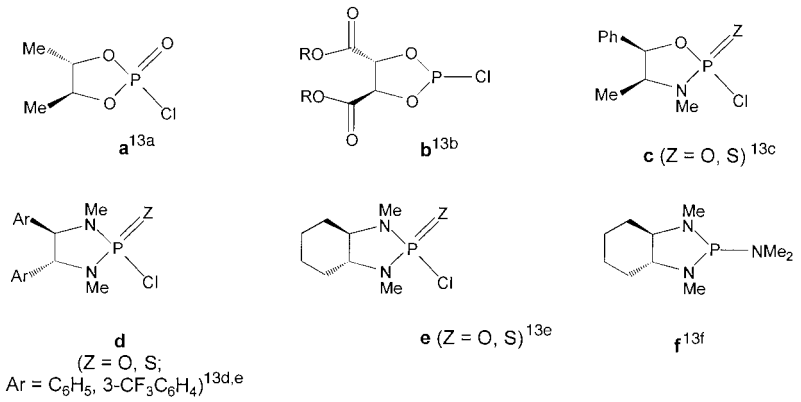
2.1. Problem 1. Assaying enantiopurity of α-hydroxyphosphonate esters

2.1.1. Synthesis and application of a chiral derivatising agent

Among the various methods available for the determination of enantioselectivity in scalemic compounds,



Scheme 2. X = O, NR (R = alkyl, aryl).



Scheme 3. Some examples of organophosphorus derivatising agents.

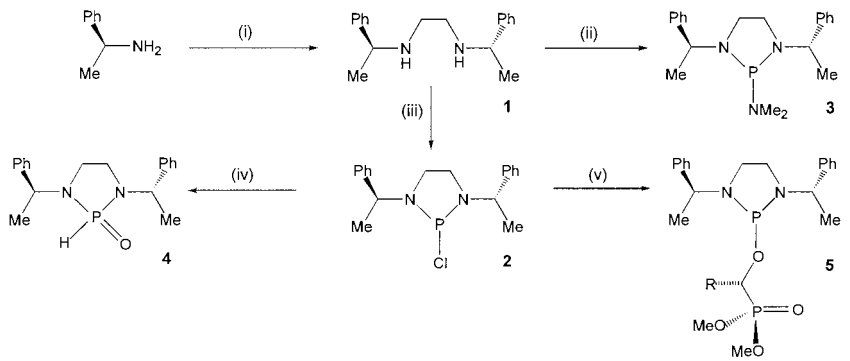
the analysis of diastereoisomers by NMR spectroscopy has a number of attractive features [12]. The technique requires the use of a suitable chiral derivatising agent (CDA) to convert the enantiomers of a scalemic compound to a pair of diastereoisomers which are then differentiated on the basis of their NMR properties.

A number of considerations influence the choice of CDA in any specific application: (i) the CDA should be readily accessible and convenient to manipulate, (ii) reaction with the substrate should be facile and should proceed without kinetic resolution or racemisation, (iii) NMR spectra should provide a chemical shift dispersion which permits effective base-line separation and accurate integration, (iv) due consideration should be given to data collection and processing, (v) the use of the CDA should help in the assignment of absolute configurations and (vi) the CDA should be inexpensive.

Arguably the most important criteria are those related to the efficiency of derivatisation without racemisation and accurate integration by ensuring adequate chemical shift dispersion. For the assay of alcohols, amines, thiols and chiral alkenes several CDAs based on organophosphorus esters or acid halides have been used over the last ten years which derivatise substrates cleanly and where analysis via $^{31}P\{^{1}H\}$-NMR spectroscopy reveals chemical shift dispersions to be invariably higher than those observed in ^{1}H-NMR spectroscopy (Scheme 3) [13]. In addition to the non-racemic derivatives illustrated in Scheme 3, a number of achiral organophosphorus reagents have been found to be useful derivatising agents [14], operating on the basis of Horeau's principle [15].

Several methods have been employed to assay enantiopurity in α-hydroxyphosphonate esters, including, Mosher and other chiral acids [16]a,b,e,f, circular dichroism [16]e, HPLC [16]g, peptide derivatives [16]c and ammonium salts [16]d. Since for our purposes we required a rapid flexible assay, we have selected a non-racemic phosphorochloridite CDA **2** derived from the chiral diamine *N,N′*-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine **1** (Scheme 4) based on the phosphorotriamidite CDA **3** reported recently by Feringa [17] for the determination of enantioselectivity in a range of chiral alcohols, thiols and amines. Indeed, the use of chiral C_2-symmetric diamine based auxiliaries in the design of chiral organophosphorus derivatising agents has been pioneered by Alexakis and co-workers [13]e,f.

We found that although CDA **2** is less stable towards



Scheme 4. (i) 0.5 1,2-$Cl_2(CH_2)_2$, 100°C, 16 h (60%); (ii) $P(NMe_2)_3$, C_6H_6, 96 h; (iii) PCl_3, 2 NEt_3, C_7H_8, 25°C, 16 h (76%); (iv) H_2O, NEt_3 (94%); (v) Esters **6**, $CDCl_3$, 25°C.

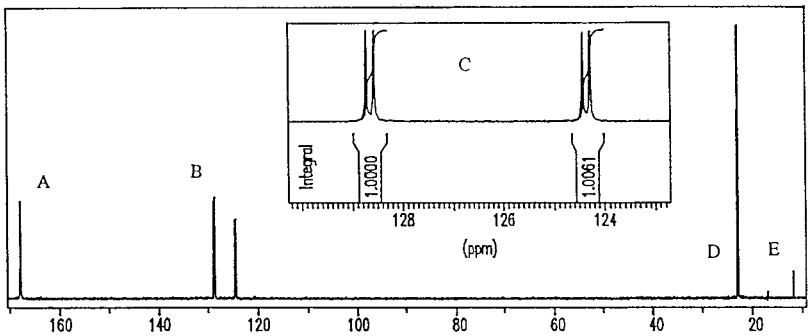


Fig. 1. $^{31}P\{^{1}H\}$-NMR of **5f**; in ppm. A = unreacted **2**; B = P(III) resonances of $\mathbf{5f_x}$ and $\mathbf{5f_y}$; C = expansion of B (data collected as described in Section 4); D = P(V) resonances of $\mathbf{5f_x}$ and $\mathbf{5f_y}$; E = **4** caused by trace hydrolysis of **2**.

hydrolysis than **3** (solutions of **2** in pre-dried $CDCl_3$ begin to hydrolyse to the H-phosphonate ester **4** [18] within one week at ca. 5°C under an atmosphere of dinitrogen) the former is significantly more reactive towards α-hydroxyphosphonate esters (seconds versus several hours respectively at ambient temperature). Moreover, we find that CDA **2** is also a more facile derivatising agent than commercially available Mosher acid chloride. Thus, a $CDCl_3$ solution comprising **2** and triethylamine at concentrations of 0.125 M and 0.25 M respectively reacts rapidly and quantitatively with a range of racemic α-hydroxyphosphonate esters of the form $(MeO)_2P(=O)CHR(OH)$ **6** to afford phosphorus(III)–phosphorus(V) adducts **5** as a mixture of diastereoisomers **x** and **y** (see Fig. 1 and Table 1 for selected data). Under our normal assay procedure (see Section 4) CDA **2** is present in excess over esters **6** (see Fig. 1) and the results displayed in Table 2 have been obtained under these conditions. However, even when **2** is present as the limiting reagent, integration of $^{31}P\{^{1}H\}$-NMR resonances reveals no evidence for kinetic resolution.

It has been reported that the use of a strong base such as triethylamine in conjunction with phosphorochloridite CDAs can lead to side reactions in the derivatisation of some alcohols [13]e. In trial reactions with CDA **2**, we have found that both triethylamine and the milder *N*-methylimidazole result in essentially no difference to measured $^{31}P\{^{1}H\}$ integrations.

2.1.2. Chemical shift dispersion and diastereoisomer resolution

Given the significantly wider chemical shift range afforded by the ^{31}P nucleus over that of ^{1}H, the former has distinct advantages in terms of being able to supply effective chemical shift dispersion and hence the baseline separation necessary for precise integration. Moreover, the presence of both phosphorus(III) and phosphorus(V) nuclei in the same molecule permits a choice of assay label.

In all derivatives of the type **5** we find (Table 2), as other workers have previously, that the greater chemical

Table 1
^{31}P-NMR Parameters for Phosphonate esters, $(MeO)_2P(O)CHR(OH)$ Derivatised using CDA 2

R	δ P(III) [a] (**5x**)	δ P(III) [a] (**5y**)	δ P(V) (**5x**; **5y**)	$\Delta J(\mathbf{x}-\mathbf{y})$
a C_6H_5	127.75(16.8)	122.21(14.2)	23.55; 23.54	+2.6
b 1-$C_{10}H_7$	127.87(17.1)	122.27(14.5)	23.77; 23.68	+2.5
c 2-$C_{10}H_7$	128.13(16.5)	123.37(15.1)	23.47; 23.47	+1.4
d 2-BrC_6H_4	126.95(14.3)	121.55(13.1)	22.93; 22.81	+1.2
e 3-BrC_6H_4	128.78(16.3)	124.02(14.6)	22.74; 22.71	+1.7
f 4-BrC_6H_4	128.68(16.0)	124.40(15.1)	22.83; 22.83	+0.9
g 4-MeC_6H_4	127.64(17.1)	122.16(14.6)	23.78; 23.77	+2.5
h 4-$MeOC_6H_4$	127.91(17.7)	122.53(15.0)	23.85; 23.85	+2.7
i 4-$O_2NC_6H_4$	126.34(10.0)	124.62(13.0)	21.75; 21.74	−3.0
j 2-$O_2NC_6H_4$	129.73(14.6)	126.62(14.8)	21.84; 21.80	−0.2
k 2-$Ph_2PC_6H_4$	128.61(17.4) [b]	122.74(17.1) [b]	23.44; 23.42	+0.3

[a] In $CDCl_3$; 300 K; ppm; 101.268 MHz; $^{3}J_{PP}$ in parentheses (Hz); 52.6 μmol solutions with respect to phosphonate.
[b] $^{5}J_{PP} = 3.0$ Hz observed only to the P(III) nucleus.

Table 2
Measured Enantioselectvities of Racemic $(MeO)_2P(O)CHR(OH)$ Derivatised using CDA 2

R	$\Delta\delta$ P(III) [a]	$\Delta\delta$ P(V) [a]	%(**5x**) − %(**5y**) [b]	E.e. [c]
a C_6H_5	5.54	0.01	50.1:49.9	0.2
b 1-$C_{10}H_7$	5.60	0.09	50.3:49.7	0.6
c 2-$C_{10}H_7$	4.76	0.00	50.1:49.8	0.3
d 2-BrC_6H_4	5.40	0.12	50.0:50.0	0.0
e 3-BrC_6H_4	4.76	0.03	49.7:50.3	0.6
f 4-BrC_6H_4	4.28	0.00	49.7:50.3	0.6
g 4-MeC_6H_4	5.48	0.01	49.5:50.5	1.0
h 4-$MeOC_6H_4$	5.38	0.00	50.2:49.8	0.4
i 2-$O_2NC_6H_4$	1.72	0.01	49.9:50.1	0.2
j 4-$O_2NC_6H_4$	3.11	0.04	49.8:50.2	0.4
k 2-$Ph_2PC_6H_4$	5.87	0.02	50.4:49.6	0.8

[a] In $CDCl_3$; 298 K; ppm; 101.268 MHz.
[b] High frequency resonance first. Determined by automated electronic integration of resonances that had essentially identical peak shapes for each diastereoisomer (Fig. 1).
[c] E.e. of **5** determined as |%**5x** − %**5y**|.

shift dispersion ($\Delta\delta_p$) is found between the phosphorus(III) nuclei (ca. 1.7–5.8 ppm) rather than the phosphorus(V) nuclei (< 0.2 ppm); indeed, the phosphorus(III) dispersions are significantly larger than those reported for related derivatives with a variety of other alcohols, amines and thiols which are commonly found in the range 0.1–2.0 ppm [17].

2.1.3. Data collection and analysis

In order to assay enantiopurity with high precision, it is necessary to be able to integrate the phosphorus(III) resonances of diastereoisomers **5** accurately. This involves not only being able to achieve a sufficiently large base-line separation but also taking account of possible differences in nuclear Overhauser effects and nuclear relaxation times.

All spectra have been recorded at 300 K on a Bruker ARX 250 spectrometer operating at 101.268 MHz for phosphorus. Initial data collection comprised a spectral width of 3049 Hz, centred on the region of the phosphorus(III) resonances and digitised with 8192 points. A pulse width of 3.8 μs was used (ca. 73° tip angle) followed by acquisition over 1.34 s, affording a digital resolution of 0.74 Hz, with inverse-gated ^{1}H decoupling and a pulse delay of 3 s to ensure complete relaxation of all ^{31}P nuclei. Under these conditions, the enantiomeric excess (e.e.) of racemic α-hydroxyphosphonate esters in each case was found to be within 1%. Following enantiopurity measurement, the ^{31}P-NMR spectra were reacquired over 26 316 Hz centred at 100 ppm (0.62 s acquisition; 1.6 Hz digital resolution; 32 K data points; 0.3 s pulse delay and broad-band ^{1}H decoupling) to confirm complete conversion of **6** to **5**, the presence of excess CDA *2* and to obtain phosphorus(V) chemical shifts (Table 1).

One of the principal problems with accurate integration in ^{31}P-NMR spectroscopy is the potentially large range of spin-lattice relaxation times (T_1) found for ^{31}P nuclei which in turn necessitates the selection of a suitable delay time between pulses to allow for complete relaxation [19]. For the purposes of measuring enantiopurity of α-hydroxyphosphonate esters, it is the difference in spin-lattice relaxation times between the measured P(III) nuclei of the two diastereoisomers ΔT_1 which governs the choice of delay time. Consequently, we have measured T_1 times for the P(III) nuclei of **5a–k** at 300 K in $CDCl_3$ solvent using the inversion recovery technique (see Section 4) and the results are reproduced in Table 3 and Fig. 2.

As is evident from the data in Table 3, the T_1 times of the phosphorus(III) nuclei for both diastereoisomers are very similar and ΔT_1[P(III)] is ca. 0.1 s. Consequently, it should be possible to perform analytically sound enantiopurity measurements (via ^{31}P-NMR inte-

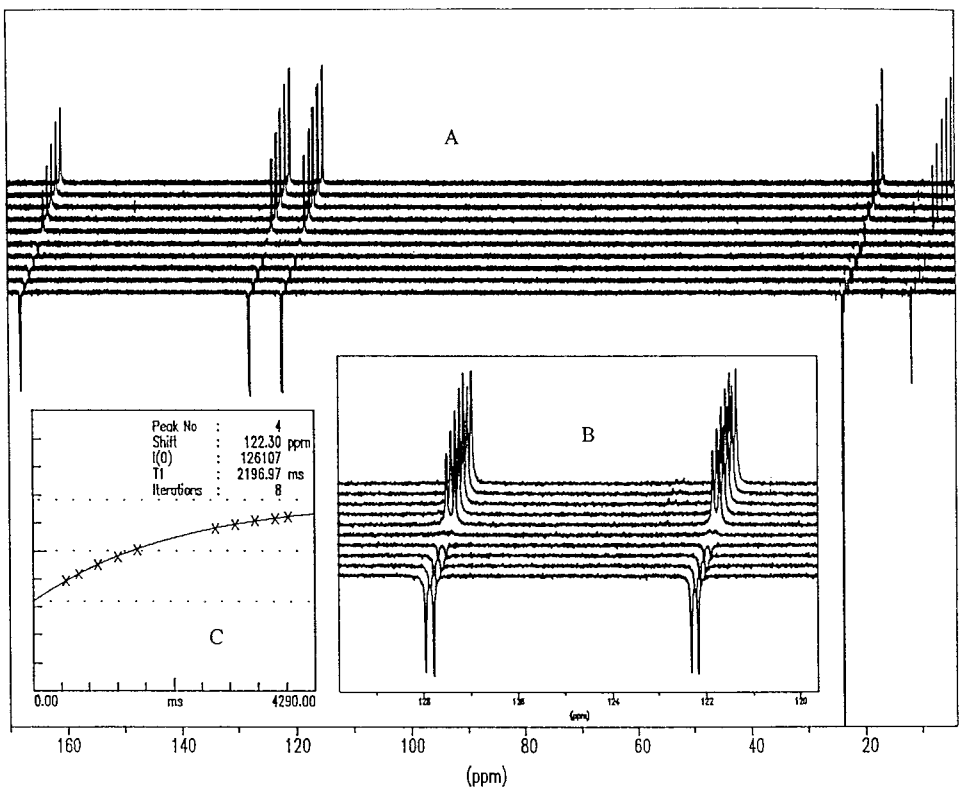


Fig. 2. A = full scale ^{31}P{^{1}H} stacked inversion recovery experiment; B = expansion of P(III) resonance region (see Section 4 for details of acquisition parameters); C = exponential plot of signal intensity versus delay time for the resonance at δ_P 122.3 ppm.

Table 3
Relaxation Parameters for Phosphonate esters, $(MeO)_2P(O)CHR(OH)$ Derivatised using CDA 2

R	T_1P(III)(**x**) [a]	T_1P(III)(**y**) [a]	T_1P(V) [b]	T_1[**2**]	T_1[**4**]
a C_6H_5	2.5	2.4	4.7	2.7	2.2
b 1-$C_{10}H_7$	2.2	2.2	4.0	2.7	2.2
c 2-$C_{10}H_7$	2.1	2.0	3.8	2.5	2.1
d 2-BrC_6H_4	2.3	2.2	4.2	2.6	2.1
e 3-BrC_6H_4	2.4	2.3	4.3	2.8	2.2
f 4-BrC_6H_4	2.3	2.2	4.2	2.8	2.1
g 4-MeC_6H_4	2.3	2.1	4.3	2.6	2.2
h 4-$MeOC_6H_4$	2.2	2.1	3.9	2.7	2.2
i 4-$O_2NC_6H_4$	2.2	2.2	3.9	2.8	2.1
j 2-$O_2NC_6H_4$	2.3	2.3	4.1	2.7	2.1
k 2-$Ph_2PC_6H_4$	1.8	1.7	2.8	2.6	2.1

[a] Determined by inversion recovery in $CDCl_3$; 52.6 μmol; 300 K; 101.268 MHz; units in seconds; values are the average of both lines of the P(III) doublets.
[b] Values given are the average T_1 values of both diastereoisomers.

grations of the P(III) resonances) using a delay time of ca. $5 \times \Delta T_1$[P(III)], ca. 0.5 s. Indeed, comparison of spectra collected with a 0.5 s delay time between pulses (as in Fig. 1) and a 3 s delay reveals no significant difference in the integrated intensities.

Although the samples for T_1 measurements were prepared (and stored prior to examination) under an oxygen-free atmosphere of dinitrogen, the samples were not contained in flame-sealed NMR tubes but in normal push-cap tubes bound with cling-film. Consequently, over the course of the inversion recovery experiment (ca. 10 h), oxygen from the air is likely to have entered the tube. Consequently, we do not wish to place too much emphasis on the absolute T_1 values, which may be slightly lower than true values (indeed, film-sealed samples which were allowed to stand in the laboratory atmosphere for up to 24 h prior to NMR examination afforded T_1 values which were lower by ca. 0.5 s). However, the inversion recovery experiments reported here have all been run under the same conditions as those used in the enantiopurity determinations (vide infra) and therefore should reflect accurately the relative T_1 values in the reaction systems.

