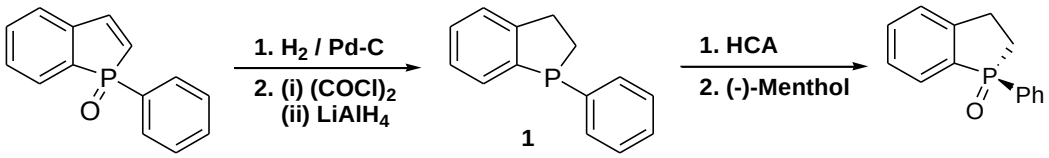
Synthesis of 2,3-dihydro-1-phenylbenzo[b]phosphole (1-phenylphosphindane) and its use as a mechanistic test in the asymmetric Appel reaction. Decisive evidence against involvement of pseudorotation in the stereoselecting step.

Damien J. Carr, Jaya Satyanarayana Kudavalli, Katherine S. Dunne, Helge Müller-Bunz and Declan G. Gilheany*

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland

declan.gilheany@ucd.ie

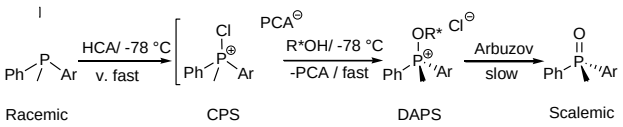


Racemic 2,3-dihydro-1-phenylbenzo[b]phosphole was obtained by reduction of 1-phenylbenzo[b]phosphole-1-oxide, itself derived by ring closing metathesis of phenylstyrylvinyl phosphine oxide. The title compound was then re-oxidised under asymmetric Appel conditions. Comparison of the sense and degree of the stereoselectivity to that obtained with an open chain analogue indicated that the ring system does not affect the selectivity of the process. This, in turn, strongly suggests that the stereoselection is not related to pseudorotamer preferences in putative phosphorane intermediates.

Pentaco-ordinate phosphorus intermediates play an important role in synthetically valuable transformations such as the Wittig reaction[1] Horner-Wadsworth-Emmons reaction[2] and reactions promoted by Mitsunobu conditions.[3] Such intermediates can undergo a fast intramolecular ligand exchange process, termed Berry pseudorotation,[4,5] that may have a significant effect on the outcome of the reaction.[6,7] However, in the case of the Appel reaction conditions,[8] while the involvement of chloro- and alkoxy-phosphonium species is

well established,[9,10,11] the extent of participation of pentaco-ordinate phosphorane intermediates is less clear.[8,9]

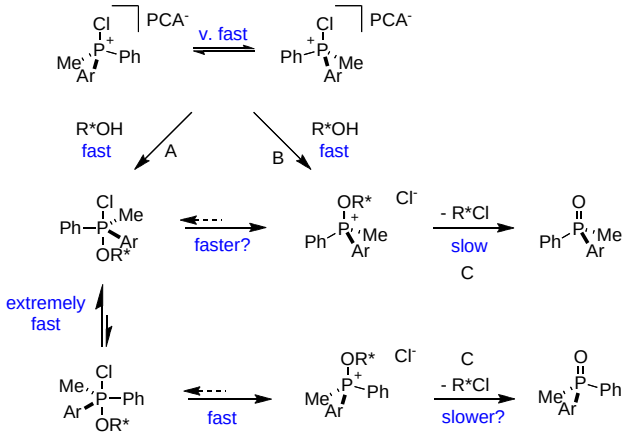
Our interest in this question arose through our development[12] of an asymmetric version of the Appel conditions (Scheme 1), whereby racemic arylmethylphenyl phosphines are treated with hexachloroacetone (HCA) and a chiral non-racemic alcohol (R*OH) to give high yields of enantioenriched phosphine oxides with enantiomeric excess (ee) up to 82%. This reaction is an effective way to make certain *P*-stereogenic phosphine oxides and bisphosphine oxides such as DiPAMPO and analogues[12,13] but is clearly limited by the moderate selectivities. As part of our studies to raise selectivity and expand substrate scope, we determined that the broad course of the reaction is as shown in Scheme 1 for arylmethylphenylphosphines.[11,14] It involves the transient generation of an intermediate chlorophosphonium salt (CPS, δP approx. 70-75 ppm), trapping by alcohol (R*OH), giving unequal amounts of a pair of diastereomeric alkoxyphosphonium salts (DAPS, δP approx. 65-70 ppm), which then undergo slow Arbuzov collapse to form scalemic phosphine oxide.