Under the above conditions of measurement, the T_1 values have analytical value in helping to select suitable delay times for the determination of enantioselectivities. In support of this, examination of Table 3 reveals that the common components of each sample, unreacted CDA **2** and by-product H-phosphonate **4** [18] have reproducible T_1 values thus attesting to the relative accuracy of the determinations for esters **6**. Interestingly, the ester with the smallest relative molecular mass, **6a** (RMM = 513) has the largest P(III) T_1 (2.5 s) whereas the most massive ester (**6k**, 696) has the smallest (1.8 s); possibly reflecting differences in the molecular correlation times of each molecule in solution [20]. Furthermore, there is a small but definite trend in the T_1 values of the phosphorus(III) nuclei with respect to the ^{31}P-NMR resonance such that the derivatives with the higher frequency resonances possess slightly larger T_1 values, although the differences are very small (ca. 0.1 s). Nevertheless, subsequent analysis of coupling constants and chemical shifts (vide infra) also reveals trends which suggest that those derivatives with the same pattern of coupling constants, chemical shifts and relaxation times possess the same relative stereochemistry and hence the same absolute configuration at the alpha-carbon site.

2.2. Problem 2. Determination of absolute configurations of α-hydroxyphosphonate esters

Being able to determine enantioselectivities readily is, however, only one half of the story. We also need to be able to determine absolute configurations at the α-carbon atoms (C_α) of the α-hydroxyphosphonate esters. To do this unambiguously would require single-crystal X-ray analyses of the diastereoisomers **5** in each

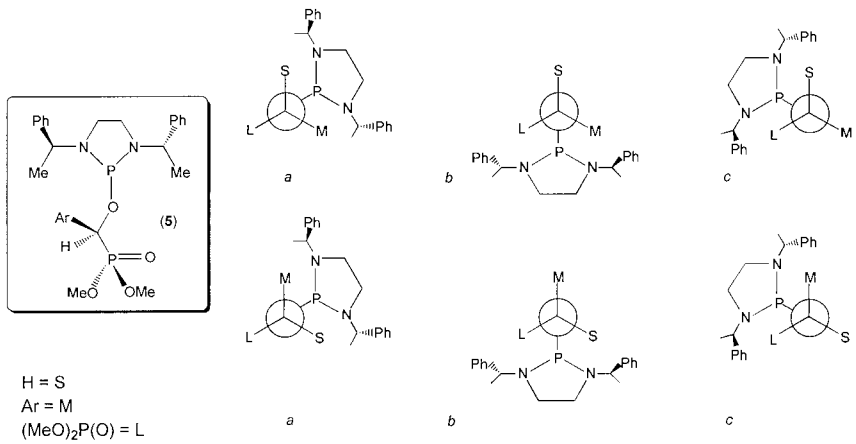


Fig. 3. View of esters down the [C_α–O] bond emphasising the conformations and different dihedral angles between phosphorus(III) and [P]CHAr(OR′) functions. L(large) = $P(O)(OMe)_2$, M(medium) = Ar, S(small) = H.

case examined which is, in practise, an unrealistic prospect.

However, with such a closely related family of compounds, it may be possible to suggest absolute configuration assignments by cross-referencing of the phosphorus(III) ^{31}P chemical shifts reported here to optical rotation measurements on authentic samples reported previously by Hammerschmidt and co-workers [21]. Fortunately, one α-hydroxyphosphonate ester is common to the series studied by both Hammerschmidt and ourselves, namely $(MeO)_2P(=O)CHPh(OH)$ **6a**, and we have therefore worked on the basis of this as a correlation point. Due to the availability of only the one correlation point, it has been necessary to examine carefully spectroscopic features within the series of adducts **5a–k** so that we may infer absolute configurations in the remainder of the series with reasonable confidence.

2.2.1. Correlating absolute configurations

Examination of $^3J_{PP}$ coupling constants in diastereoisomers **5a–k** (Table 1) reveals consistently larger values for the diastereoisomer with the higher frequency ^{31}P-NMR shift (diastereoisomer **x**) in all cases except those derived from 2-NO_2 and 4-NO_2 substituted benzaldehydes. Since, this coupling parameter is likely to be influenced significantly by the [P—O—C—P] dihedral angle through a Karplus relationship [22], we interpret this trend in terms of a similar conformational preference for the corresponding diastereoisomer throughout the series. Energetically more favoured staggered conformational isomers for each epimer are outlined in Fig. 3. The slightly larger $^3J_{PP}$ values of the **x** isomers may indicate a greater preference for the anti-periplanar conformer ***a*** in these isomers, where the larger (L) substituents occupy positions of maximum separation [23].

Examination of the ^{1}H{^{31}P}-NMR spectra (selectively decoupled) of **5a–k** reveals that $^2J_{PH}$ and $^3J_{PH}$ coupling constants between phosphorus(V) (^2J) and phosphorus(III) (^3J) and [P]C*H*RO-, exhibit subtle yet significant trends such that the diastereoisomers of **5** with the high frequency phosphorus(III) resonance (stereoisomer **x**) correlate with the low frequency methine resonance and that the low frequency methine resonance consistently displays the lower $^2J_{PH}$ (Δ^2J_{x-y} negative) and higher $^3J_{PH}$ ($\Delta^2 J_{x-y}$ positive) by ca. 0.3–1.0 Hz (Table 4 and Fig. 4). Such trends seem reasonable since the $^3J_{PH}$ couplings, just as the $^3J_{PP}$ parameters described above, are envisaged to be strongly dependent upon the dihedral angle [P(III)–O–C–H] illustrated in Fig. 3 which, in turn, will be a weighted average of all possible conformations (principally *a*, *b* and *c*). Consequently, these trends in NMR chemical shift and coupling parameters imply a consistency of molecular conformation for each diastereoisomer **x** and **y** due to a consistency of steric interactions resulting from the same relative (and thus in this case absolute) configuration at the alpha-carbon atoms in this family of compounds.

Table 4
^{1}H-NMR Parameters for Phosphonate esters, $(MeO)_2P(O)CHR(OH)$ Derivatised using CDA 2

5	δ_x [a]	δ_y [a]	^2J_x [b]	^2J_y [b]	^3J_x [b]	^3J_y [b]	Δ^2J [d]	Δ^3J [d]
a	5.17	5.20	14.6	15.2	8.0	7.5	−0.6	+0.5
b	6.00	6.11	15.2	15.6	7.3	6.2	−0.4	+1.1
c	5.34	5.38	14.8	15.2	7.5	6.8	−0.4	+0.7
d	5.76	5.95	14.6	15.2	7.6	7.0	−0.6	+0.6
e	5.12	5.16	15.0	15.4	7.6	7.3	−0.4	+0.3
f	5.11	5.14	14.8	15.3	7.6	7.2	−0.5	+0.4
g	5.13	5.17	14.2	14.6	7.7	7.2	−0.4	+0.5
h	5.11	5.16	14.1	14.6	7.6	7.3	−0.5	+0.3
i	6.50	6.58	16.6	17.0	4.0	3.7	−0.4	+0.3
j	5.24	5.26	16.2	16.7	6.1	5.6	−0.5	+0.5
k	6.61 [c]	6.75 [c]	14.8	15.2	9.4	8.6	−0.2	+0.8

[a] Chemical shift of the [P]C*H*R(OH) methine resonance for the diastereoisomers which correspond to the higher frequency (***x***) and lower frequency (***y***) phosphorus(III) resonance respectively.
[b] Coupling between phosphorus(III) (^3J) and phosphorus(V) (^2J) and the methine hydrogen for diastereoisomers **5x** and **5y** in Hz.
[c] $^4J_{PH}$ of 10 Hz observed between the [P]C*H*R(OR′) methine resonance and the Ph_2P phosphorus atom.
[d] Difference in couplings (Hz) between diastereoisomers **x** and **y**, (**x**−**y**).

The empirical data collected in Table 4 suggest that the diastereoisomers corresponding to the high frequency phosphorus(III) and low frequency [P]CHR(OR′) methine resonances of compounds **5** have the same stereochemistry for each derivative which in turn suggests that if we are able to assign absolute configurations to any one of these adducts then, by inference, we have assigned the remainder.

2.2.2. Calibration of the enantiopurity assay

We have prepared scalemic $(MeO)_2P(=O)$-CHPh(OH) using a slightly modified version of the enzyme-mediated method reported by Hammerschmidt [21]. Racemic $(MeO)_2P(=O)CHPh[OC(O)Me]$ is readily obtained upon treatment of $(MeO)_2P(=O)CHPh(OH)$ **6a** with acetyl chloride and triethylamine (Scheme 5). Enzymatic hydrolysis of $(MeO)_2P(=O)CHPh$-[OC(=O)Me] with lipase F—AP 15 affords scalemic $(MeO)_2P(=O)CHPh(OH)$ in 33% yield after column chromatography (NMR analysis of the unpurified product mixture reveals an extremely clean, essentially complete 50% conversion). Polarimetry returns an optical rotation $[\alpha]_D$ of −30.4° ($c = 0.5$, acetone, 20°C) consistent with the dominant enantiomer having the *S* configuration and in agreement with the published procedure [18]. Compositional analysis of this scalemic product using the CDA **2** reveals an e.e. of 83(1)%, in which it is the low frequency ^{31}P resonance which dominates (Scheme 5). Consistently, hydrolysis of the

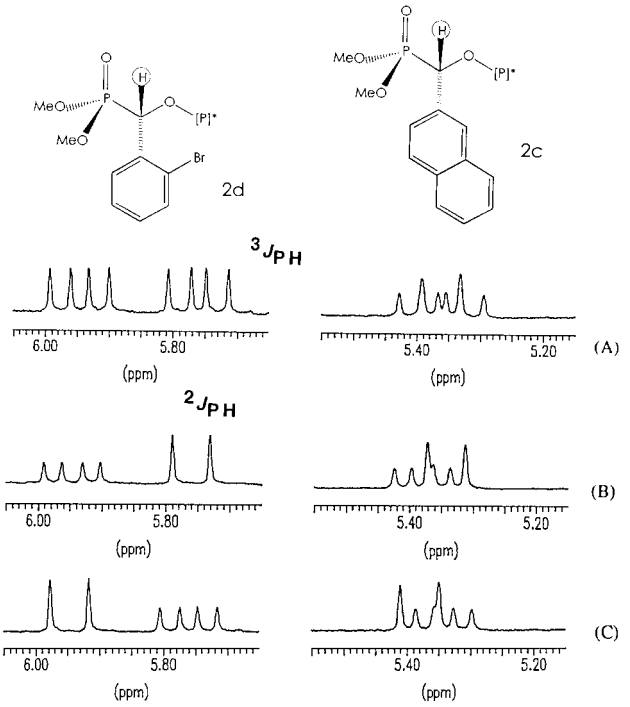
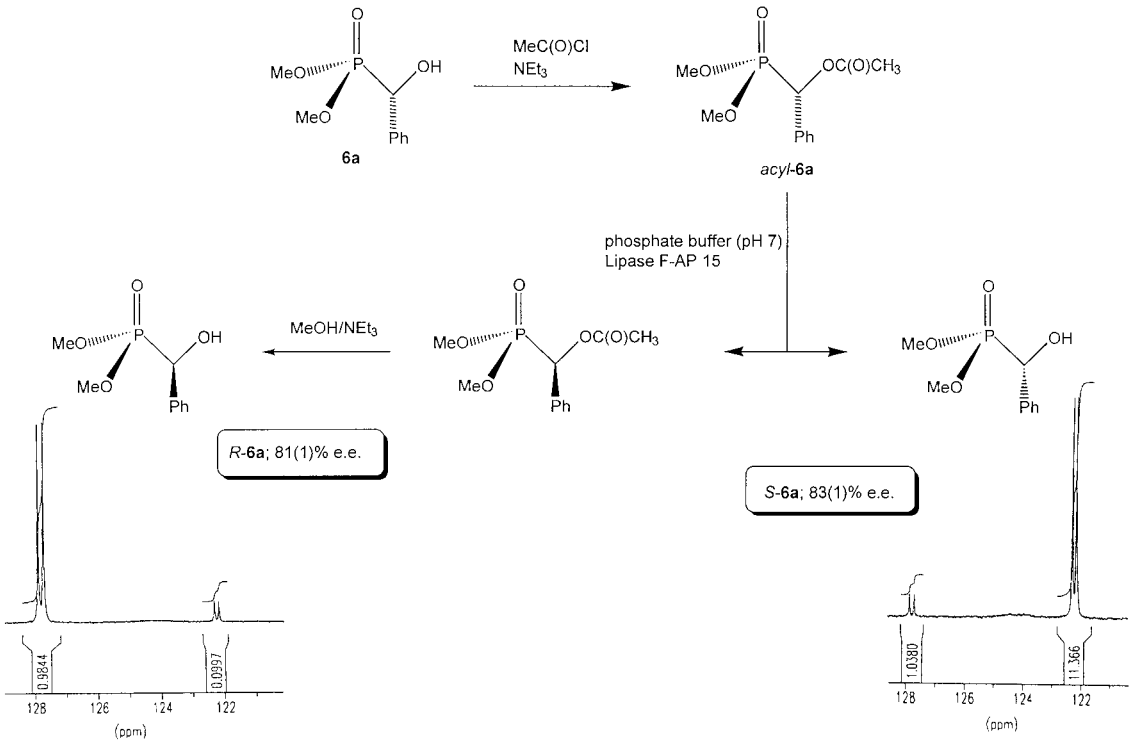


Fig. 4. [P]CHR(OR′) methine hydrogen resonances of both diastereoisomers **x** (low frequency multiplet) and **y** (high frequency multiplet) of **5d** and **5c**. (A) Fully coupled ^{1}H-NMR spectra of **5d** (left) and **5c** (right). (B) ^{1}H{^{31}P} spectra, decoupled selectively at the higher frequency phosphorus(III) (**x**) resonance. (C) ^{1}H{^{31}P} spectra, decoupled selectively at the lower frequency phosphorus(III) (**y**) resonance. [P]* = {*N*,*N*′-bis[1-(*S*)-phenylethyl]-2-chloro-1,3,2-diazaphospholidine.

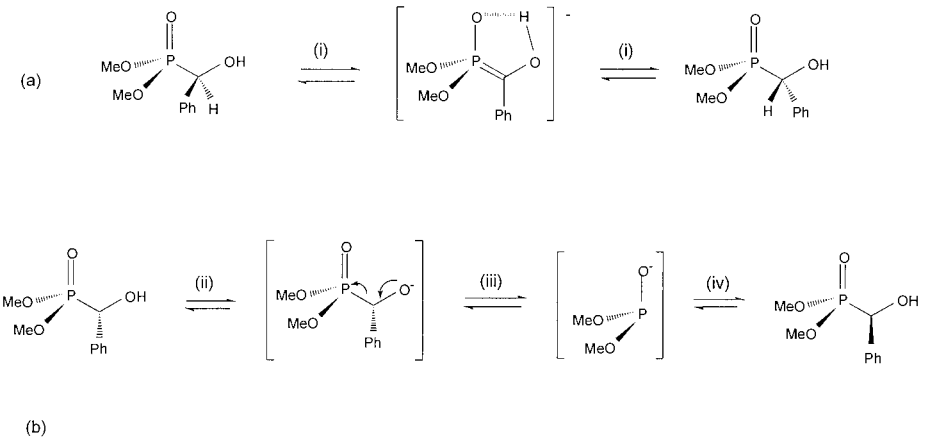
unconverted acetylphosphonate ester with MeOH/NEt_3 (since phosphonate esters are susceptible towards base-catalysed transesterification, the presence of methanol ensures that any exchange is degenerate) affords $(MeO)_2P(=O)CHPh(OH)$ with an optical rotation $[\alpha]_D$ of $+29.2°$ ($c = 0.5$, acetone) and an e.e. of 81(1)% (CDA **2**) in which it is the high frequency ^{31}P resonance which dominates. Consequently, we may assign the lower frequency resonance to the *S* enantiomer and the higher frequency resonance as belonging to the *R* enantiomer and by inference (vide supra) we propose the same order of assignment in all the other benzaldehyde derivatives described herein.

2.3. Problem 3. Configurational stability of α-hydroxyphosphonate esters

Since the catalysts used here are amphoteric (vide infra), it is necessary to confirm that α-hydroxyphosphonate esters are configurationally stable under conditions commensurate with our catalytic protocols. Racemisation may be envisaged to be possible through two principal mechanisms as shown in Scheme 6; (a) deprotonation at C_α followed by non-face-selective reprotonation of an intermediate prochiral enolate and (b) reversible aldehyde extrusion. Mechanism (a) is perhaps the less likely of the two but nevertheless, we have probed this possibility by treating



Scheme 5. Lipase (F-AP 15) catalysed hydrolysis of *rac*-$(MeO)_2P(O)CHPh(OAc)$ and partial $^{31}P\{^1H\}$-NMR spectra of derivatised fractions.



Scheme 6. Possible mechanisms for base-catalysed racemisation of α-hydroxyphosphonate esters. (i) Base (0.5 mol equiv. NEt_3); $CDCl_3$, D_2O; (ii) Base; (iii) aldehyde extrusion; (iv) $RCHO,H^+$.

$(MeO)_2P(O)CHPh(OH)$ with triethylamine (1 equiv.) in $CDCl_3$ containing excess (ca. 2–30 equivs.) D_2O and testing for incorporation of deuterium at C_α. No such incorporation was observed over a period of three weeks at ambient temperature. The operation of reversible extrusion mechanism (b) was probed by a crossover experiment in which $(MeO)_2P(O)CHPh(OH)$ (δ_P 24.5 ppm) and 4-BrC_6H_4CHO (0.8 equiv.) were mixed in $CDCl_3$ solvent in the presence of triethylamine (1 equiv.). After two weeks at ambient temperature (ca. 20°C), $^{31}P\{^1H\}$ and ^{1}H-NMR spectroscopy did reveal evidence for the formation of the expected product of crossover, $(MeO)_2P(O)CH(CHC_6H_4Br\text{-}4)(OH)$ (δ_P 24.0 ppm) although in only very low levels ($< 2\%$); addition of a sample (ca. 20 mg) of pure $(MeO)_2P(O)CH(CHC_6H_4Br\text{-}4)(OH)$ to the final product mixture confirmed the presence of this material in the reaction mixture suggesting that although such a mechanism is possible under the conditions applied it is extremely slow. Consequently, this lack of evidence for facile base-catalysed racemisation of α-hydroxyphosphonate esters suggests that the stereochemical integrity of the Pudovik products is maintained under conditions compatible with catalysis as long as the reaction times are held to days (and below) rather than weeks. Thus, since most of the catalytic runs reported here with amino alcohols are complete on the timescale of hours, we can be confident of operating under a regime in which product racemisation is not a serious problem.

Since the most effective catalyst systems contain metal ions (vide infra), the possibility of metal-catalysed racemisation of the product α-hydroxyphosphonate esters was examined. Such a process may be facilitated by a similar overall scenario to Scheme 6 in which binding of the α-hydroxyphosphonate ester to a metal centre through a chelate ring should be favourable [24] and should result in a lowering of the pK_a of adjacent hydrogen atoms. Thus, a solution comprising $(MeO)_2P(O)CHPh(OH)$, $Zn(OSO_2CF_3)_2$ (10 mol%) and D_2O (12.5 equiv.) in $CDCl_3$ was allowed to stand under an atmosphere of nitrogen for 17 days at ambient temperature and although H/D exchange occurred at the hydroxy site (broad resonance at δ_H 3.2), no incorporation of deuterium at the alpha carbon site was observed by ^{1}H-NMR spectroscopy. Furthermore, when the same experiment was performed in the presence of NEt_3 (1 mol equiv.) this result was unaffected. The alternative mechanistic pathway, reversible aldehyde extrusion, has been probed by treating $(MeO)_2P(O)CHPh(OH)$ and 4-BrC_6H_4CHO (1 mol equiv.) with $Zn(OSO_2CF_3)_2$ (10 mol%) both in the absence and presence of NEt_3 (1 equiv.); the former protocol results in $< 2\%$ aldehyde exchange after 17 days at 25°C whilst the latter protocol produced ca. 10% exchange after 7 days at 25°C. We conclude that racemisation via the expected mechanisms may potentially be problematic under certain conditions but may be minimised if (i) both Lewis acid and Lewis base catalysts are used at low loading levels and (ii) hydrophosphonylation is performed on a timescale of hours rather than days under ambient conditions.

2.4. Problem 4. Catalyst design in the asymmetric Pudovik reaction

2.4.1. Introduction

The Pudovik reaction may be run under several experimental protocols; thermal [25], sonochemical [26], basic [27], acidic [28] and metal-mediated [29]. With the exception of the ultrasound catalysed process, which is thought to proceed via a radical mechanism, the generally accepted mechanism for the Pudovik reaction involves the attack of a $\sigma^3\lambda^3$ phosphorus nucleophile [30] on the carbon atom of the [C=X] reagent (X = O, S, CR_2, NR). In order to facilitate this reaction, it is necessary to generate a lone-pair of electrons on phos-

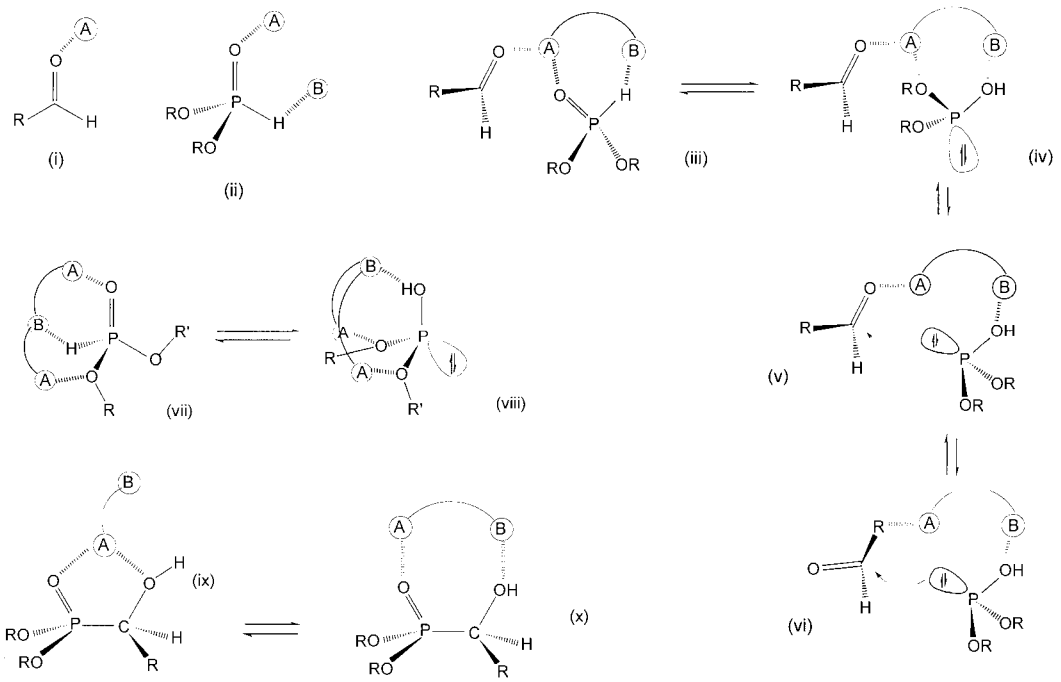
phorus by a formal reduction of the $\sigma^4\lambda^5$ H-phosphonate starting material (Scheme 2). Very few protocols have combined this redox chemistry with the introduction of asymmetry through chiral catalysis and those that have, invariably involve complex and/or aerobically-sensitive catalyst systems which afford modest enantioselectivities (e.e. values) [31].

2.4.2. Catalyst design strategy

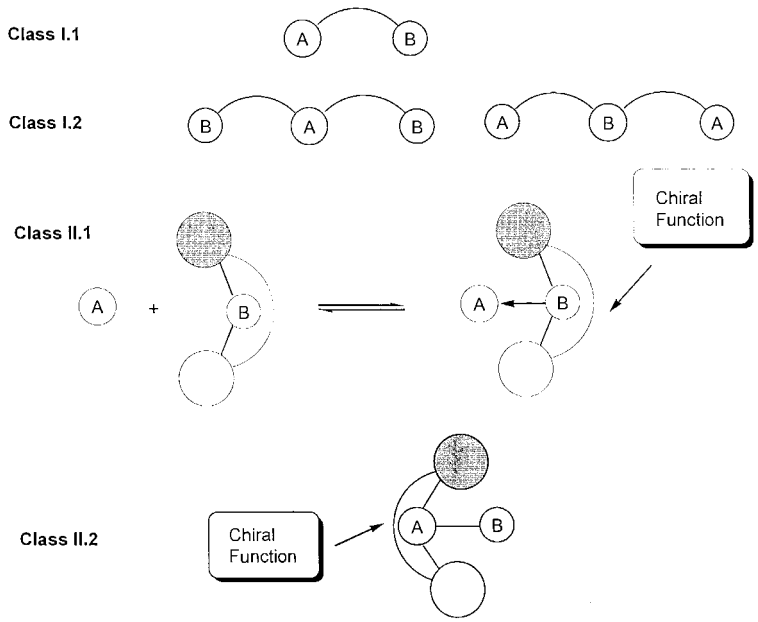
The binding and activation of carbonyl molecules may be achieved using either a single [32] or multiple Lewis acidic binding site (based on either hydrogen-bonding [33], coordinate dative bonding [34] or a combination of the two [35]). Similarly, a Lewis acid should be capable of binding the phosphoryl oxygen atom of an H-phosphonate ester and lowering the pK_a such that deprotonation should be significantly more facile [36]. In a similar fashion, it is possible to bind and activate both substrates simultaneously at the same or different Lewis acid sites. This has the advantage of manipulating the Pudovik reaction towards an intramolecular addition wherein the enthalpy of binding both substrates offsets the unfavourable entropy involved in bringing three species together in a single transition state. However, simultaneous activation also presents a potentially serious problem in an addition process such as the Pudovik reaction; the product α-hydroxyphosphonate ester is also able to bind to the catalytic site thus leading to competitive product inhibition. This problem may be expected to be particularly serious in those cases where a single metal centre acts as the Lewis acid due to chelate ring formation [Scheme 7(ix)] [24]. The problem should be less severe with a bimetallic catalytic site but is always likely to be problematic when the binding profiles of both substrates and products are similar.

In Scheme 7 are highlighted a selection of interaction motifs between reagents and products of the Pudovik reaction and putative catalysts. The binding topology of the catalyst sites is built around both Lewis acidic (A) and Lewis basic (B) functionalities; they are amphoteric molecules [11]b. Consequently, different classes of catalyst may be envisaged depending upon the nature and disposition of A and B sites. These different classes may both interact differently with substrates and reagents and may suffer from differing degrees of competitive product inhibition [e.g. Scheme 7(ix)–(x)].

We have selected two classes of hydrophosphonylation catalyst for examination, each class divided further into two sub-classes I.1, I.2 and II.1 and II.2 (Scheme 8). Class I.1 systems are based on a pair of binding sites, one Lewis acidic and one Lewis basic, in which the acidic site is a hydrogen-bond donor and the basic site is a hydrogen-bond acceptor (organo-nitrogen base). Class I.2 systems are analogous but contain multiple interaction sites (e.g. two acid and one base site or one acid and two base sites). Class II.1 and Class II.2 systems both contain a single acid and single base site, the Lewis acid function being a metal ion and the base function being either an organo-nitrogen, organo-oxygen or organo-carbon group. The principal difference between the two classes is that in the former, the Lewis



Scheme 7. Possible interaction modes between substrates/products of the Pudovik reaction and putative catalytic sites.



Scheme 8. Four classes of amphoteric catalyst system for the hydrophosphonylation of carbonyls. *Class I.1*: One hydrogen-bonding Lewis acid (A) and one hydrogen-bonding Lewis base (B) site. *Class I.2*: Multiple hydrogen-bonding Lewis acid and/or Lewis base sites. *Class II.1*: One metal ion Lewis acid and one Lewis base site, which may act also as a donor ligand to the metal. *Class II.2*: One metal ion Lewis acid and one Lewis base site, the latter an oxygen, carbon or nitrogen function bound covalently and directly to the metal ion.

base site doubles as a chiral ligand whose interaction with the Lewis acidic metal is reversible whilst in the latter class, Lewis acid and Lewis base sites are directly bonded covalently within a chiral environment (Scheme 8).

2.4.3. Class I.1 catalysts

In 1983 Wynberg and co-workers reported that chiral amino alcohols, such as the cinchona alkaloids quinine and quinidine, catalysed the addition of dimethyl-H-phosphonate to 2-nitrobenzaldehyde with an enantioselectivity $< 28\%$ [16]a. Since amino alcohols are examples of amphoteric (Class I) reagents containing Lewis basic (nitrogen) and hydrogen-bonding Lewis acidic (hydroxyl group) functions, we envisage that both functions play a part in facilitating this transformation. Indeed, in their original report the authors comment that esterification of the hydroxy group results in complete loss of stereoselectivity. In our hands, we were unable to achieve the same levels of both catalytic turnover and

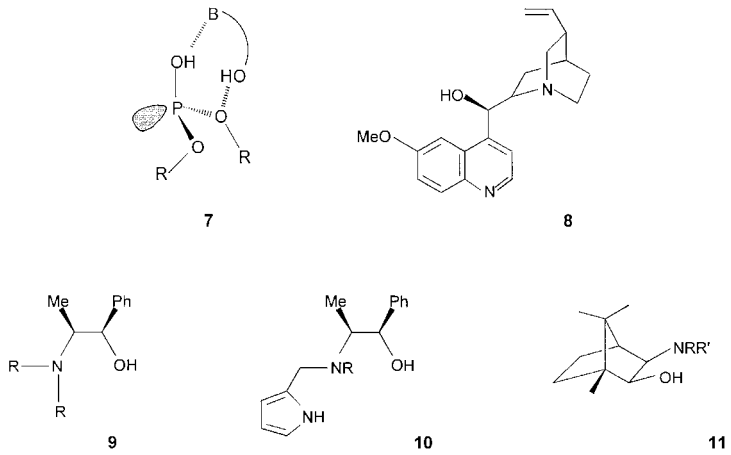
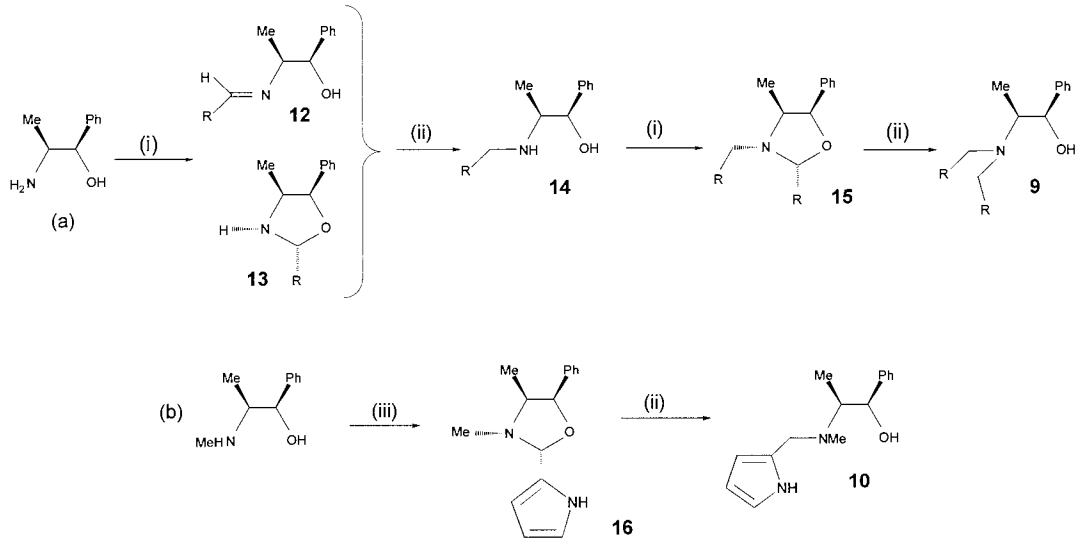
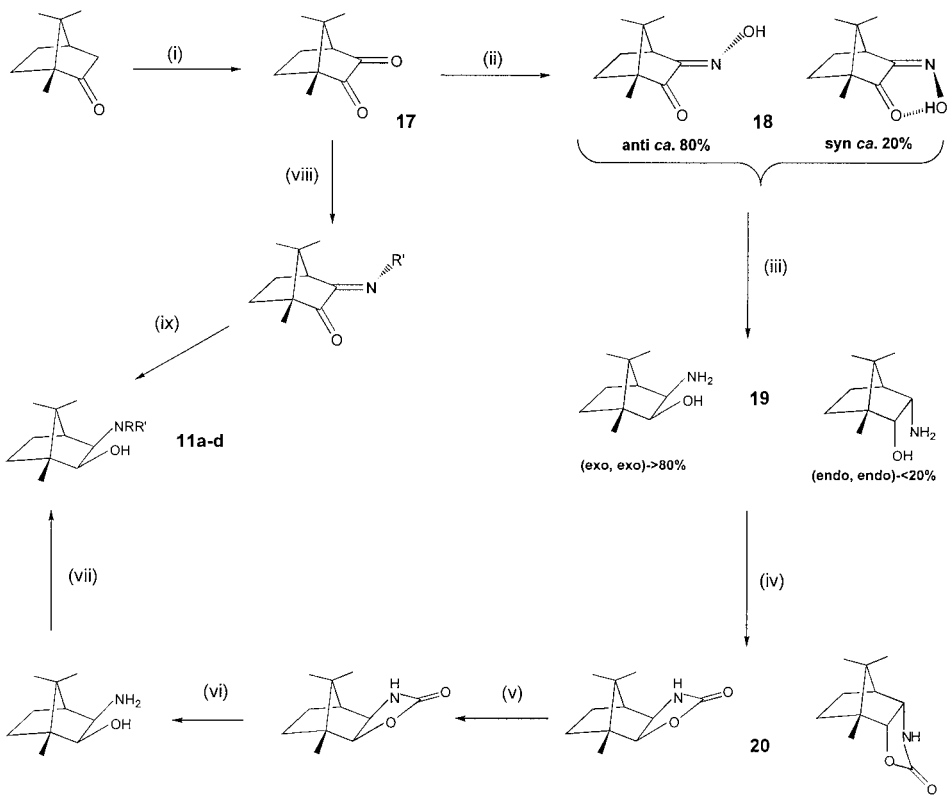


Fig. 5. R = alkyl, aryl; B = Base. **8** quinine. **9a** R = Me, **9b** R = $C_6H_4CH_2$, **9c** R = 3,5-$(MeO)_2C_6H_2CH_2$. **10** R = Me. **11a** R = R′ = Me; **11b** R = H, R′ = ^{i}Pr; **11c** R = H, R′ = ^{n}Bu; **11d** R = H, R′ = Et.



Scheme 9. (i) RCHO (R = C_6H_5 **a** series; 3,5-$(MeO)_2C_6H_3$ **b** series); (ii) $LiAlH_4$; (iii) 2-$CHOC_4H_3NH$.

enantioselectivity of this reaction under the conditions reported. However, changing solvent from toluene to CH_2Cl_2 and moving from 2-nitrobenzaldehyde to unsubstituted benzaldehyde resulted in clean catalysis. In addition, we have assayed a range of amphoteric chiral amino alcohol systems as catalysts for the model addition reaction of dimethyl-H-phosphonate to benzaldehyde, the results of which are described below.



Scheme 10. (i) SeO_2, Ac_2O, reflux 8 h; NaOH, H_2O; steam distil (78%); (ii) $[H_3NOH]Cl$, EtOH, NaOAc, 48 h 25°C (88%); (iii) $LiAlH_4$, Et_2O, 3 h 25°C; NaOH, H_2O; (iv) $(EtO)_2C=O$; (v) Recrystallise Et_2O–hexane (1:2 v/v) (31%); (vi) NaOH, H_2O; (vii) MeI (xs), NaOH (R = R′ = Me); (viii) $R'NH_2$, H^+ (R′ = ^{i}Pr, Bu, Et; R = H; 65–83%); (ix) $NaBH_4$, EtOH (42–58%).

2.4.3.1. Syntheses of chiral amino alcohols. We have selected a number of chiral amino alcohols, **8–11** as shown in Fig. 5, which vary in several important features, (i) steric manifold, (ii) flexibility and (iii) the number of hydrogen bonding interactions possible. Amino alcohols **8–10** are based on a flexible, chiral backbone where the nitrogen-bound substituent may be varied. The camphor backbone of **11a–d** provides a more rigid framework which may, in turn, promote more intimate contact between the amphoteric catalyst and the active phosphonylating species. Amino alcohols **9–11** have been prepared by modifications of literature procedures (Schemes 9 and 10) [37–43].

2.4.3.2. Assaying Class I.1 catalysts in the asymmetric Pudovik reaction. Compounds **8–11** have been screened as catalysts for the hydrophosphonylation (at ca. 296 K) of benzaldehyde (PhCHO) using dimethyl phosphite [$(MeO)_2P(O)H$], each at 2.0 M concentration with a catalyst concentration of 0.2 M concentration (10 mol%) unless noted otherwise. Solvent systems, reaction times, yields, enantioselectivities and absolute configurations are reproduced in Table 5 and complete details presented in Section 4.

One potential problem associated with the use of secondary amino alcohol catalysts such as **11b − d** is the possibility of oxazolidine formation between the aldehyde and the catalyst, in a similar manner to established reactions with ephedrine (see Scheme 9). Such a side-reaction would give rise to a nitrogenous catalyst with a significantly different structural profile to that desired, specifically it would remove the hydroxyl hydrogen and consequently the possibility of further hydrogen bonding. Amino alcohol catalysts **11c** and **11d** were indeed found to react with benzaldehyde generating the corresponding oxazolidines (**21a,b** Scheme 12) during catalysis albeit in low yields. Treatment of amino alcohol **11c** with benzaldehyde in toluene solution at 80°C furnished the corresponding *R*-oxazolidine (confirmed by n.O.e. experiments) **21** in ca. 95% diastereoselectivity. This mixture was shown subsequently to be a poor catalyst for the Pudovik reaction, less than 1% of α-hydroxyphosphonate ester being detected after 48 h. Since amino alcohol **11c** affords 100% conversion to α-hydroxyphosphonate ester within 24 h (25°C), we can be confident that oxazolidine **21** does not influence the observed stereoselectivity of the catalytic run. We presume that this inability to catalyse reaction effectively is connected to steric effects of the nitrogen base being contained within a ring. Indeed, we have subsequently exploited the lack of catalytic activity of polycyclic oxazolidines in Class II.1 and II.2 catalyst systems (vide infra).