Scheme 1. The asymmetric Appel process. HCA: hexachloroacetone; CPS: chlorophosphonium salt; DAPS diastereomeric alkoxyphosphonium salts; PCA: pentachloroacetonide.

The likely routes for the source of the stereoselection in the conversion of CPS to DAPS are shown in Scheme 2 along with their required relative rates. Pathway A posits formation of diastereomeric pentaco-ordinate alkoxychlorophosphoranes, which would be expected to undergo rapid interconversion *via* Berry pseudorotation. Selection could then be as a result of the unequal distribution of pseudorotamers (dynamic thermodynamic resolution) or by their

unequal rates of collapse to DAPS (dynamic kinetic resolution) or both. A rather different possibility is shown as Pathway B: reaction of the chiral alcohol with rapidly interconverting CPS to generate directly the unequal mixture of diastereomers (also a dynamic kinetic resolution). The selectivity engendered by either Pathways A and B might also be either augmented or diminished by unequal rates of the Arbusov collapse to oxides (Pathway C) if the DAPS species can interconvert. However our preliminary studies11 indicated that their ratios (as measured by ^{31}P NMR spectroscopy) remained relatively unchanged during the course of the reaction and usually corresponded fairly consistently with the ees in the product oxides.



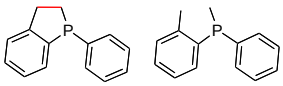
Scheme 2: Possible sources of stereoselection in the asymmetric Appel process.

Faced with these multiple possibilities, we sought ways to simplify our analysis and we report here our studies focused on the possible involvement of the pentaco-ordinate species (Pathway A) primarily by the synthesis of a compound designed to reveal its influence.

Rationale for the Test Compound. Previously we had seen no evidence in the ^{31}P NMR spectra of our reaction mixtures (in toluene solvent) for the intervention of pentaco-ordinate species, which might be expected in a region of moderately low field shift (δ -30 to -60 ppm)[15] in this solvent, but we were aware that this did not rule it out completely. Therefore we sought a system that should affect the rate of Berry pseudorotation, in turn imparting a

potential difference in stereoselectivity. Inclusion of the phosphorus atom in a ring, especially five-membered, is a well-known stratagem in phosphorus chemistry shown in many instances to impact dramatically kinetics and mechanism.[7,16] We chose 2,3-dihydro-1-phenylbenzo[b]phosphole (1-phenylphosphindane, **1**), as being the cyclic analog of methylphenyl(*o*-tolyl)phosphine **(2**, Figure 1). The latter had been studied extensively by us in the asymmetric Appel process and had given the previous best enantioselectivity (up to 82% ee).[12,14(b)] The linking of two of the ligands at phosphorus into a five-membered ring introduces a limit on the number of possible pseudo-rotamers because the ring can span easily only equatorial-axial positions.[4(b)] The presence of the ring is also expected to slow Berry pseudorotation[4(c),16(b)] so that if it is indeed involved in the stereoselection process, we should expect a substantial change in ee when compared to **2** under the same conditions. We would also increase our chances of detecting the pentaco-ordinate species by ^{31}P NMR spectroscopy, since the ring would also be expected to slow its decomposition.[16(b),(d)]

Figure 1. Comparison of phosphines **1** and **2**

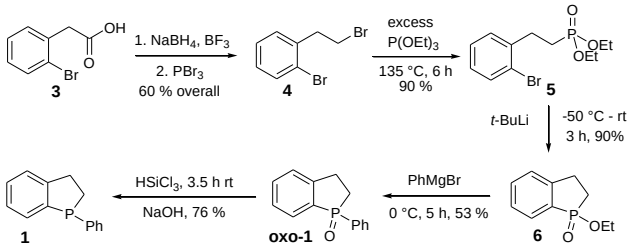


1 **2**

Compounds such as **1** are a valuable synthetic challenge in their own right; for example as ligands for catalytic asymmetric hydrogenation.[17,18] but most syntheses of benzophospholanes of type **1** have drawbacks.[19] Herein, we report the efficient synthesis of the title compound, its subsequent use in the asymmetric Appel process, the absolute configuration of the resulting oxide and the implications for the origin of the stereoselectivity of the reaction.