Our working hypothesis for Class I.1 catalysts is that enantioselectivity results from intimate chemical interaction between the $\sigma^3\lambda^3$ secondary phosphite tautomer and the corresponding amino alcohol through both NH and OH hydrogen bonds (possibly as in **7**, Fig. 5). However, in order for this chelation to result in effective stereocontrol, it is necessary for the hydrogen-bonding interactions to induce a pronounced conformational preference in the alkoxy residues of the phosphito anion which in turn controls the facial approach of a carbonyl substrate. For this to be successful, three criteria must be met; (i) chelate ring formation via hydrogen bonding should not be fluxional on the timescale of the phosphonylation reaction, (ii) hydrogen bonding should occur preferentially at only one of the phosphite alkoxy groups, failure to do so would lead to diastereoisomers, and (iii) effective control over the conformations of the alkoxy residues may be best achieved through sterically demanding substituents on the amino alcohol in close

Table 5
Rate and Selectivity Data in the Catalysed Addition of $(MeO)_2P(O)H$ to PhCHO

Catalyst[a]	Solvent	Yield (%)	Time (h)	ATR[b]	E.e.[c,d]	*R*/*S*[d]
8	THF	> 95	96	> 99	2.9(2)	*S*
8	CH_2Cl_2	> 95	96	> 99	5.4(3)	*S*
8	mix[e]	> 95	96	> 99	4.5(2)	*S*
9a	toluene	> 98	96	> 102	0[f]	–
9b	toluene	2	144	1.4	–	–
9c	toluene	2	168	1.2	–	–
10	toluene	> 98	18	> 544	1.0(1)	*S*
11a	toluene	92	648	14	8.3(7)	*S*
11b	toluene	> 94	27	> 348	1.8(5)[g]	*S*
11c	toluene	> 99	24	> 413	0[f]	–
11d	toluene	> 99	24	> 413	0[f]	–
23[h]	toluene	0	24	–	–	–
23[i]	toluene	18	168	21	26(1)	*S*
23[j]	toluene	42	216	39	42(1)	*S*
23[k]	toluene	99	0.3	66000	4(1)	*S*
24	toluene	< 8	> 500	3	–	–
24[l]	toluene	> 97	0.25	> 77600[m]	6(1)	*R*
8[l]	toluene	> 95	0.1	> 190000[m]	9(1)	*S*
11a[l]	toluene	> 95	0.1	> 190000[m]	2(1)	*S*

[a] All catalytic runs were performed at 298 K with PhCHO and $(MeO)_2P(O)H$ substrates at 2.0 M in the solvents indicated and 10 mol% catalyst loading in each run except those with **11a** and **23** catalysts which were 5 mol%.
[b] Average turnover rate h^{-1} ($\times 10^{+3}$).
[c] In %; e.s.d values determined using the equation $\{\Sigma_n(x_i - x)^2/n(n-1)\}^{1/2}$ where x is the mean value of n (at least 5) determinations [51].
[d] Determined by $^{31}P\{^1H\}$-NMR spectroscopy using CDA **2**.
[e] CH_2Cl_2:toluene (1:1 v/v).
[f] No enantioselectivity observed by the assay procedure of CDA **2**.
[g] Sample analysed after washing with toluene to remove the catalyst (see text).
[h] No added $Zn(OSO_2CF_3)_2$ or NEt_3.
[i] $Zn(OSO_2CF_3)_2$ (5 mol%).
[j] $Zn(OSO_2CF_3)_2$ (5 mol%) and NEt_3 (5 mol%).
[k] $Zn(OSO_2CF_3)_2$ (5 mol%) and NEt_3 (1 equiv.).
[l] $ZnEt_2$ at 5 mol%.
[m] These represent minimum values; actual ATR values may be substantially higher.

proximity to the hydroxy function. We believe that the most effective levels of stereocontrol in the Pudovik reaction require that all three criteria be satisfied.

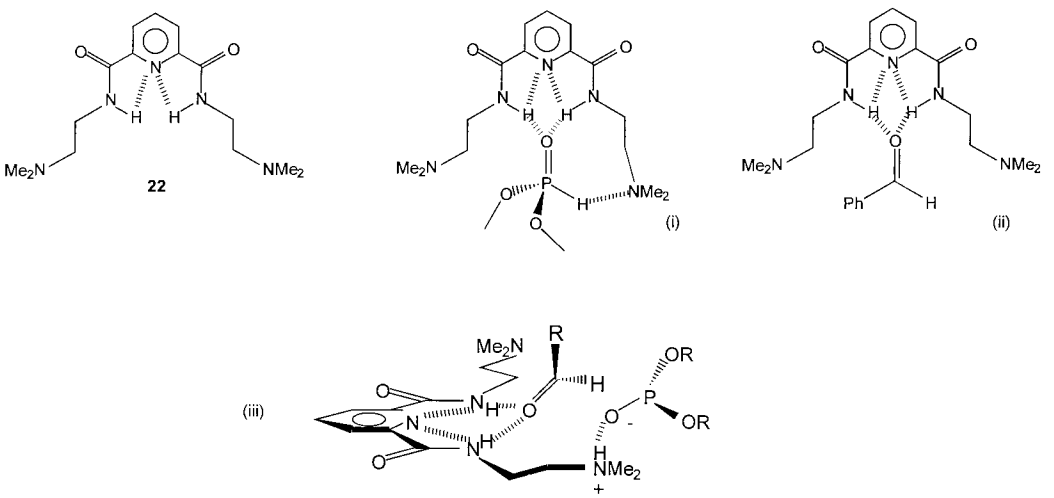
As revealed in Table 5, none of the amino alcohols screened were found to afford significant stereoselectivity in the trial Pudovik reaction. Although it is difficult to pin-point precise reasons for the poor selectivity several comments can be made in the light of the above criteria of our working hypothesis.

Wynberg et al. report the highest enantioselectivities (e.e. 28%) in the quinine and quinidine catalysed Pudovik reaction with *o*-nitrobenzaldehyde whilst *o*-chlorobenzaldehyde returns an e.e. of only 10% [16]a, [44]. In light of this, an e.e. of 2–5% in the quinine catalysed hydrophosphonylation of benzaldehyde is perhaps not unreasonable considering the reduction in steric demand at the reactive carbonyl carbon atom. These authors also report that hydroxyl group binding is important since acylation of this function in quinine results in zero enantioselectivity and that enantioselectivity increases as the size of the phosphorus-bound alkoxy substituent R increases (**7** in Fig. 5) consistent with a greater steric effect through preferred orientations of these functions. We had envisaged that, should hydroxyl hydrogen bonding be important, solvent effects may influence enantioselectivity. Specifically, moving from a hydrogen bond acceptor solvent such as THF to toluene or CH_2Cl_2 should result in increased enantioselectivity. This does appear to be the case (Table 5) although the increase is small. Two further scenarios may also be envisaged to contribute to low enantioselectivities; the relatively weak nature of the hydrogen bonding [45] (each hydrogen bond is worth ca. 4–40 kJ mol^{-1}) may result in decomplexation and consequently a lessening of the influence that the chiral functionalities can have over the active site phosphorus atom and secondly, even in chelate ring formation, the chiral functions may be too far removed from the phosphorus atom to influence aldehyde face control effectively. Consequently, we have moved away from Class I.1 catalysts based on simple chiral amphoteric amino alcohols and focused attention on developing more potent systems.

2.4.4. Class I.2 catalysts

Whereas Class I.1 catalysts comprised essentially two hydrogen-bond interactions, Class I.2 systems are envisaged to have multiple interaction sites and, ultimately, a more rigid binding interaction profile. However, in our initial investigations of Class I.2 type catalysts we wished to lay the foundations for more advanced systems by developing a model system capable of (i) binding the carbonyl via hydrogen bonding better than the H-phosphonate ester, (ii) activating the H-phosphonate and (iii) facilitating the hydrophosphonylation reaction. Considerations of enantioselectivity were not addressed in this model study since we needed to answer four important questions before tackling the more involved process of building in asymmetry. (1) Could we design a compound which would interact with a planar C_s symmetric carbonyl such as benzaldehyde more strongly than a pyramidal C_s symmetric substrate such as dimethyl-H-phosphonate; (2) would that compound also activate the H-phosphonate substrate; (3) would that compound act as a hydrophosphonylation catalyst and (4) is competitive product inhibition likely to be a problem? Each of these questions is addressed below.

Compound **22** is an example of a [—B—A—B—] type molecule containing two basic dimethylamino functions (B-sites) tethered to a pyridinedicarboxamide framework. The pyridine nitrogen atom results in preorientation of the carboxamide functions through hydrogen bonding [46] whilst still being available to hydrogen bond to both carbonyl and H-phosphonate substrates



Scheme 11. Amphoteric receptor **22**. Possible modes of interaction and activation of (i) dimethyl-H-phosphonate; (ii) benzaldehyde and (iii) carbonyl and phosphito anion simultaneously.

Table 6
^{1}H-NMR titration data for the interaction of amphoteric receptor 22 with dimethyl-H-phosphonate

[Receptor][a]	[$(MeO)_2$-P(O)H][a]	δ_H [b]	$\Delta\delta_H$ [b]	1/[$(MeO)_2$-P(O)H][c]	$1/\Delta\delta_H$
0.01	–	8.01	–	–	–
0.01	0.095	8.34	0.33	10.53	3.03
0.01	0.148	8.52	0.51	6.76	1.96
0.01	0.150	8.55	0.54	6.67	1.85
0.01	0.167	8.59	0.58	5.99	1.72
0.01	0.199	8.70	0.69	5.03	1.45
0.01	0.353	9.09	1.08	2.83	0.93

[a] Mol dm^{-3}.
[b] ppm.
[c] Mol^{-1} dm^3.

[Scheme 11(i) and (ii)]. The carboxamide hydrogens were identified in the ^{1}H-NMR spectrum as a broadened triplet resonance (coupling to the adjacent methylene hydrogens) at δ_H 8.20 ($\Delta_{1/2}$ 17 Hz, 0.1 M, $CDCl_3$, 298 K) which diminished in intensity upon treatment with D_2O due to chemical exchange. Having synthesised **22**, we must address Problem 1; interaction studies.

An interaction between the phosphonyl oxygen atom of $(MeO)_2P(O)H$ and the carboxamide hydrogens of receptor **22** is revealed from ^{1}H-NMR titrations experiments (possibly as illustrated in Scheme 11). Thus, the carboxamide hydrogen chemical shift is displaced from δ_H 8.01 (C_6D_6, 1×10^{-2} M) to sequentially higher frequency upon being treated with increasing amounts of H-phosphonate (Table 6). Similar ^{1}H-NMR titration experiments with benzaldehyde as guest molecule (possibly as shown in Scheme 11) reveal similar perturbations in carboxamide chemical shifts (Table 7). Subsequent construction of the respective 1:1 isotherms, as double reciprocal plots [47], support 1:1 complex formation although in both cases, interaction of receptor and guest is relatively weak, $K_{11}(P) = 0.34$ mol^{-1} dm^3 and $K_{11}(A) = 0.53$ mol^{-1} dm^3 respectively (Fig. 6a,b). Thus, although host–guest interactions are weak (host–guest

Table 7
^{1}H-NMR titration data for the interaction of amphoteric receptor 22 with benzaldehyde

[Receptor][a]	[PhCHO][a]	δ_H [b]	$\Delta\delta_H$ [b]	1/[PhCHO][c]	$1/\Delta\delta_H$
0.01	–	8.01	–	–	–
0.01	0.065	8.37	0.36	15.38	2.78
0.01	0.118	8.65	0.64	8.47	1.56
0.01	0.129	8.72	0.71	7.75	1.41
0.01	0.143	8.78	0.77	6.99	1.30
0.01	0.147	8.82	0.81	6.80	1.24
0.01	0.238	9.16	1.15	4.20	0.87

[a] Mol dm^{-3}.
[b] ppm.
[c] Mol^{-1} dm^3.

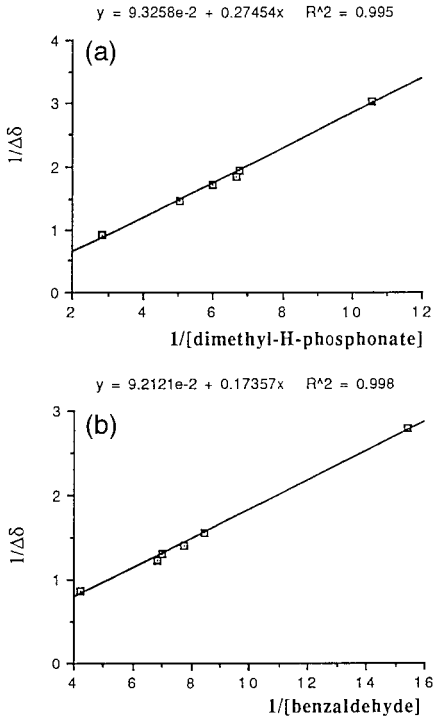


Fig. 6. Double reciprocal plots of the 1:1 binding isotherms for the interaction of amphoteric receptor **22** with ligand L in C_6D_6 solvent (300 K). (a) L = $(MeO)_2P(O)H$ and (b) L = PhCHO. Data is analysed according to the equation; $1/\Delta = 1/\{\Delta_{11}\cdot K_{11}\cdot[L]_o\} + 1/\Delta_{11}$ (see Section 4 for further details).

binding in enzyme systems may typically be several orders of magnitude greater than this), it is clear that the interaction of receptor **22** with benzaldehyde is quantitatively similar to that with $(MeO)_2P(O)H$, although ca. 1.5 times larger in the case of the aldehyde. The significance of such small differences in interaction constant have yet to be investigated.

We chose to tackle Problems 2 and 3 together since active catalysis would entail activation of the H-phosphonate reagent (the Pudovik reaction does not proceed at a measurable rate at ambient temperature in the absence of **22**). As expected, compound **22** is an effective catalyst for the Pudovik reaction between PhCHO and $(MeO)_2P(O)H$ (2 M in each component) in dry toluene solvent at 298 K under a dinitrogen atmosphere, at a catalyst loading of 5 mol%, affording α-hydroxyphosphonate ester $(MeO)_2P(O)CHPh(OH)$ as the sole product. Under these conditions, ca. 40% of **22** will be bound by H-phosphonate and ca. 51% by aldehyde [48] but unfortunately, the interaction constants are not sufficiently large to achieve catalyst saturation at suitable concentration levels, higher concentrations lead to product precipitation, so that our kinetic analysis described below was not achieved under saturation conditions.

Analysis of rate data according to second order kinetics [49] affords a rate constant of 5.9×10^{-2} mol^{-1}

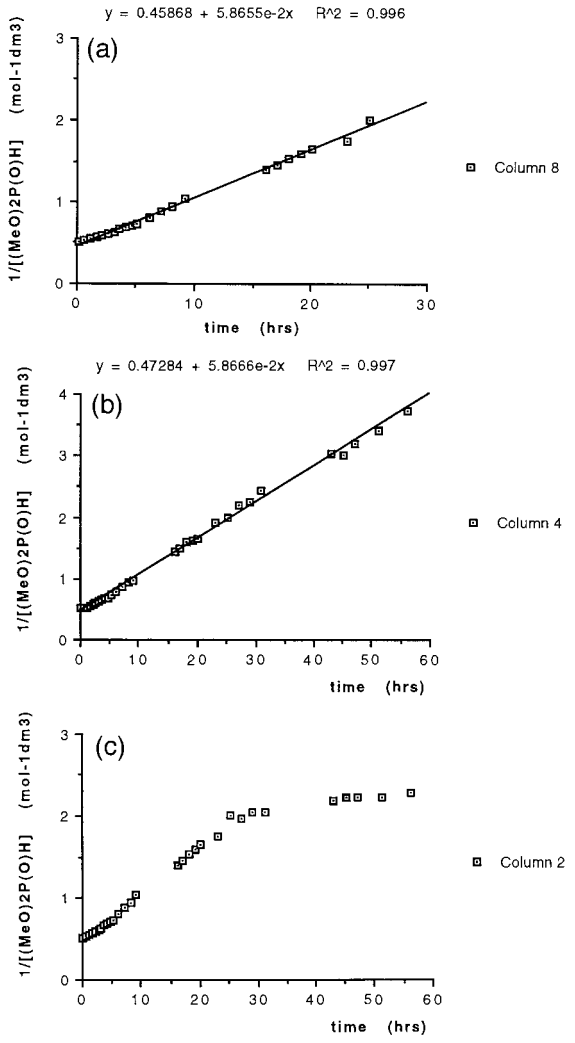


Fig. 7. Second order kinetic plots for the reaction between PhCHO [A] and $(MeO)_2P(O)H$ [P] in toluene solvent (300 K), according to the equation $1/[P] = k_2 \cdot t + 1/[P_o] \cdot [P]_o = [A]_o = 2.0$ M; [Catalyst] = 0.1 M. (a) Catalyst = **22** (ca. 2 half-lives, ca. 15 turnovers); (b) catalyst = NEt_3 (ca. 3 half-lives, ca. 17 turnovers); (c) catalyst = **22** (ca. 3 half-lives, ca. 17 turnovers).

dm^{-3} h^{-1} which is comparable to that obtained when using NEt_3 as a catalyst (5 mol%) under exactly analogous conditions (Fig. 7a,b) [2]. Neglecting any inherent differences in basicity, since **22** contains two basic functions per molecule, **22** is approximately half as active a catalyst as is NEt_3. Indeed, the presence of amino groups in **22** is crucial for catalytic activity, since a modified receptor, in which both dimethylamino groups are replaced by methyl groups does not catalyse the reaction at all under the above conditions. Consequently, under these conditions substrate binding via pyridinedicarboxamide hydrogen bonding alone is insufficient to facilitate the Pudovik reaction in the absence of a base. A cartoon reflecting how **22** may catalyse hydrophosphonylation is outlined in Scheme 11(iii).

Problem 4, the possibility of competitive product inhibition, may also be addressed through the kinetic data above. Notice how the data in Fig. 7a support linearity only over ca. 2 half-lives of reaction, corresponding to 75% conversion or 15 catalytic turnovers. When these data are extended beyond two half-lives as in Fig. 7c, deviations from second order behaviour become apparent as the reaction becomes retarded by a factor greater than second order kinetics predicts. That this behaviour does not appear in the corresponding reaction catalysed by NEt_3 (Fig. 7b is plotted over three half-lives) suggests that deactivation of reaction is due to competitive product inhibition caused by the binding of $(MeO)_2P(O)CHPh(OH)$ to **22**. Indeed, this proposal is supported by ^{1}H-NMR studies which show that the carboxamide hydrogen resonance in **22** is perturbed from δ_H 8.01 to 8.17 ppm in the presence of 1 mol equivalent of $(MeO)_2P(O)CHPh(OH)$ [3].