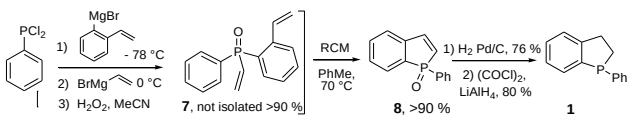
Synthesis of the Test Compound. Our initial, fairly traditional, synthesis (route A) of compound **1** is outlined in scheme 3. Reduction[20] and bromination[21] of 2-bromophenylacetic

acid **3** afforded dibromide **4** in 60% overall yield, which was then subjected to Arbusov reaction with triethylphosphite to give a good yield of phosphonate **5**. A notable issue in the latter reaction was the side reaction of ethyl bromide and triethylphosphite. Consumption of the dibromide required very substantial excess of triethylphosphite, resulting in the production of ethyl diethylphosphonate in significant excess over the product **5** (ratio of 4:1) from which it had to be purified by careful high vacuum distillation. Intramolecular cyclisation of **5** with *t*-BuLi to 1-ethoxy-2,3-dihydrophosphole-1-oxide **6** proceeded in high yield but the yield of the subsequent conversion to 2,3-dihydro-1-phenylphosphole-1-oxide (**oxo-1**) with phenyl magnesium bromide could not be raised above 53%, despite extensive attempted optimization. Ironically this latter problem may be related to the reduced reactivity of the five-membered cyclic pentaco-ordinated phosphorus intermediate, the stratagem of this research in the first place. Perhaps for similar reasons, the deoxygenation of **oxo-1** with trichlorosilane was also rather unsatisfactory, with difficulties in the isolation of the product and, notably, the persistent presence of **oxo-1** following the reduction.



Scheme 3: The synthesis of **oxo-1** *via* route A

Although we were able to access our target by Route A, the problems encountered prompted us to explore an alternative ring-closing metathesis (RCM) route.[22] In contrast to Route A, the phenyl group could be in place prior to the formation of the benzophospholane. The RCM procedure we chose (Route B) is given in Scheme 4.



Scheme 4: The synthesis of **oxo-1** *via* route B. RCM performed with Hoveyda-Grubbs 2nd Generation Catalyst.

Starting from dichlorophenylphosphine sequential addition of the Grignard reagent derived from 2-bromostyrene at low temperature, followed by vinyl magnesium bromide resulted in the formation of phenylstyrylvinyl phosphine (not isolated), oxidized *in situ* immediately to corresponding oxide **7**. The latter was unstable, decomposing upon attempted purification, so the crude product was used directly in the next step without purification. For the ring-closing metathesis, Hoveyda-Grubbs 2nd generation catalyst was found to be optimal resulting in the formation of 1-phenylbenzo[b]phosphole-1-oxide, **8**, with >90% conversion as judged by ^{31}P NMR spectroscopy. Compounds of this type are also of interest in their own right,[23] notably Matano and co-workers recently used **8** in electronic studies of its dimer and related compounds,[24] but, again, syntheses are unsatisfactory. The exocyclic double bond of phosphole oxide **8** was hydrogenated with ease to give **oxo-1** with an overall isolated yield from dichlorophenylphosphine of 80%. For the final deoxygenation of **oxo-1**, we were able to utilise a novel methodology recently reported by our laboratory involving pre-treatment with oxalyl chloride (which generates a chlorophosphonium salt) followed by reduction with lithium aluminum hydride.[14,25] This methodology was applied to the direct conversion of **oxo-1** to phosphine **1** in a good yield of 80 % isolated with only trace amounts of oxide in the final material.

Testing in the asymmetric Appel process. With the synthesis of compound **1** established we turned to probe the mechanism of the asymmetric Appel process. Both **1** and **2** were treated with HCA and chiral alcohol at a number of temperatures with the results shown in Table 1.

Table 1. Results of asymmetric Appel process as applied to phosphines 1 and 2.[a]

Entry	Alcohol	Temperature °C	oxo-1[c] ee[b]	oxo-2[c] ee[b]
1	(-)-menthol	0	50	50
2	(-)-menthol	-44	62	66
3	(-)-menthol	-80	80	76
4	(-)-8-phenylmenthol	-80	82	75

a) HCA 0.11 M, phosphine 0.11 M, alcohol 0.132 M, for detailed procedure: see experimental section, yields >95 %, no other products visible in ^{31}P NMR spectra; *b*) measured by CSP-HPLC; *c*) Configuration of **oxo-1** determined to be (*R*) - see text; **oxo-2** configuration determined to be (*R*) previously.[27]