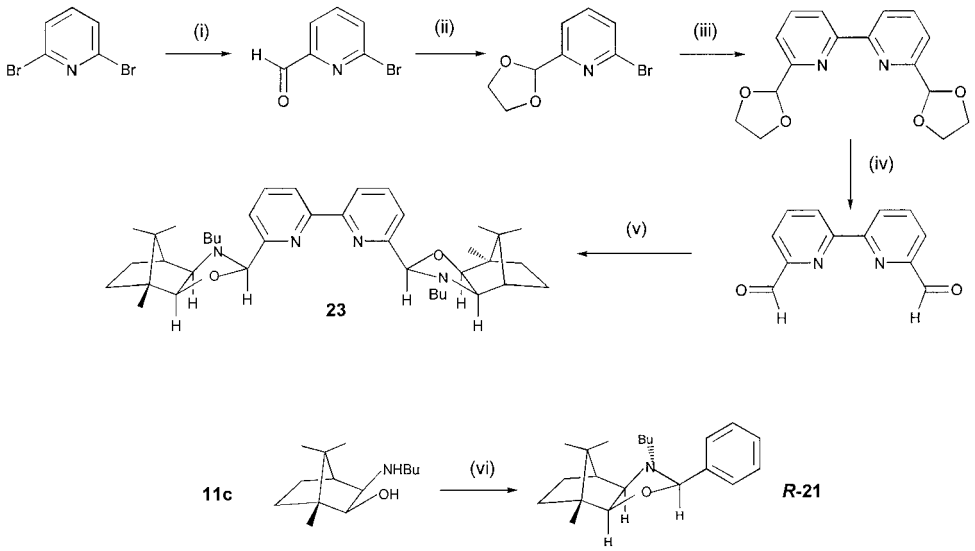
Thus, we have addressed four major problems involving Class I.2 catalyst systems based on the pyridinedicarboxamide architecture which lead us to conclude that; (i) effective catalysis is slow but clean with hydrogen-bonded Lewis acid and nitrogenous Lewis base catalysts, (ii) competitive product inhibition may be problematic.

2.4.5. Class II.1 and II.2 catalysts. Metallo-organic systems

Both Class I.1 and I.2 catalysts described above contain hydrogen-bonding Lewis acid sites. One of the major problems with this approach is that catalysis is too sluggish to be performed at low temperature with the result that the hydrogen bonding network possesses insufficient binding and orientating capacity to influence stereoselectivity. We need to increase both substrate–catalyst binding and the rate of catalysis. In this regard an electrophilic metal ion is a far more potent Lewis acid than a hydrogen bond. Indeed, the most active hydrophosphonylation catalysts yet reported have been based on rather exotic metallo-organic systems [31]. In seeking to develop a strategic approach to catalyst design, we have started from the premise that, just as in hydrogen-bonded Class I systems, both Lewis acidic and Lewis basic functions are necessary components. Indeed, we were supported in this premise by our

[2] The same catalytic reaction also proceeds cleanly under aerobic conditions, returning a second order rate constant of 4.7×10^{-2} mol^{-1} dm^3 h^{-1}.

[3] Unfortunately, solubility problems have prevented us from measuring the interaction constant.



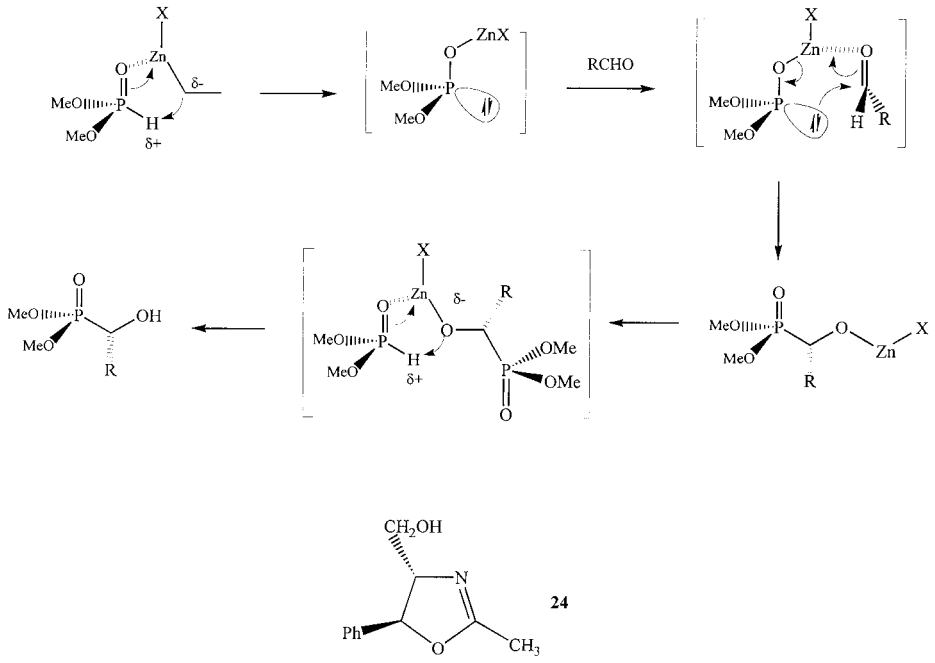
Scheme 12. (i) ^{n}BuLi, $HC(O)NMe_2$, Et_2O (54%); (ii) $(CH_2OH)_2$, H^+, C_6H_6 (72%); (iii) $NiCl_2(PPh_3)_2$, Zn, NEt_4I, THF (30%); (iv) HCl_{aq} (77%); (v) **11c**, H^+, C_7H_8 [(4*R*,4′*R*):(4*S*,4′*S*) = 24:1; 32%]; (vi) PhCHO, C_7H_8 (4*R*:4*S* = 24:1; 56%).

observation that whilst zinc triflate $[Zn(O_3SCF_3)_2]$ (10 mol%) failed to catalyse the addition of $(MeO)_2P(O)H$ to PhCHO in CH_2Cl_2 solvent under ambient conditions, addition of a catalytic (10 mol%) quantity of NEt_3 resulted in 9.1 turnovers within 60 min. For comparison, in the absence of the metal salt, NEt_3 alone (10 mol%) resulted in 1.5 turnovers during the same period. A similar result was observed also with $[Zn(O_3SCF_3)_2]$ and pyridine, where pyridine (5 mol%) alone did not catalyse phosphonylation over a period of 44 h but upon addition of $[Zn(O_3SCF_3)_2]$ (5 mol%), 11 turnovers were achieved within 44 h. Clearly, the amphoteric systems are some 6–10 times more active, under the above conditions, than base alone.

We are examining two types of Class II catalyst system, II.1 and II.2 which differ in the nature of interaction between Lewis acid and Lewis base sites. Our investigations of a particular Class II.1 catalyst are described here along with preliminary observations on more active, but achiral, Class II.2 systems.

Our Class II.1 catalysts are combinations of metal salts (Lewis acid) and chiral nitrogen bases based on the 6,6′-difunctionalised-2,2′-bipyridine scaffold such as **23** (Scheme 12) [11]c. Our initial, rather naive, thinking was to allow for the possibility of coordination complex formation between the metal ion and chiral bipyridine whilst still allowing for the bipyridine to function as a base as well as ligand (Scheme 8). In this manner, a proportion of [P—C] bond formation would take place within a chiral environment whilst essentially all H-phosphonate activation would be facilitated by a chiral base. Indeed, ^{1}H-NMR titration experiments suggest an interaction between **23** and $[Zn(O_3SCF_3)_2]$ consistent with the coordination of both nitrogen atoms to the metal [4] and the results of using **23** in the hydrophosphonylation of PhCHO with $(MeO)_2P(O)H$ reveal (Table 5) that **23** is inactive as a catalyst (5 mol%) in the absence of a metal salt but catalysis results on the addition of a catalytic (5 mol%) quantity of $[Zn(O_3SCF_3)_2]$ to afford $(MeO)_2P(O)CHPh(OH)$ with an e.e. of 26%, the highest we had yet obtained. Further improvements in enantioselectivity to 42% resulted from the co-addition of a catalytic (5 mol%) amount of NEt_3 although selectivity subsequently decreases upon a large increase in the amount of NEt_3 presumably due to competitive achiral catalysis. However, turnover rates were extremely slow (Table 5) and examination of preliminary rate data revealed that competitive inhibition was a problem. Nevertheless, these results suggested to us that we had both a viable strategy and chiral environment, we needed to strengthen the interaction between chiral ligand and metal so that a larger fraction of catalysis occurred within a chiral environment. This has led us to consider Class II.2 catalysts in which both Lewis acidic and basic functions are directly and covalently coordinated (Scheme 8). At least two factors suggest this to be a fruitful strategy: (1) all of the previously published and successful hydrophosphonylation catalysts belong to this class of system [31] and (2) we have found that an achiral member of the Class II.2 system, diethylzinc

[4] (a) A more thorough examination of this solution equilibrium is currently in progress. (b) We envisage that product inhibition may result from the chelation of $(MeO)_2P(O)CHPh(OH)$ to Zn^{2+} a hypothesis which has ample literature precedent [24] and one which we are currently investigating in more detail.



Scheme 13. Proposed mechanism for the hydrophosphonylation of aldehydes mediated by Class II.2 catalysts.

(Lewis acid = zinc and Lewis base = ethyl) is an extremely potent and extremely selective hydrophosphonylation catalyst. For example, $ZnEt_2$ catalyses the 100% chemoselective and regioselective addition of $(MeO)_2P(O)H$ to PhCHO to afford $(MeO)_2P(O)CHPh(OH)$ with an average turnover rate (measured over 1 h in toluene solvent at 298 K) of ca. 115 h^{-1} compared to ca. 1 h^{-1} for NEt_3 under analogous conditions. A plausible mechanistic pathway is outlined in Scheme 13.

In preliminary investigations, we have found that mixtures of $ZnEt_2$ with chiral amino alcohols such as **8, 11a** and the commercially available oxazoline **24** (Scheme 13) each produce active (Table 5) hydrophosphonylation catalysts (5 mol% loading in $ZnEt_2$ and chiral ligand) although, enantioselectivities are poor. Nevertheless, we note that the presence of $ZnEt_2$ appears to have resulted in an increased enantioselectivity with quinine **8** to almost twice that in the absence of metal as well as increasing turnover rates at least tenfold. We presume that one principal reason for the poor stereoselectivities is, by analogy with Class I systems, that the source of chirality in the auxiliaries used is too remote from the active [P–C] bond-forming region.

3. Conclusion

Our studies here represent a logical starting point for examining catalyst design for the enantioselective hydrophosphonylation of carbonyls. We have developed and calibrated an effective method of determining enantiopurity and absolute configuration in α-hydroxyphosphonate esters. We have also examined the configurational stability of α-hydroxyphosphonate esters under catalytic conditions such that catalyst compatibility can be assessed readily. We have used a 'bottom-up' approach to catalyst design, starting with the most simple chiral bases and amino alcohols (Class I.1 systems), which are not particularly effective, moving on to slightly more intricate amphoteric receptors which exploit hydrogen-bonding (Class I.2 systems). However, our results support the findings of others [31] that Class II systems will afford far more effective and stereoselective catalysts. To this end we have designed a new class of chiral bipyridine exemplified by **23** which contains a chiral function 'proximal' to the metal binding site and which affords much improved stereoselectivities (< 40% e.e.) over simple chiral amino alcohols. Our current efforts are directed towards (i) developing variants of **23** suitable for use as hydrophosphonylation co-catalysts in conjunction with electropositive metal alkyls and (ii) examining and manipulating the source(s) of regio- and stereocontrol in such systems. The results of these and related studies in phospho-transfer chemistry will be the subject of future contributions.

4. Experimental

4.1. General

All reactions and manipulations were performed as described previously [50]. NMR spectra were obtained

on JEOL FX90Q, JEOL FX100, Bruker ARX 250 MHz and AM 400 instruments operating at 100.0 MHz, 250.133 MHz or 400.132 MHz for ^{1}H, 100.614 MHz or 62.895 MHz for ^{13}C and 36.2 MHz or 101.614 MHz for ^{31}P. Deuterated solvents were dried by flash filtration on a column of basic alumina (Brockmann Grade I). All spectra are referenced internally using either the residual solvent resonance for ^{1}H and ^{13}C, TMS as δ_H and $\delta_C = 0$ ppm or the methyl hydrogen resonance of toluene (internal reference) as 2.11 ppm (in C_6D_6 with reference to TMS = 0 ppm). 85% H_3PO_4 was used as external reference for ^{31}P at zero ppm. All spectra are reported at 298 K in either C_6D_6 or $CDCl_3$ unless stated otherwise; the ^{13}C and ^{31}P spectra being run under conditions of broad-band ^{1}H decoupling except for the determinations of enantioselectivities (vide infra). Multiplicities are as; dd = double doublet, d = doublet, s = singlet, br-s = broad singlet, m = multiplet, t = triplet. High resolution mass spectrometry was performed by the mass spectrometric service of the School of Chemistry on a VG Autospec instrument operating in the electron impact mode (70 eV). Preparative chromatography was carried out using Merck grade 9385, 230–400 mesh (40–63 μm) silica gel. Optical rotations were recorded on an Optical Activity AA 10 polarimeter operating at 589.44 nm. The compounds PCl_3, NEt_3, $ClCH_2CH_2Cl$, $(MeO)_2P(O)H$, *N*-methyl morpholine, (*S*)-α-phenylethylamine {$[\alpha]^{20}$ −38.9° (neat); Lit: −39° Aldrich}, (+)-camphor {$[\alpha]^{25}$ +44.8° (*c* = 10, EtOH); Lit: +44.1° Aldrich} and all carbonyl compounds were purchased from commercial sources and were either recrystallised (solid carbonyls), chromatographed on a short column of Brockmann Grade I basic alumina ($ClCH_2CH_2Cl$), distilled under nitrogen [NEt_3, liquid carbonyls, $(MeO)_2P(=O)H$] or used as received [PCl_3, $LiN(SiMe_3)_2$ as a 1 M solution in THF, metal salts]. The lipase F–AP 15 *(Rhizopus oryzae)* was a gift from Amano Enzyme Europe Ltd. *N,N′*-bis[1-(*S*)-phenylethyl]-1,2-ethylenediamine was prepared using an appropriate literature procedure [17].

4.2. Synthesis of {*N,N′*-bis[1-(S)-phenylethyl]-2-chloro-1,3,2-diazaphospholidine (CDA) **2**

This was prepared as described previously [11]a. $[\alpha]^{20}$ −38.9° (*c* = 1; $CHCl_3$); Lit: −39° (*c* = 1; $CHCl_3$) [14] · δ_H 7.47–7.12 (m, 10 H, Ph-*H*), 4.22 (s broad, 2H, C*H*), 3.04 (m, 4H, CH_2), 1.69 (dd, 6H, $^{3}J_{HH}$ 6.8, $^{4}J_{PH}$ 2.2, CH_3). δ_C 142.68 (s, Ar-C_{ipso}), 128.63–127.02 (Ar-C), 57.87 (s broad, *C*H), 48.72 (broad, *C*H_2), 22.72 (broad, *C*H_3). δ_p 167.2 (s). Found: C, 64.9; H, 7.1; N, 8.3. $C_{18}H_{22}N_2PCl$ requires C, 65.0; H, 6.7; N, 8.4. Found: M^+, 332.1222. Calc. for $C_{18}H_{22}N_2PCl^{35}$: M, 332.1209.

4.3. Syntheses of α-hydroxyphosphonate esters $(MeO)_2P(O)CHR(OH)$

The synthetic procedure employed, essentially the same in each case, is described in detail only for compound (R = 1-naphthyl). The purity of each compound was assayed via ^{1}H, ^{13}C and ^{31}P-NMR spectroscopy prior to screening with CDA **2**.

4.3.1. $(MeO)_2P(=O)CH(1\text{-}C_{10}H_7)OH$

$LiN(SiMe_3)_2$ (13.78 cm^3 of a 1.0 M soln. in THF; 1 Eq.) was added dropwise to a solution of dimethyl-H-phosphonate (1.26 cm^3, 13.78 mmol) in toluene (20 cm^3), maintained at −78°C in a dry-ice–acetone slush bath and the mixture allowed to warm to room temperature over the course of 1 h. Upon cooling again to −78°C, a sample of 1-napthaldehyde (1.87 cm^3, 13.78 mmol) was added, the mixture allowed to warm to room temperature and then stirred for 2 h. After this time, a saturated aqueous solution of NH_4Cl (20 cm^3) was added and the resulting mixture stirred for 30 min. The crude product was then extracted into toluene (3 × 15 cm^3), the organic layers combined and dried over Na_2SO_4, filtered, and the volatiles removed under reduced pressure to afford the crude product. Subsequent recrystallization from pentane–toluene (2:1 v/v) afforded the pure product as colourless crystals (0.46 g, 13%). δ_H 8.07–7.25 (m, 7H, Ph-H), 5.88 (d, 1H, $^{2}J_{PH}$ 11.6, PC*H*), 4.55 (br-s, 1H, CO*H*), 3.64 (d, 3H, $^{3}J_{PH}$ 10.5, POCH_3), 3.52 (d, 3H, $^{3}J_{PH}$ 10.4, POCH_3). δ_C 148.13 (s, ArC), 133.59 (s, ArC), 132.64 (s, ArC), 130.74 (d, J_{PC} 6.2, ArC), 128.87 (d, J_{PC} 3.3, ArC), 128.73 (s, ArC), 126.20 (s, ArC), 125.62 (d, J_{PC} 5.6, ArC), 125.37 (d, J_{PC} 3.3, ArC), 123.37 (s, ArC), 67.10 (d, $^{1}J_{PC}$ 161.6, PCH), 53.86 (d, $^{2}J_{PC}$ 7.1, PO*C*H_3), 53.55 (d, $^{2}J_{PC}$ 7.5, PO*C*H_3). δ_p 24.58 (s). *(MeO)$_2$P(=O)CH(C$_6$H$_5$)OH* ***6a***.— (35%). δ_H 7.50–7.21 (m, 5H, Ph-H), 5.04 (d, 1H, $^{2}J_{PH}$ 11.1, PC*H*), 4.97 (br-s, 1H, CO*H*), 3.68 (d, 3H, $^{3}J_{PH}$ 10.5, POCH_3), 3.66 (d, 3H, $^{3}J_{PH}$ 10.3, POCH_3). δ_C 136.43 (Ar-C_{ipso}), 128.32, 127.01, 128.13 (Ar-C), 70.49 (d, $^{1}J_{PC}$ 159.8, P*C*H), 53.94 (d, $^{2}J_{PC}$ 7.2, PO*C*H_3), 53.59 (d, $^{2}J_{PC}$ 7.4, PO*C*H_3). δ_p 25.04 (s). *(MeO)$_2$P(=O)CH(2-C$_{10}$H$_7$)OH* ***6c***.— (7%). δ_H 7.95–7.18 (m, 7H, Ph-H), 5.23 (d, 1H, $^{2}J_{PH}$ 11.2, PC*H*), 4.40 (br-s, 1H, CO*H*), 3.71 (d, 3H, $^{3}J_{PH}$ 9.1, POCH_3), 3.67 (d, 3H, $^{3}J_{PH}$ 10.1, POCH_3). δ_C (quaternary carbons not observed), 133.87 (s, ArC), 133.17 (s, ArC), 128.11 (s, ArC), 127.67 (s, ArC), 126.20 (s, ArC), 126.07 (s, ArC), 124.77 (d, J_{PC} 4.3, ArC), 70.80 (d, $^{1}J_{PC}$ 159.6, P*C*H), 53.94 (d, $^{2}J_{PC}$ 7.0, PO*C*H_3), 53.68 (d, $^{2}J_{PC}$ 7.4, PO*C*H_3). δ_p 24.15 (s). *(MeO)$_2$P(=O)CH(2-BrC$_6$H$_4$)OH* ***6d***.— (42%). δ_H 7.79–7.14 (m, 4H, Ph-H), 5.58 (d, 1H, $^{2}J_{PH}$ 11.4, PC*H*), 5.09 (br-s, 1H, CO*H*), 3.78 (d, 3H, $^{3}J_{PH}$ 10.6,