Our premise is that, if Berry pseudorotation is involved in the stereoselection, then significantly different selectivity should result on introduction of the ring. However, the results obtained[26] with (-)-menthol (entries 1-3) show that across a wide temperature range, the selectivity obtained with phosphine **1** tracks well that with phosphine **2**. For completeness, we also checked selectivity with a different alcohol, choosing (-)-8-phenylmenthol as it had previously shown a slightly different selectivity profile compared to (-)-menthol.[12] Again, there was no significant difference (entry 4). The reaction of **1** was also followed by ^{31}P NMR spectroscopy and signals corresponding to diastereomeric alkoxyphosphonium salts (DAPS) were observed (δP 89.3 and 89.5 ppm). However, at no point during the reaction did we observe a signal for a chloroalkoxyphosphorane. These results provide powerful evidence against the involvement of pentaco-ordinate intermediates and associated Berry pseudorotation in the stereoselectivity of the asymmetric Appel process.

Finally, it remained to check that the absolute configurations of the product oxides were the same. We had previously established that **(*R*)-oxo-2** is the major enantiomer produced with (-)-menthol.[27] Crystallization of scalemic **oxo-1** obtained from the process proved unsuccessful, and we had to resort to preparative CSP-HPLC of the racemic material. Crystals grown of the major enantiomer, were re-confirmed as such by analytical CSP-HPLC and one was analysed by single crystal X-ray crystallography (details in ESI). The absolute

configuration was indeed found to be (*R*), that expected if phosphines **1** and **2** are comparable within the asymmetric Appel manifold.

In conclusion we have developed two routes to the phosphindane core structure. Route A provides the possibility for variation of the pendant substituent at phosphorus by the use of alternative nucleophiles with phosphonate **6**. Route B is a short efficient synthetic route to both 1-phenylbenzo[b]phosphole oxide **8** and 1-phenyl-2,3,dihydrobenzo[b]phosphole **1**, with scope for application toward the synthesis of analogues with a central benzophospholane core. Likewise variation on the alkyl ring could be achieved by functionalisation of the double bond in oxide **8** or having pre-installed functionality before the RCM step. Most importantly, the availability of Route B allowed us to study stereoselection in our asymmetric oxidation of tertiary phosphines, which provided strong evidence against the involvement of Berry pseudorotation in the selecting process.

Experimental Section

General Experimental All reagents were purchased from commercial sources and unless noted otherwise used as received without further purification. All dry solvents were processed through a Grubbs type solvent purification system and stored over molecular sieves (4Å). All molecular sieves were flame dried in a flask and heated to ~200 °C with a heat gun under vacuum prior to use. Flash Chromatography was performed on silica, particle size 0.04-0.06 mm. NMR spectra were recorded at 25 °C on 300-600 MHz spectrometers. Chemical shifts are reported in δ (ppm) relative to internal Me_4Si. ^{13}C NMR were assigned with the aid of two-dimensional cross coupling experiments. All NMR of air or moisture sensitive samples were made up under nitrogen in dry $CDCl_3$ in a Schlenk tube designed specifically for NMR preparation which could be dried and back-filled *via* standard Schlenk technique. $CDCl_3$ was dried over activated molecular sieves (4Å) under atmosphere of

nitrogen and stored in a Schlenk flask over sieves. High resolution mass spectrometry was carried out on a electrospray ionisation mass spectrometer with a TOF analyzer. IR spectra were obtained on a FTIR spectrometer, and are reported here in units of cm^{-1}. Samples were prepared as thin films between NaCl plates. Phenyl(methyl)(*o*-tolyl)phosphine and its corresponding oxide were synthesized as per previous reports by our group.[10]