POCH_3), 3.68 (d, 3H, $^3J_{PH}$ 10.4, POCH_3). δ_C 136.47 (s, ArC), 132.55 (s, Ar-C_{ipso}), 123.12 (s, ArC), 129.60 (s, ArC), 129.55 (s, ArC), 127.62 (s, Ar-C), 69.42 (d, $^1J_{PC}$ 161.6, P*C*H), 54.09 (d, $^2J_{PC}$ 7.1, PO*C*H_3), 53.66 (d, $^2J_{PC}$ 7.2, PO*C*H_3). δ_p 23.98 (s). *(MeO)$_2$P(=O)CH(3-BrC$_6$H$_4$)OH* ***6e***.— (63%). δ_H 7.67–7.19 (m, 4H, Ph-H), 5.03 (d, 1H, $^2J_{PH}$ 9.2, PC*H*), 5.03 (br-s, 1H, CO*H*), 3.73 (d, 3H, $^3J_{PH}$ 10.5, POCH_3), 3.71 (d, 3H, $^3J_{PH}$ 10.4, POCH_3). δ_C 138.96, (s, Ar-C_{ipso}), 131.14 (s, ArC), 129.93 (s, ArC), 129.79 (s, ArC), 125.64 (s, ArC), 122.43 (Ar-C), 69.86 (d, $^1J_{PC}$ 160.3, P*C*H), 54.14 (d, $^2J_{PC}$ 7.1, PO*C*H_3), 53.68 (d, $^2J_{PC}$ 7.4, PO*C*H_3). δ_p 23.46 (s). *(MeO)$_2$P(=O)CH(4-BrC$_6$H$_4$)OH* ***6f***.— (41%). δ_H 7.49 (d, 2H, $^3J_{HH}$ 8.0, Ph-*H*), 7.35 (d 2H, $^3J_{HH}$ 8.6, Ph-*H*), 5.01 (d, 1H, $^2J_{PH}$ 11.3, PC*H*), 4.94 (br-s, 1H, CO*H*), 3.70 (d, 3H, $^3J_{PH}$ 10.5, POCH_3), 3.69 (d, 3H, $^3J_{PH}$ 10.4, POCH_3). δ_C 135.64 (d, J_{PC} 1.9, Ar-C_{ipso}), 131.43 (d, J_{PC} 2.5, ArC), 128.66 (d, J_{PC} 5.8, ArC), 122.12 (d, J_{PC} 4.0, ArC), 69.90 (d, $^1J_{PC}$ 160.6, P*C*H), 54.06 (d, $^2J_{PC}$ 7.3, PO*C*H_3), 53.61 (d, $^2J_{PC}$ 7.5, PO*C*H_3). δ_p 23.46 (s). *(MeO)$_2$P(=O)CH(4-MeC$_6$H$_4$)OH* ***6g***.— (37%). δ_H 7.37 (d, 2H, $^3J_{HH}$ 8.1, Ph-*H*), 7.16 (d, 2H, $^3J_{HH}$ 7.8, Ph-*H*), 5.00 (d, 1H, $^2J_{PH}$ 10.6, PC*H*), 4.48 (br-s, 1H, CO*H*), 3.70 (d, 3H, $^3J_{PH}$ 9.7, POCH_3), 3.65 (d, 3H, $^3J_{PH}$ 9.4, POCH_3), 2.34 (s, 3H, CH_3-Ar). δ_C 137.90 (s, ArC), 133.43 (Ar-C_{ipso}), 129.02 (s, ArC), 126.97 (s, ArC), 70.39 (d, $^1J_{PC}$ 160.3, P*C*H), 53.82 (d, $^2J_{PC}$ 7.1, PO*C*H_3), 53.52 (d, $^2J_{PC}$ 7.3, PO*C*H_3), 21.12 (s, *C*H_3-Ar). δ_p 24.47 (s). *(MeO)$_2$P(=O)CH(4-MeOC$_6$H$_4$)OH* ***6h***.— (39%). δ_H 7.41 (d, 2H, $^3J_{HH}$ 8.9, Ph-*H*), 6.90 (d, 2H, $^3J_{HH}$ 8.8, Ph-*H*), 4.98 (d, 1H, $^2J_{PH}$ 10.2, PC*H*), 4.21 (br-s, 1H, CO*H*), 3.80 (s, 3H, CH_3O-Ar), 3.71 (d, 3H, $^3J_{PH}$ 10.5, POCH_3), 3.66 (d, 3H, $^3J_{PH}$ 10.3, POCH_3). δ_C 159.56 (s, ArC), 128.42 (Ar-C_{ipso}), 128.42 (s, ArC), 113.85 (s, ArC), 70.16 (d, $^1J_{PC}$ 161.5, P*C*H), 55.21 (s, *C*H_3O-Ar), 53.79 (d, $^2J_{PC}$ 7.1, PO*C*H_3), 53.56 (d, $^2J_{PC}$ 7.3, PO*C*H_3). δ_p 24.48 (s). *(MeO)$_2$P(=O)CH(4-O$_2$NC$_6$H$_4$)OH* ***6i***.— (62%). δ_H 8.23 (d, 2H, $^3J_{HH}$ 8.7, Ph-*H*), 7.68 (d, 2H, $^3J_{HH}$ 8.9, Ph-*H*), 5.22 (d, 1H, $^2J_{PH}$ 12.4, PC*H*), 5.04 (br-s, 1H, CO*H*), 3.78 (d, 3H, $^3J_{PH}$ 10.5, POCH_3), 3.76 (d, 3H, $^3J_{PH}$ 10.6, POCH_3). δ_C 147.62 (s, ArC), 143.89 (Ar-C_{ipso}), 127.62 (s, ArC), 123.44 (s, Ar-C), 69.93 (d, $^1J_{PC}$ 158.7, P*C*H), 54.42 (d, $^2J_{PC}$ 7.1, PO*C*H_3), 53.71 (d, $^2J_{PC}$ 7.6, PO*C*H_3). δ_p 23.46 (s). *(MeO)$_2$P(=O)CH(2-O$_2$NC$_6$H$_4$)OH* ***6j***.— (22%). δ_H 8.03–7.41 (m, 4H, Ph-H), 6.30 (d, 1H, $^2J_{PH}$ 14.0, PC*H*), 5.98 (br-s, 1H, CO*H*), 3.74 (d, 3H, $^3J_{PH}$ 10.4, POCH_3), 3.72 (d, 3H, $^3J_{PH}$ 10.6, POCH_3). δ_C 147.41 (s, ArC), 132.65 (Ar-C_{ipso}), 133.33 (s, ArC), 128.89 (s, ArC), 128.37 (s, ArC), 124.57 (Ar-C), 65.37 (d, $^1J_{PC}$ 161.9, P*C*H), 54.48 (d, $^2J_{PC}$ 7.3, PO*C*H_3), 53.58 (d, $^2J_{PC}$ 7.4, PO*C*H_3). δ_p 22.86 (s). *(MeO)$_2$P(=O)CH(2-Ph$_2$PC$_6$H$_4$)OH* ***6k***.— (47%). δ_H 7.96–7.08 (m, 14H, Ph-H), 6.19 (dd, 1H, $^2J_{PH}$ 11.7, $^3J_{PH}$ 9.3, PC*H*), 4.05 (br-s, 1H, CO*H*), 3.56 (d, 3H, $^3J_{PH}$ 10.6, POCH_3), 3.49 (d, 3H, $^3J_{PH}$ 10.4, POCH_3). δ_C 142.23 (d, J_{PC} 25.7, ArC), 137.47 (d, J_{PC} 9.7, ArC), 136.04 (d, J_{PC} 9.3, ArC), 134.89 (s, ArC), 133.92 (d, J_{PC} 19.8, ArC), 133.21 (d, J_{PC} 18.9, ArC), 129.65 (s, ArC), 128.57 (d, J_{PC} 8.4, ArC), 128.46 (d, J_{PC} 1.6, ArC), 128.37 (d, J_{PC} 4.5, ArC), 68.01 (dd, $^1J_{PC}$ 160.9, $^3J_{PC}$ 31.7, P*C*H), 53.59 (d, $^2J_{PC}$ 7.2, PO*C*H_3), 53.26 (d, $^2J_{PC}$ 7.5, PO*C*H_3). δ_p 24.59 (s, P=O), −18.18 (s, PPh_2).

4.4. General procedure for the assay of enantiopurity of α-hydroxyphosphonate esters using CDA

A sample of the α-hydroxyphosphonate ester **6** under investigation (52.6 μmol) was weighed out into a small vial (quantities varied from ca. 11–21 mg depending upon R) in a nitrogen filled dry box. To this solid was added 0.6 cm^3 of a dry $CDCl_3$ deoxygenated solution comprising CDA **2** at (0.125 M) and triethylamine at (0.25 M) at room temperature which affords a molar ratio of **6**:**2**:NEt_3 of ca. 1:1.4:2.8. The mixture was transferred to a 5 mm NMR tube, sealed under nitrogen and shaken briskly to ensure complete dissolution. The reaction mixture remained clear throughout, neither the adducts nor the triethylammonium chloride precipitated from solution at this level of concentration. After 15 min the $^{31}P\{^1H\}$-NMR spectrum (101.268 MHz) was collected (256 scans) on a Bruker ARX 250 MHz spectrometer over a spectral width of 3048.8 Hz centred on the phosphorus(III) resonances, (3.8 μs pulse; 8192 data points; 1.344 s acquisition time and 0.74 Hz digital resolution) with a 3 s pulse delay between scans to allow relaxation and inverse-gated proton decoupling to reduce nuclear Overhauser effects. Slight line-broadening (2 Hz) was applied to the FIDs to aid sensitivity without compromising baseline separation. The FIDs were Fourier transformed and phased automatically, the same phase corrections being applied for each sample. Automated electronic integration gives the relative proportions of diastereoisomers as listed in Table 2 from which enantioselectivities can be computed readily. Integrations performed by manual-phasing were the same within the overall error limit of 1%. Following this, the spectrum was re-acquired over 26 316 Hz (0.62 s acquisition; 1.6 Hz digital resolution; 0.3 s pulse delay and broad-band ^1H decoupling) to ensure complete conversion of **6** to **5**, the presence of excess CDA **2**, and to obtain the chemical shifts of the phosphorus(V) nuclei.

Due to the steady deterioration of CDA **2** over a period of months when stored at room temperature under a static atmosphere of dinitrogen, the concentration of H-phosphonate **4**, formed due to hydrolysis, increases. Whilst this in itself is not a problem and does not lead to any side-reaction with the α-hydroxyphosphonate ester, an accompanying impurity is also produced which gives rise to a low intensity yet signifi-

cantly broadened resonance centred at δ_p 124 ($\Delta_{1/2}$ ca. 130 Hz), within the range of the integration window for the assay. Since this impurity occurs only in samples of **2** which are several months old, we have consistently prepared and used all samples of **2** within that period thus eliminating the effects of this impurity.

4.5. Inversion recovery experiments

Samples for inversion recovery experiments were prepared in $CDCl_3$ solvent in 5 mm NMR tubes under an atmosphere of dinitrogen in exactly the same way as described above for the measurements of enantiopurity. Samples were deoxygenated by purging with dinitrogen gas for ca. 30 s prior to sealing with cling-film. Spin-lattice relaxation times T_1 were measured at 300 K on an ARX 250 MHz instrument using a standard Bruker pulse sequence package modified to provide inverse-gated ^{1}H decoupling (to lessen the effects of potential n.O.e. differences) and a delay time of 15 s between pulse sequences to allow for complete relaxation. A crude experiment first locates the approximate delay times to achieve a null signal followed by selection of delay times to provide at least four data points on either side of this null signal. Signal intensity was plotted against delay time and T_1 values computed by curve fitting using the standard Bruker WINNMR package according to the Levenberg–Marguardt algorithm, $I_\tau = I_o[1 - 2A\exp^{-\tau/T_1}]$ where I_τ and I_o represent signal intensity after delay time τ and with no delay respectively and A is a variable parameter.

4.6. Enzyme-catalysed hydrolysis of α-acylphosphonate esters

The procedure used to hydrolyse α-acyloxy-α-phenylmethyldimethylphosphonate $(MeO)_2P(=O)CHPh[OC(=O)Me]$ *acyl*-**6a** was a slight modification of that reported by Hammerschmidt [18]. α-Acyloxy-α-phenylmethyldimethylphosphonate was synthesised by the reaction of **6a** with acetyl chloride in the presence of triethylamine [18].

A mixture of *t*-butylmethyl ether and hexane (4 cm^3, 1:3 v/v) was added to racemic α-acyloxy-α-phenylmethyldimethylphosphonate *acyl*-**6a** (0.26 g, 1.00 mmol) followed by the addition of aqueous phosphate buffer solution (pH 6.86, 15 cm^3) and the mixture stirred vigorously in a constant temperature water bath maintained at 35°C whilst 0.5 M aqueous NaOH was added to adjust the pH of the mixture to 7. Lipase F–Ap 15 was added (0.1 g) and the pH again adjusted to 7 by addition of NaOH. The mixture was then stirred for 18 h whilst maintaining pH at 7 by manual titration with NaOH. After the required time, reaction was quenched by the addition of aqueous HCl (2 M) until the pH of the mixture reached 4. The mixture was then filtered through celite, the filtrate extracted into ethyl acetate (3×25 cm^3), the organic layers separated, combined and dried over $MgSO_4$. Unreacted ester and hydrolysis product α-hydroxy-α-phenylmethyldimethylphosphonate **6a** were separated by column chromatography on silica gel using the solvent system CH_2Cl_2–ethyl-acetate (5:1 v/v). *Acyl*-**6a** elutes first followed by scalemic **6a** (0.072 g, 33%). The latter was analysed subsequently by polarimetry and NMR spectroscopy revealing $[\alpha]^D = -30.4°$ ($c = 0.5$, acetone) and e.e. = 83(1)% in favour of the *S*-enantiomer (average of three determinations) respectively. Unhydrolysed *acyl*-**6a** was converted subsequently to **6a** by stirring with a mixture of dry methanol (5 cm^3) and triethylamine (1 cm^3) for 24 h, following the method of Hammerschmidt [18] to afford a further crop of scalemic **6a** (0.068 g, 31%) now enriched in the *R*-enantiomer. $[\alpha]^D = +29.2°$ ($c = 0.5$, acetone) and e.e. = 81(1)% (average of three determinations).

4.7. Investigations of the configurational stability of α-hydroxyphosphonate esters

A $CDCl_3$ solution of $(MeO)_2P(O)CHPh(OH)$ (26.6 mg, 0.123 mmol) was treated with NEt_3 (12.5 mg, 0.123 mmol) and D_2O (ca. 35 mg, 1.75 mmol) under an atmosphere of dinitrogen. ^{1}H-NMR spectra were acquired at regular intervals over the course of 3 weeks revealing no incorporation of deuterium at the alpha-carbon site.

The possibility of reversible aldehyde extrusion was probed by $^{31}P\{^1H\}$ and ^{1}H-NMR examination of a $CDCl_3$ solution containing $(MeO)_2P(O)CHPh(OH)$ (21.6 mg, 0.1 mmol) (δ_p 24.5) and 4-BrC_6H_4CHO (18.5 mg, 0.1 mmol chosen since the 4-halobenzaldehydes have a similar reactivity to benzaldehyde and afford satisfactory ^{31}P-NMR shift resolution) and NEt_3 (38 mg, 0.38 mmol 0.5 equivs.). After 8 days at ambient temperature, NMR spectroscopy revealed a resonance at δ_p 24.0 consistent with formation of the crossover product $(MeO)_2P(O)CH(4\text{-}BrC_6H_4)(OH)$ (confirmed by addition of a small quantity, 20 mg, of authentic compound to this mixture). However, since this resonance constituted $< 2\%$ of the product mixture, exchange is a very slow process under these conditions.

The possibility of metal-catalysed racemisation, via both (i) H/D exchange and (ii) aldehyde extrusion mechanisms, was explored in $CDCl_3$ solution. A standard solution (**A**) containing $(MeO)_2P(O)CHPh(OH)$ (0.25 g, 1.16 mmol) and $Zn(OSO_2CF_3)_2$ (42 mg, 0.12 mmol 10 mol%) was made up to 10 cm^3 in $CDCl_3$ under a dinitrogen atmosphere. (i) To a 0.86 cm^3 volume of this standard solution in a 5 mm NMR tube was added D_2O (35 mg, 1.75 mmol) at ambient temperature and the tube shaken. After 17 days, ^{1}H-NMR spectroscopy revealed H/D exchange at the hydroxy site

but no exchange at the alpha-carbon site (integration of the alpha-CH resonance against the OMe resonance). An identical experiment, performed in the presence of NEt_3 (13.9 μl, 1 equiv.) as an additional component, again revealed no H/D exchange at C_α within 7 days at ambient temperature. (ii) An 0.86 cm^3 aliquot of standard solution **A** was treated with 4-BrC_6H_4CHO (18.5 mg, 1 equiv.) at ambient temperature and analysed by ^1H and ^{31}P-NMR spectroscopy. The sample was unchanged after 24 h but after 14 days a small amount (< 2%) of C_6H_5CHO was observed in the ^1H-NMR presumably due to extrusion from $(MeO)_2P(O)CHPh(OH)$. Repeating this experiment with NEt_3 (1 equiv.) as an additional component resulted in slightly more crossover product being observed (ca. 10%) after 7 days at ambient temperature.

*4.8. Reaction of (1R,2S)-norephedrine with benzaldehyde. Synthesis of **12a** and **13a***

A CH_2Cl_2 solution of (1*R*,2*S*)-norephedrine (2.05 g, 13.58 mmol) and benzaldehyde (1.38 cm^3, 13.58 mmol) was stirred over 4 Å molecular sieves at room temperature for 24 h. The resulting solution was filtered and the volatiles removed under reduced pressure to afford a sticky yellow solid, found to consist of a mixture of three products (2.95 g, 91% isolated). The major component (75% of mixture) was assigned as the benzylidine imine **12a** whilst the two minor products (25%) were assigned as epimeric oxazolidines **13a** in a 2:1 ratio on the basis of ^1H-NMR spectroscopy. *Major product*: δ_H 8.21 (s, 1H, imine proton), 8.01–7.19 (m, 10H, Ph-*H*), 4.81 (d, 1H, $^3J_{HH}$ 4.38, PhC*H*O), 3.65 (m, 1H, $^3J_{HH}$ 6.93, C*H*Me), 1.13 (d, 1H, $^3J_{HH}$ 6.53, CH*Me*). δ_C 160.63 (s, imine *C*), 141.42–126.07 (Ph-*C*), 76.97 (s, Ph*C*HO), 71.10 (s, *C*HMe), 16.23 (s, CH*Me*). *Oxazolidines:* δ_H 8.01–7.19 (m, 10H, Ph-*H*), 6.03 and 5.58 (s, 1H, C2-*H*), 5.08 (d, 2H, $^3J_{HH}$ + 7.75, PhC*H*O), 3.82 and 3.65 (m, 1H, $^3J_{HH}$ 6.93, C*H*Me), 0.76 (d, 3H, $^3J_{HH}$ 6.78, CH*Me*), 0.74 (d, 3H, $^3J_{HH}$ 6.63, CH*Me*). δC 141.42 (s, Ph-C_{ipso}), 136.1 (s, Ph-C_{ipso}), 130.79–126.07 (Ph-*C*), 91.78 (s, *C*2), 81.67 and 81.28 (s, Ph*C*H), 58.48 and 56.63 (s, *C*HMe), 16.17 and 15.36 (s, CH*Me*). *m/z* 239 (M^+). Found: C 80.0; H 7.3; N 5.7; $C_{16}H_{17}NO$ requires C 80.3; H 7.2; N 5.9.