2-(2-Bromophenyl)ethanol.[20] To a solution of 2-bromophenylacetic acid (10 g, 46.5 mmol, 1 eq.) in dry THF (20 mL) cooled in an ice water bath, $NaBH_4$ pellets (2.28 g, 60.4 mmol, 5.2 eq. of hydride) were added under flow of nitrogen in lots over 15 min. To this $BF_3.Et_2O$ (8.6 mL, 70 mmol, 1.5 eq.) was added dropwise by syringe over 15 minutes. A white precipitate was noted. The mixture was allowed to stir at room temperature for 24 h and was monitored by ^1H NMR by sampling the mixture and carrying out a work up as below. Once complete the THF was removed under reduced pressure and the mixture was quenched by addition of HCl (100 mL, 1 M). To this ethyl acetate was added (50 ml) and the mixture was washed with sat. $NaHCO_3$ (50 mL × 2) followed by a final wash with brine (50 mL× 2). The organic layer was further dried over Na_2SO_4 and concentrated under reduced pressure to yield a pale yellow oil. (7.40 g, 70 %). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.54-7.52 (m, 1H, ArH), 7.29-7.19 (m, 2H, ArH), 7.10-7.03 (m, 1H, ArH) 3.84 (t, *J* = 7.5 Hz, 2H, HO-C**H$_2$**) 3.00 (t, *J* = 7.5 Hz 2H, Ar-C**H$_2$**). In accordance with literature, used without further purification.

(2-Bromophen-1-yl)ethyl bromide (4).[21] The oil from the previous procedure was added to a nitrogen-flushed 2-neck round bottomed flask equipped with a condenser. To this neat PBr_3 (3.8 mL, 40mmol, 1.2 eq.) was added slowly *via* syringe dropwise over 30 min at room temperature. This was heated to 80 °C and stirred at this temperature for 2 h. The mixture was cooled to 0 °C. Diluted with DCM (100 mL) and quenched with sat. $NaHCO_3$ (2 × 50

mL) and finally washed with distilled H_2O (2 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to an oil. This was purified using flash chromatography on silica (80:20 cyclohexane/ethyl acetate) to afford a clear oil. (7.57 g, 85 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.5 (d, *J* = 8.4 Hz, 1H, Ar**H**), 7.27-7.24 (m, 2H, Ar**H**), 7.14-7.08 (m, 1H, Ar**H**), 3.58 (t, *J* = 7.5 Hz, 2H, Br-C**H$_2$**), 3.28 (t, *J* = 7.6 Hz, 2H, Ar-C**H$_2$**). In accordance with literature, used without further purification.

Diethyl 2-(2-bromophen-1-yl)ethylphosphonate (5). In a dry nitrogen-flushed flask a neat mixture of **4** (5.6 g, 21.3 mmol, 1 eq) and triethylphosphite (16 mL, 96 mmol, 4.5 eq.) was stirred at 135 °C. When the reaction was complete (6 h, by ^{31}P NMR), the side product, ethyl diethylphosphite was removed by high vacuum distillation leaving behind the required product as a colourless liquid. (6.48 g, 94 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53 (d, *J*= 7.6 Hz, 1H, Ar**H**), 7.24-7.26 (m, 2H, Ar**H**), 7.06-7.11 (m, 1H, Ar**H**), 4.06-4.16 (m, 4H, O-C**H$_2$**), 2.98-3.07 (m, 2H, P-C**H$_2$**), 2.03-2.13 (m, 2H, Ar-C**H$_2$**), 1.33 (t, *J* = 7.1 Hz, 6H, C**H$_3$**);. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.2, 132.9, 130.2, 128.1, 127.6, 124.0, 61.6 (d, $^2J_{PC}$ = 6.5 Hz O-**C**H_2), 29.4 (d, $^2J_{PC}$ = 3.9 Hz Ar-**C**H_2), 25.8 (d, $^1J_{PC}$ = 139.3 Hz, P- **C**H_2), 16.4 (d, $^3J_{PC}$ = 6.1 Hz, **C**H_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 30; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{19}BrO_3PH$ 321.0255; Found 321.0267. IR δ 3054, 2985, 1265 (P=O) cm^{-1}. Used without further purification.

1-Ethoxy-2,3-dihydrobenzo[b]phosphole-1-oxide (6). In a dry nitrogen-flushed flask a solution of **5** (3.0 g, 9.3 mmol, 1 eq.) in dry THF (30 mL) was added and cooled under nitrogen in a dry ice-acetone bath. *t*-BuLi (1.7 M in pentane, 11.0 mL, 18.7 mmol 2.1 eq.) was added dropwise *via* syringe over 30 min. After the mixture was stirred for 1 h at -78 °C, the solution was allowed to warm to room temperature when the mixture turned pale yellow