*4.9. Synthesis of N-benzyl-(1R,2S)-ephedrine **14a***

A solution of *N*-benzylidine-(1*R*,2*S*)-ephedrine (5.32 g, 22.23 mmol) dissolved in THF solvent (20 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (2.11 g, 55.58 mmol) in THF (15 cm^3) at ambient temperature. Upon complete addition, the turbid yellow solution was refluxed under an atmosphere of dinitrogen for 18 h, after which time the solution had become colourless. The mixture was then quenched by addition of water (2 cm^3) followed by aqueous NaOH solution (3.0 cm^3, 15% w/v) and the gelatinous mixture stirred for 1 h. Filtration and removal of the volatiles under reduced pressure afforded **14a** as a clear liquid. (4.37 g, 81%). δ_H 7.34–7.00 (m, 10H, Ph-*H*), 4.75 (d, 1H, $^3J_{HH}$ 3.90, PhC*H*O), 3.84 (s, 2H, PhCH_2), 2.98 (dq, 1H, $^3J_{HH}$ 6.50, C*H*Me), 0.85 (d, 3H, $^3J_{HH}$ 6.53, CH*Me*). δ_C 141.41 (s, Ph-C_{ipso}), 140.16 (s, Ph-C_{ipso}), 128.54 (s, ArC), 128.08 (s, ArC), 127.15 (s, ArC), 127.05 (s, ArC), 126.13 (s, ArC), 73.22 (s, Ph*C*HO) 57.78 (s, *C*HMe), 51.28 (s, Ph-CH_2), 14.68 (s, CH*Me*). Found: M^+,. Calc. for $C_{16}H_{19}NO$: M,.

*4.10. Reaction of N-benzyl-(1R,2S)-ephedrine with benzaldehyde. Synthesis of (2RS, 4SS, 5RR)-3-aza-3-benzyl-4-methyl-1-oxa-2,5-diphenylcyclopentane **15a***

To a solution of *N*-benzyl-(1*R*,2*S*)-ephedrine (4.23 g, 17.54 mmol) dissolved in CH_2Cl_2 (30 cm^3), benzaldehyde (1.78 cm^3, 17.54 mmol) was added and the resulting mixture heated at reflux for 24 h. The solution was filtered and the volatile materials removed under reduced pressure to afford a sticky yellow solid, which was shown to consist of two isomeric products which were identified by ^1H-NMR spectroscopy as isomeric oxazolidines **15a** in a 7:3 ratio. (5.35 g, 92%). *Major product:* δ_H 8.20–7.16 (m, 15H, Ph-*H*), 5.07 (d, 1H, $^3J_{HH}$ 8.6, PhC*H*O), 5.06 (s, 1H, C2-*H*), 3.81 (d, 2H, $^2J_{HH}$ 14.1, CH_2), 3.56 (d, 2H, $^2J_{HH}$ 14.1, CH_2), 3.22 (dq, 1H, $^3J_{HH}$ 6.5, C*H*Me), 0.51 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*). δ_C 139.14–126.16 (Ph-*C*), 96.88 (s, *C*2), 82.19 (s, Ph*C*HO), 61.89 (s, *C*HMe), 54.88 (s, CH_2), 17.23 (s, CH*Me*). *Minor Product:* δ_H 8.20–7.16 (m, 15H, Ph-*H*), 5.49 (d, 1H, $^3J_{HH}$ 8.6, PhC*H*O), 5.06 (s, 1H, C2-*H*), 3.81 (d, 2H, $^2J_{HH}$ 14.1, CH_2), 3.56 (d, $^2J_{HH}$ 14.1, CH_2), 3.55 (m, 1H, $^3J_{HH}$ 6.5, C*H*ME), 0.51 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*). δ_C 139.14–126.16 (Ph-*C*), 94.02 (s, *C*2-carbon), 81.92 (s, Ph*C*HO), 57.56 (s, *C*HMe), 49.48 (s, CH_2), 8.43 (s, CH*Me*). Found: C 82.5; H 7.3; N 4.1; $C_{23}H_{23}NO$ requires C 83.9; H 7.1; N 4.3. Found: [M-H^+], 328.1680. Calc. for $C_{23}H_{22}NO$: [M-H]$^+$, 328.1701.

*4.11. Synthesis of N,N-dibenzyl-(1R,2S)-ephedrine **9a***

A THF (20 cm^3) solution of the product mixture from Experiment 4.11 (5.02 g, 15.18 mmol) was added dropwise to a stirred suspension of $LiAlH_4$ (1.44 g, 37.95 mmol) in THF (15 cm^3). Upon addition the mixture was treated as described in Experiment 4.10 to afford the crude product as a clear oil. (3.86 g, 77%). Column chromatography of a portion of the above mixture (0.96 g) employing a two-stage eluent system of light petroleum (60–80°C)–Et_2O (100 cm^3; 4:1 v/v)

followed by light petroleum (60–80°C)–Et_2O (200 cm^3; 3:2 v/v) afforded pure amino alcohol **9a** as a clear viscous liquid (0.75 g, 78% recovery). δ_H 7.37–7.15 (m, 15H, Ph-*H*), 4.73 (d, 1H, $^3J_{HH}$ 6.23, PhC*H*O), 3.69 (d, 1H, $^2J_{HH}$ 13.9, PhCH_2), 3.47 (d, 1H, $^2J_{HH}$ 13.9, PhCH_2) 3.08 (q, 1H, $^3J_{HH}$ 6.65, C*H*Me), 2.52 (s, broad, 1H, -O*H*), 1.15 (d, 3H, $^3J_{HH}$ 6.78, CH*Me*). δ_C 143.19 (s, 1H, Ph-C_{ipso}), 139.86 (s, 1H, Ph-C_{ipso}), 128.7 (s, ArC), 128.56 (s, ArC), 128.20 (s, ArC), 128.01 (s, ArC), 127.25 (s, ArC), 126.85 (s, ArC), 126.72 (s, ArC), 75.68 (s, Ph*C*HO), 58.46 (s, *C*HMe), 54.59 (s, Ph*C*H_2), 9.11 (s, CH*Me*). Found: M^+, 331.1935. Calc. for $C_{23}H_{25}NO$: M, 331.1936. $[\alpha]^D = -14.2°$ ($c = 5.4$, CH_2Cl_2).

4.12. Reaction of (1R,2S)-norephedrine with 3,5-dimethoxybenzaldehyde. Synthesis of **12b** and **13b**

(1*R*,2*S*)-Norephedrine (2.04 g, 13.47 mmol) was dissolved in CH_2Cl_2 (30 cm^3) and stirred over 4 Å molecular sieves at room temperature. 3,5-Dimethoxybenzaldehyde (2.24 g, 13.47 mmol) was added to this solution and the mixture stirred for 24 h. The resulting solution was then filtered and the volatiles removed under reduced pressure to afford a cloudy viscous liquid, shown to consist of a mixture of three isomeric products by ^{1}H-NMR spectroscopy. The major component of this mixture was assigned to imine **12b** and the two minor components oxazolidine epimers **13b**. (3.57 g, 89%). *Major product: Imine* — δ_H 8.20 (s, 1H, imine proton), 7.38–7.25 (m, 5H, Ph-*H*), 6.89 (d, 2H, $^4J_{HH}$ 2.38, H_{ortho}), 6.54 (t, 1H, $^4J_{HH}$ 2.38, H_{para}), 4.84 (d, 1H, $^3J_{HH}$ 3.93, PhC*H*O), 3.83 (s, 6H, O*Me*), 3.83 (m, 1H, $^3J_{HH}$ 3.8, C*H*Me), 1.10 (d, 3H, $^3J_{HH}$ 6.55, CH*Me*). δ_C 160.33 (s, imine carbon), 141.02 (s, C_{ipso}), 138.12 (s, C_{ipso}), 128.16–126.19 (Ph-*C*), 105.95 (s, C_{ortho}), 103.36 (s, C_{para}), 76.87 (s, Ph*C*HO) 70.71 (s, *C*HMe), 55.48 (s, O*Me*) 15.836 (s, CH*Me*). *Minor products. Oxazolidines* — δ_H 7.39–7.25 (m, 10H, Ph-*H*), 6.85 (dd, 4H, $^4J_{HH}$ 2.38 and $^4J_{HH}$ 0.75, H_{ortho}), 6.48 (t, 1H, $^4J_{HH}$ 2.25, H_{para}), 5.60 (s, broad, 1H, C2-*H*), 5.12 (d, 1H, $^3J_{HH}$ 7.7, PhC*H*O), 3.83 (m, 1H, $^3J_{HH}$ 3.88, C*H*Me), 0.78 (d, 3H, $^3J_{HH}$ 6.65, CH*Me*). δ_C 141.02–126.19 (Ph-*C*), 103.89 (s, C_{ortho}), 100.71 (s, C_{para}), 91.80 (s, *C*2), 81.29 (s, Ph*C*HO), 58.52 (s, *C*HMe), 55.48 (s, O*Me*), 15.83 (s, CH*Me*). δ_H 7.39–7.25 (m, 10H, Ph-*H*), 6.75 (dd, 4H, $^4J_{HH}$ 2.38 and $^4J_{HH}$ 0.75, H_{ortho}), 6.42 (t, 1H, $^4J_{HH}$ 2.55, H_{para}), 6.02 (s, broad, 1H, C2-*H*), 3.64 (dq, 1H, $^3J_{HH}$ 6.55 and $^4J_{HH}$ 0.7, C*H*Me), 0.79 (d, 3H, $^3J_{HH}$ 6.68, CH*Me*). δ_C 141.01–126.19 (s, Ph-*C*), 103.86 (s, C_{ortho}), 100.27 (s, C_{para}), 91.67 (s, *C*2), 81.58 (s, Ph*C*HO), 56.58 (s, *C*HMe), 55.39 (s, O*Me*), 15.37 (s, CH*Me*). Found: M^+, 299.1510. Calc. for $C_{18}H_{21}NO_3$: M, 299.1521.

4.13. Synthesis of N-(3,5-dimethoxybenzyl)-(1R,2S)-ephedrine **14b**

A solution of *N*-3,5-dimethoxybenzylidine-(1*R*,2*S*)-ephedrine (3.57 g, 12.51 mmol) dissolved in THF (20 cm^3) was added dropwise with care to a stirred suspension of $LiAlH_4$ (1.19 g, 31.28 mmol) in THF (15 cm^3). Upon complete addition the solution was refluxed under nitrogen for 24 h before quenching by the careful addition of water (2 cm^3) followed by aqueous NaOH solution (3.0 cm^3, 15% w/v) to give a gelatinous mixture. Further stirring for 1 h, filtration and removal of the volatiles materials under reduced pressure afforded compound **14b** as a clear liquid which was found to be sufficiently pure for further reaction. (3.86 g, 77%). δ_H 7.58–7.16 (m, 5H, Ph-*H*), 6.42 (d, 2H, $^4J_{HH}$ 2.3, H_{ortho}), 6.32 (t, 1H, $^4J_{HH}$ 2.4, H_{para}), 4.70 (d, 1H, $^3J_{HH}$ 4.0, PhC*H*O), 3.75 (s, 1H, CH_2), 3.73 (s, 6H, O*Me*), 2.92 (dq, 1H, $^3J_{HH}$ 6.6 and 4.0, C*H*Me), 0.82 (d, 3H, $^3J_{HH}$ 6.5, CH*Me*). δ_C 142.60 (s, C_{ipso}), 141.38 (s, C_{ipso}), 128.07 (s, ArC), 127.06 (s, ArC), 126.12 (s, ArC) 105.95 (s, C_{ortho}), 104.50 (s, C_{para}), 73.36 (s, Ph*C*HO), 57.72 (s, *C*HMe), 55.29 (s, OCH_3), 51.33 (s, CH_2), 13.84 (s, CH_3). Found: C 71.8; H 7.7; N 4.4; $C_{18}H_{23}NO_3$ requires C 71.7; H 7.7; N 4.7.

4.14. Reaction of N-(3,5-dimethoxybenzyl)-(1R,2S)-ephedrine with 3,5-dimethoxybenzaldehyde. Synthesis of (2RS,4SS,5RR)-3-aza-3-(3′,5′-dimethoxybenzyl)-2-(3′,5′-dimethoxyphenyl)-4-methyl-1-oxa-5-phenylcyclopentane **15b**

N-3,5-Dimethoxybenzyl-(1*R*,2*S*)-ephedrine (2.83 g, 9.38 mmol) was dissolved in ethanol (30 cm^3) and stirred over 4 Å molecular sieves at room temperature. A few drops of glacial acetic acid and 3,5-dimethoxybenzaldehyde (1.56 g, 13.58 mmol) were added to this solution and the mixture refluxed for 48 h. The resulting solution was filtered, removal of the volatiles under reduced pressure afforded a viscous yellow liquid, which was found to consist of two compounds identified as oxazolidine epimers **15b** by ^{1}H-NMR spectroscopy. (2.72 g, 96%). *Major isomer:* δ_H 7.42–7.24 (m, Ph-*H*), 6.88 (d, 2H, $^4J_{HH}$ 2.3, H_{ortho}), 6.45 (t, 1H, $^4J_{HH}$ 2.3, H_{meta}), 5.15 (d, 1H, $^3J_{HH}$ 7.5, PhC*H*O), 5.08 (s, 1H, C2-*H*), 3.73 (m, 2H, $^3J_{HH}$ 7.0, CH_2), 3.65 (s, 12H, OMe), 3.22 (dq, 1H, $^3J_{HH} = 6.6$ and 7.5, C*H*Me), 0.65 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*). δ_C 160.78 (s, C_{ipso}), 128.02–126.18 (Ph-*C*), 107.13 (s, C_{ortho}), 106.35 (s, C_{ortho}), 101.13 (s, C_{para}), 98.86 (s, C_{para}), 96.73 (s, *C*2), 82.16 (s, Ph*C*HO), 62.13 (s, *C*HMe), 55.32 (s, O*Me*), 55.22 (s, O*Me*), 55.01 (s, CH_2), 17.03 (s, CH*Me*). *Minor isomer:* δ_H 7.42–7.24 (m, Ph-*H*), 6.80 (d, 2H, $^4J_{HH}$ 2.3, H_{ortho}), 6.30 (t, 1H, $^4J_{HH}$ 2.3, H_{meta}), 5.52 (d,

1H, $^3J_{HH}$ 7.5, PhC*H*O), 5.46 (s, 1H, C2-*H*), 3.73 (m, 2H, $^3J_{HH}$ 7.0, CH_2), 3.65 (s, 12H, O*Me*), 3.60 (dq, 1H, $^3J_{HH}$ = 6.6 and 7.5, C*H*Me), 0.69 (d, 3H, $^3J_{HH}$ 6.6, CH*Me*). δ_C 160.50 (s, C_{ipso}), 128.02–126.18 (Ph-*C*), 106.42 (s, C_{ortho}), 105.79 (s, C_{ortho}), 101.04 (s, C_{para}), 98.62 (s, C_{para}), 93.92 (s, *C*2), 81.83 (s, Ph*C*HO), 57.77 (s, *C*HMe), 55.38 (s, O*Me*), 55.27 (s, O*Me*), 49.84 (s, *C*H_2), 9.03 (s, CH*Me*). Found: M^+, 448.2117. Calc. for $C_{27}H_{30}NO_5$: M, 448.2124.

4.15. Synthesis of N,N-bis-(di-3,5-dimethoxybenzyl)-(1R,2S)-ephedrine **9b**

A solution of (4*S*, 5*R*)-2-(3,5-dimethoxybenzyl)-3-(3,5-dimethoxyphenyl)-4-methyl-5-phenyl oxazolidine (2.72 g, 9.39 mmol) dissolved in THF (20 cm^3) was added dropwise to a stirred suspension of $LiAlH_4$ (0.8 g, 23.48 mmol) in THF (15 cm^3), cautiously. Upon complete addition the solution was refluxed under dinitrogen for 24 h followed by quenching with the careful addition of water (2 cm^3) followed by aqueous NaOH solution (3.0 cm^3, 15% w/v) to give a gelatinous mixture. Further stirring for 1 h, filtration and removal of the volatiles under reduced pressure afforded crude **9b** as a clear viscous liquid (2.65 g, 63%). Further purification of the compound was achieved by percolation column chromatography on silica gel. Crude product (0.5 g) was suspended on a short column of silica gel (5–7 g) and eluted with toluene (100 cm^3) followed by toluene–EtOAc (25:2 v/v; 300 cm^3). The desired product was eluted with the latter solvent system as a clear oil (0.35 g, 69% recovery). δ_H 7.32–7.17 (m, 5H, Ph-*H*), 6.37 (d, 4H, $^4J_{HH}$ 2.35, H_{ortho}), 6.32 (t, 2H, $^4J_{HH}$ 2.33, H_{para}), 4.72 (d, 1H, $^3J_{HH}$ 6.7, PhC*H*O), 3.72 (s, 12H, O*Me*), 3.64 (d, 2H, $^2J_{HH}$ 13.83, CH_2), 3.40 (d, 2H, $^2J_{HH}$ 13.83, CH_2), 3.14 (q, 1H, $^3J_{HH}$ 6.78, C*H*Me), 1.18 (d, 3H, $^3J_{HH}$ 6.71, CH*Me*). δ_C 160.65 (s, Ph-C_{ipso}) 143.29 (s, Ph-C_{ipso}), 142.42 (s, Ph-C_{ipso}), 128.06 (s, ArC), 127.27 (s, ArC), 126.88 (s, ArC), 106.6 (s, C_{ortho}), 99.06 (s, C_{para}), 76.05 (s, Ph*C*HO), 58.45 (s, *C*HMe), 55.20 (s, O*Me*), 54.77 (s, *C*H_2), 9.16 (s, CH*Me*). Found: C 71.6; H 7.1; N 3.0; $C_{27}H_{33}NO_5$ requires C 71.8; H 7.4; N 3.1. Found: M^+, 451.2376. Calc. for $C_{27}H_{33}NO_5$: M, 451.2359.

4.16. Reaction of (1R,2S)-ephedrine with pyrrole-2-carboxaldehyde. Synthesis of (2RS, 4SS,5RR)-3-aza-3-, 4-dimethyl-1-oxa-5-phenyl-2-(2′-pyrrole)cyclopentane **16**

(1*R*,2*S*)-Ephedrine (0.98 g, 5.96 mmol) was dissolved in CH_2Cl_2 (20 cm^3) and stirred over 4 Å molecular sieves, pyrrole-2-carboxaldehyde (0.57 g, 5.96 mmol) was added to the solution and the mixture stirred for 24 h at room temperature. Filtration and removal of the volatiles under reduced pressure afforded a white solid which appeared, on the basis of NMR spectroscopy to consist of a single isomer of **16** (1.3 g, 90%). Recrystallisation from pentane–toluene (20:1 v/v) at −35°C afforded the title compound as white crystals (0.42 g). δ_H 8.70 (s, broad, 1H, pyrrole N*H*), 7.38–7.25 (m, 5H, Ph-*H*), 6.85 (m, 1H, pyrrole *H*), 6.37 (m, 1H, pyrrole *H*), 6.20 (m, 1H, pyrrole *H*), 5.11 (d, 1H, $^3J_{HH}$ 8.13, PhC*H*O), 4.83 (s, 1H, C2-*H*), 2.94 (dq, 1H, $^3J_{HH}$ 8.0 and 6.43, C*H*Me), 2.20 (s, 1H, N*Me*), 0.77 (d, 3H, $^3J_{HH}$ 6.43, CH*Me*). δ_C 139.95 (s, Ph-C_{ipso}), 128.44 (s, Ph-C_{ipso}), 127.94 (s, Ph-*C*), 127.69 (s, Ph-*C*), 127.63 (s, Ph-*C*), 118.45 (s, pyrrole-*C*), 109.42 (s, pyrrole-*C*), 108.45 (s, pyrrole-*C*), 92.34 (s, *C*2), 82.03 (s, Ph*C*HO), 63.70 (s, *C*HMe), 35.84 (s, N*Me*), 14.96 (s, CH*Me*). Found M^+, 242.1417. $C_{15}H_{18}N_2O$ requires; M^+, 242.1419. Found: C 74.5; H 7.7; N 11.6; $C_{15}H_{18}N_2O$ requires C 74.4; H 7.5; N 11.6.

4.17. Synthesis of N-(pyrrole-2′-methyl)-N-methyl-(1R,2S)-ephedrine **10**

A solution of (4*S*, 5*R*)-2-pyrrole-*N*-methyl-4-methyl-5-phenyl-oxazolidine (5.3 g, 21.9 mmol) was dissolved in THF solvent (20 cm^3) and added dropwise to a stirred suspension of $LiAlH_4$ (1.97 g, 54.8 mmol) in THF solution (20 cm^3) over the course of ca. 20 min. Upon complete addition the mixture was refluxed under an atmosphere of dinitrogen for 36 h. The reaction was then quenched by the cautious addition of water (1.0 cm^3) followed by aqueous $NaHCO_3$ solution (2.7 cm^3, 15% w/v) and a further aliquot of water (1.0 cm^3). The gelatinous solution was stirred for 1 h, filtered and the volatiles removed under reduced pressure to afford compound **10** as a white solid. Recrystallisation from toluene–pentane (1:1 v/v) afforded **10** as white crystals (3.38 g, 68%). δ_H 7.78 (s, broad, 1H, pyrrole N*H*), 7.31–7.12 (m, 5H, Ph-*H*), 6.45 (m, 1H, pyrrole *H*), 5.98 (m, 1H, pyrrole *H*), 5.87 (m, 1H, pyrrole *H*), 4.65 (d, 1H, $^3J_{HH}$ 3.88), 3.48 (s, 2H, CH_2), 2.85 (dq, 1H, $^3J_{HH}$ 6.7, C*H*Me), 2.11 (s, 3H, N*Me*), 0.98 (d, 3H, $^3J_{HH}$ 6.7, CH*Me*). δ_C 143.45 (s, Ph-C_{ipso}), 129.60 (s, Ph-C_{ipso}), 128.14 (s, Ph-*C*), 127.33 (s, Ph-*C*), 126.43 (s, Ph-*C*), 117.02 (s, pyrrole-*C*), 107.70 (s, pyrrole-*C*), 106.51 (s, pyrrole-*C*), 75.18 (s, Ph*C*HO), 62.76 (s, *C*HMe), 51.77 (s, *C*H_2), 37.90 (s, N*Me*), 9.29 (s, CH*Me*). *m/z* 243 $(M\text{-}H)^+$. Found: C 73.8; H 8.2; N 11.5; $C_{15}H_{20}N_2O$ requires C 73.7; H 8.3; N 11.5.

4.18. Systems based on the 1,7,7-trimethyl[2.2.1]heptane scaffold **17–20**

(1*R*,4*S*)-2,3-bornanedione **17** was synthesised using the published procedure of selenium dioxide oxidation of (1*R*,4*S*)-camphor [43]j. (83%, mp 199–200°C, Lit. 198°C [43]j; Found: C 72.3; H 8.7; $C_{10}H_{14}O_2$ requires C 72.3; H 8.4).

Keto-oximine **18** was synthesised as a mixture of stereoisomers using the published method, room temperature treatment of (1*R*,4*S*)-2,3-bornanedione **17** with hydroxylamine hydrochloride and sodium acetate. (89%, mp 151–156°C, Lit. [[41]l] 155°C (*anti*), 117°C (*syn*); Found: C 66.5; H 8.6; N 7.7; $C_{10}H_{15}NO_2$ requires C 66.3; H 8.3; N 7.7) [40]b.

Reduction of **18** with $LiAlH_4$ in diethylether [41]b affords a mixture of [*exo,exo*] and [*endo,endo*] (1*R*,4*S*)-3-amino-2-hydroxy-1,7,7-trimethyl(2.2.1)heptane **19** in a ca. 85:15 ratio (70%). Separation and isolation of isomerically pure [*exo,exo*]-**19** was achieved by conversion to oxazolidinone **20** (Found: C 67.9; H 8.9; N 7.3; $C_{11}H_{17}NO_2$ **20** requires C 67.7; H 8.7; N 7.2) by reaction with diethylcarbonate followed by recrystallisation from hexane–ethyl acetate (2:1 v/v) according to the published procedure (30%; Found: C 70.1; H 11.3; N 8.1; $C_{10}H_{19}NO$ **19** requires C 71.0; H 11.2; N 8.3) [43]f.

Alkylated amino alcohols **11a–d** were prepared as described previously [41]h. **11a:** Found: C 72.2; H 12.9; N 7.0; $C_{12}H_{23}NO$ requires C 73.1; H 11.7; N 7.1. **11b:** Found: C 73.4; H 12.7; N 6.6; $C_{13}H_{25}NO$ requires C 73.9; H 11.8; N 6.6. **11c:** Found: C 74.3; H 12.3; N 6.2; $C_{14}H_{27}NO$ requires C 74.6; H 12.0; N 6.2. **11d:** Found: C 72.8; H 12.0; N 7.0; $C_{12}H_{23}NO$ requires C 73.1; H 11.7; N 7.1.

*4.19. Synthesis of bis-(N,N-dimethylethyl)-2,6-pyridinedicarboxamide **22***

2,6-Pyridinedicarboxylic acid (15.5 g, 7.6 mmol) was added to neat thionyl chloride (136 g, 83.2 cm^3, 1.14 mol) and heated at reflux for 18 h to afford a clear pale yellow oil. Excess thionyl chloride was removed in vacuo to afford 2,6-pyridinedicarboxylchloride as a white crystalline solid (18.7 g, 99%). A dichloromethane solution of 2,6-pyridinedicarboxylchloride (3.21 g, 15.7 mmol in 32 cm^3) was added dropwise to a stirred solution of *N,N*-dimethylethylenediamine (2.76 g, 31.3 mmol) and triethylamine (32.9 cm^3, 236 mmol) in dichloromethane (165 cm^3). The resulting clear orange solution was stirred for 1 h after which time a slight precipitate had developed. The dichloromethane solution was removed under reduced pressure to afford a deep red viscous liquid. This liquid was extracted into toluene (3×15 cm^3), filtered and all the volatile materials removed under reduced pressure to afford a red liquid. This liquid was dissolved in the minimum amount of dichloromethane and passed down three columns of Florisil (25 g each), each time eluting with ca. 150 cm^3 of dichloromethane. All the aliquots were combined and the volatiles removed under reduced pressure to afford **22** as a yellow, waxy solid. Recrystallisation from toluene afforded **22** as colourless crystals (1.32 g, 27%). δ_H (0.1 M $CDCl_3$, 25°C) 8.20 (br t, 2H,-C(O)N*H*-), 8.18 (d, 2H, $^3J_{HH}$ 7.7, C_5H_3N-H_m), 7.86 (t, 1H, $^3J_{HH}$ 7.7, C_5H_3N-H_p), 3.44 (dt, 4H, $^3J_{HH}$ 5.8, HNCH_2), 2.41 (t, 4H, $^3J_{HH}$ 6.0, CH_2NMe_2), 2.16 (s, 12H, NMe_2). δ_C (0.1 M $CDCl_3$) 163.54 (s, -C(O)NH), 148.83 (s, C_5H_3N-C_o), 138.70 (s, C_5H_3N-C_p), 124.67 (s, C_5H_3N-C_m), 58.20 (s, *C*H_2NMe_2), 45.32 (s, NMe_2), 37.04 (s, $HNCH_2$). Found: M^+, 307.2003. Calc. for $C_{15}H_{25}N_5O_2$: M, 307.2003.

4.20. Binding studies with bis-(N,N-dimethylethyl)-2,6-pyridinedicarboxamide

Binding constants for both dimethyl-H-phosphonate [K_{11}(P)] and benzaldehyde [K_{11}(A)] with amphoteric receptor **22** have been determined in C_6D_6 solution at 298 K with a receptor concentration of 0.01 M and increasingly larger molar equivalents of substrate. The chemical shift dependence of the carboxamide hydrogen resonance of amphoteric receptor **22** as a function of the concentration of substrate (dimethyl-H-phosphonate or benzaldehyde) was determined by ^{1}H-NMR titration with increasing molar concentrations of substrate. The results of this analysis for both dimethyl-H-phosphonate and benzaldehyde are collected in Tables 6 and 7. The data in these tables have been analysed according to the 1:1 binding isotherm: [47]

$$\frac{1}{\Delta} = \frac{1}{\Delta_{11} \cdot K_{11} \cdot [L]} + \frac{1}{\Delta_{11}}$$

$$\Delta = \delta_{22}(\text{obs}) - \delta_{22}(\text{pure}) \text{ and } \Delta_{11} = \delta(\text{complex}) - \delta_{22}(\text{pure}) (\text{both } \Delta \text{ values are in ppm}).$$

Since both $[L]_o \gg [\mathbf{22}]$ and the measured binding constants are small we are able to make the approximation, $[L] = [L]_o$ where [L] is the concentration of uncomplexed ligand (either dimethyl-H-phosphonate or benzaldehyde) and $[L]_o$ is the total concentration of added ligand. A double reciprocal plot of the data in Tables 6 and 7, $1/\Delta$ versus $1/[L]_o$ as shown in Fig. 5, affords binding constants for organophosphorus (Fig. 6a) and aldehyde (Fig. 6b) substrates of K_{11}(P) 0.34 mol^{-1} dm^3 and K_{11}(A) 0.53 mol^{-1} dm^3 respectively.

4.21. Kinetic studies on the bis-(N,N-dimethylethyl-2,6-pyridinedicarboxamide catalysed addition of dimethyl-H-phosphonate to benzaldehyde

A mixture consisting of dimethyl-H-phosphonate (367 μl, 4.0 mmol), toluene (227 μl) and 0.20 M receptor **22** solution (1.0 cm^3, 0.2 mmol) was placed in a 10 mm NMR tube fitted with a 5 mm insert containing reference and lock solvent (C_6D_6). To this solution was added benzaldehyde (407 μl, 4.0 mmol) so that the total volume of the reaction system was maintained at 2.0

cm^3 The reaction was then followed at 298 K by $^{31}P\{^1H\}$-NMR spectroscopy by monitoring the intensities of both dimethyl-H-phosphonate (δ_p 11.8) and the product α-hydrnxybenzyldimethylphosphonate (δ_p 24.3). Spectra were recorded with a 2 s pulse delay and inverse gated ^1H decoupling in order to minimise differences in ^{31}P T_1 relation times and differential n.O.e. effects dues to decoupling. The results were analysed according to standard second order kinetics through the rate equation; $1/[P] = k_2 \cdot t + 1/[P]_o$, where P = $(MeO)_2P(O)H$ and $[P]_o$ represents the initial concentration of P at time $t = 0$ [49]. A plot of $1/[P]$ versus time (h) affords the second order rate constant $k_2 = 5.9 \times 10^{-2}$ mol^{-1} dm^3 h^{-1} from the gradient (Fig. 7a). The above protocol was repeated under exactly the same conditions of temperature, solvent and concentrations but replacing receptor **22** with triethylamine (1.0 cm^3 of a 0.20 M triethylamine solution, 0.2 mmol). Again monitoring the progress of reaction via $^{31}P\{^1H\}$-NMR spectroscopy and analysis through second order kinetics $\{1/[P] = k_2 \cdot t + 1/[P]_o\}$ affords a second order rate constant $k_2 = 5.9 \times 10.2$ mol^{-1} dm^3 h^{-1} (Fig. 7b).

Unfortunately, we have been unable to perform saturation kinetic experiments, where receptor **22** exists in a bound form throughout the course of reaction. This is due to a combination of the small binding constants observed between **22** and the substrates and solubility of both catalyst and product α-hydroxyphosphonate ester. If the fraction of bound catalyst **22** is represented as R_P when bound to dimethyl-H-phosphonate and R_A when bound to benzaldehyde, C = amphoteric receptor catalyst **22**; P = dimethyl-H-phosphonate; A = benzaldehyde; CP = catalyst—H-phosphonate and CA = catalyst—aldehyde complex; $K_{11} = 1{:}1$ binding constant.

$$C + P \; CP \quad K_{11}(P) = 0.34\,mol^{-1}dm^3$$

$$C + A \; CA \quad K_{11}(A) = 0.53\,mol^{-1}dm^3$$

$$R_p = [CP]/[C]_T \text{ and } R_A = [CA]/[C]_T$$

where $[C]_T$ is the total concentration of catalyst added.

$$K_{11}(P) = [CP]/[C] \cdot [P] \quad (1)$$

now since $[P] \gg [C]$, the approximation $[P] = [P]_o$ can be made to afford

$$K_{11}(P) = [CP]/[C] \cdot [P]_o \quad (2)$$

Noting that;$[CP] = R_P \cdot [C]_T$ and $[C] = [C]_T - [CP]$ we can substitute in Eq. (2) to afford;

$$K_{11}(P) = [C]_T \cdot \frac{R_P}{\{[C]_T - [C]_T\} \cdot R_p} \cdot [P]_o \quad (3)$$

this can be rearranged to afford;

$$R_P = \frac{K_{11}(P) \cdot [P]_o}{1 + K_{11}(P) \cdot [P]_o} \quad (4)$$

Similar manipulations for the benzaldehyde system lead to;

$$R_A = \frac{K_{11}(A) \cdot [A]_o}{1 + K_{11}(A) \cdot [A]_o} \quad (5)$$

Under the initial concentration conditions used in the above kinetic studies, [**22**] = 0.1 M, $[(MeO)_2P(O)H]$ = [PhCHO] = 2.0 M, ca. 40% of the catalyst will be bound to $(MeO)_2P(O)H$ and ca. 51% bound to PhCHO at the start of reaction, a total of 90% complexation. That this does not achieve complete initial saturation is due to the low binding constants (0.34 mol^{-1} dm^3 and PhCHO 0.53 mol^{-1} dm^3 respectively). As reaction proceeds, the concentrations of both substrates will decrease and consequently the degree of substrate complexation will decrease but product complexation will increase. If substrate starting concentrations in excess of 3 M were possible, then > 51% of the catalyst would be bound by phosphite and > 59% by aldehyde, enough to ensure saturation for at least the start of reaction. However, at this concentration level product solubility in toluene is problematic compromising any meaningful kinetic data. We have also examined the same system with benzaldehyde as reaction solvent. Under these pseudo first-order conditions we achieve concentrations of only 9.7 M in PhCHO and 0.1 M in phosphite (pure benzaldehyde is 9.8 M) which unfortunately still does not provide saturation kinetics (83% of catalyst will be bound by aldehyde and only 3% by phosphite under these conditions).

4.22. General screening procedure for catalysis assay

All reactions were performed in oven-dried 10 mm NMR tubes fitted with a 5 mm NMR tube insert containing C_6D_6 to provide deuterium lock. The NMR tube reaction vessel was loaded in either a dinitrogen-filled dry box or on a Schlenk line with PhCHO (407 μl, 0.425 g, 4.0 mmol) and $(MeO)_2P(O)H$ (367 μl, 0.440 g, 4.0 mmol) followed by a measured volume of a standard solution of the catalyst to be tested made up in the required solvent to a concentration of 0.4 M (1.0 cm^3) and the total volume of the reaction mixture then made up to 2.0 cm^3 (microsyringe) with solvent. This loading procedure affords a concentration profile within the reactor of PhCHO (2.0 M), $(MeO)_2P(O)H$ (2.0 M) and catalyst (0.2 M). The time of initiation of reaction was taken as that time when the catalyst was added. Reaction progress was then monitored in situ by $^{31}P\{^1H\}$-NMR spectroscopy on a JEOL FX 90Q spectrometer (36.2 MHz for ^{31}P) where both $(MeO)_2P(O)H$ (δ_p 11.7) and product $(MeO)_2P(O)CHPh(OH)$ (δ_p 24.9) can be distinguished readily. Upon completion of reaction, the solvent was removed under reduced pressure and the crude product mixture analysed using the enan-

tiopurity assay procedure described in Experiment 4.4 (ca. 11 mg of crude mixture are sampled with a standard CDA solution containing **2** at 0.125 M and NEt_3 at 0.25 M). We have found that the crude product often appears as a sticky solid, possibly caused by retention of aromatic solvents or the presence of unreacted (always $< 5\%$) starting materials or catalyst. Consequently, it is necessary to ensure complete mixing of the crude product and we find that sampling of at least four fractions is a reasonable measure to be confident of a homogeneous mixture and consequently a representative assay. We found subsequently, that removal of the catalyst from the crude product mixture by washing with either toluene or pentane does not compromise the enantiopurity of the product α-hydroxyphosphonate and may therefore be used prior to measurements of enantiopurity.

Due to the steady deterioration of CDA **2** over a period of months when stored at room temperature under a static atmosphere of dinitrogen, the concentration of H-phosphonate **4**, formed due to trace hydrolysis, increases. Whilst this in itself is not a problem and does not lead to any side-reaction with the α-hydroxyphosphonate ester, an accompanying impurity is also produced which gives rise to a low intensity yet significantly broadened resonance centred at δ_p 124 ($\Delta_{1/2}$ ca. 130 Hz), within the range of the integration window for the assay. Since this impurity occurs only in samples of **2** which are over 4–5 months old, we have consistently prepared and used all samples of **2** within that period and have thus eliminated the effects of this impurity [5].

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[5] We have not investigated the nature of this impurity but since it is most prevalent in old (> 4 months) samples of **2** which contain significant amounts of H-phosphonate **4**, one possibility is a condensation product between **2** and **4** to form a [P—O—P] species, a reaction which is well precedented. This would give rise to δ_p signals in the correct region (> 100 ppm) and also account for the broadness of the signal by coupling to four quadrupolar ^{14}N nuclei as part of a second order $A_2XX'A'_2$ spin system.

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