and it was stirred for a further 30 min. This was then cooled to -50 °C and it was quenched by adding water (25 mL) dropwise *via* syringe and diluted subsequently with ethyl acetate (100 mL). This was allowed to warm to room temperature and the separated organic layer was washed with brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure to yield a pale yellow oil. The crude product was purified by flash chromatography on silica (90:10 cyclohexane/ethyl acetate) to yield the desired product as a colourless oil. (1.63 g, 90.5 % yield).; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (apparent t, *J* = 8.4 Hz, 1H, Ar**H**$_{peri}$), 7.44-7.53 (m, 1H, Ar**H**), 7.28-7.38 (m, 2H, Ar**H**), 4.00-4.26 (dq *J* = 7 Hz, 2H, O-C**H**$_2$), 3.04-3.19 (m, 2H, P-**C**$\mathbf{H_2}$), 2.08-2.24 (m, 2H, Ar-C**H**$_2$), 1.32 (t, *J* = 7.0 Hz, 3H, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 146.2 (d, J_{PC} = 37.5 Hz Ar), 132.6 (d, $^4J_{PC}$ = 2.5 Hz, Ar), 130.3 (d, $^1J_{PC}$ = 130.8 Hz Ar), 127.6 (d, J_{PC} = 9.0 Hz Ar), 127.3 (d, $^3J_{PC}$ = 10.8 Hz Ar), 126.9 (d, $^3J_{PC}$ = 12.9 Hz Ar), 61.1 (d, $^2J_{PC}$= 6.5 Hz, O-**C**H_2), 26.0 (d, $^3J_{PC}$ = 6.5 Hz Ar-**C**H_2), 23.7 (d, $^1J_{PC}$ = 96.5Hz), 16.5 (d, $^3J_{PC}$ = 6.1 Hz, **C**H_3); ^{31}P NMR (121 MHz, $CDCl_3$) δ = 65.3 ; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}O_2PH$ 197.0731; Found 197.0727, IR δ 2983, 2936, 1598, 1211 (P=O) cm^{-1}

1-Phenyl-2,3-dihydrobenzo[b]phosphole-1-oxide (oxo-1 route A). A dry nitrogen-flushed flask was charged with a solution of **6** (0.75 g, 3.82 mmol 1 eq.) in dry THF (50 mL) and cooled in an ice water bath. Phenylmagnesium chloride (2.0 M in THF, 2.66 mL, 5.34 mmol, 2.5 eq.) was added dropwise *via* syringe over 30 min and stirred for 15 min at 0 °C. This mixture was slowly heated to reflux for 6 h and a dark brown color was noted. The mixture was cooled to -10 °C and the THF removed under reduced pressure. To this of ethyl acetate (100 mL) was added and the mixture was quenched with aq. HCl (1.0 M) at -10 °C until a neutral pH was obtained. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to yield a dark oil. This was purified by a flash chromatography on silica (ethyl acetate: cyclohexane 70:30) to yield the desired product as a

pale yellow solid. Subsequent recrystallisation from hot ethyl acetate and cyclohexane afforded pale yellow crystals. (0.35g, 53.5 %); mp 73-77 °C. See below for characterization.

1-Phenyl-2,3,dihydrobenzo[b]phosphole (1) (*via* silane reduction). To a solution of **oxo-1** (0.5 g, 2.14 mmol) in toluene (10 mL) was added trichlorosilane (3.0 mL, 21.4 mmol). The reaction mixture was stirred at room temperature for 3.5 h. After hydrolysis with excess 30 % NaOH (10 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 x 25 mL).The combined extracts were washed with water (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated, yielding (0.35 g, 76 %) of **1** as a pale yellow oil. See below for characterization.

Phenyl(*o*-vinylphenyl)(vinyl)phosphine oxide (7): To a dry nitrogen-flushed 2-neck flask charged with magnesium turnings (0.28 g, 11.5 mmol, 1 eq.) a solution of 2-bromostyrene (2.6 g, 14 mmol 1.2 eq.) in dry THF (5 mL) was added (1 mL) dropwise *via* syringe at room temperature and initiation was noted. The remaining 2-bromostyrene solution (4 mL) was added dropwise *via* syringe over 10 min followed by dry THF (10 mL). This was heated to reflux and stirred for 3 hours until magnesium was consumed. In a dry nitrogen-flushed 2 neck flask a solution of dichlorophenylphosphine (2.1 g, 11.5 mmol, 1 eq.) was prepared in dry THF (100 mL). This was cooled to - 78 °C using a dry ice acetone bath. To this the above prepared Grignard solution was added *via* syringe dropwise over 20 min and a yellow colour was noted upon addition. This was allowed to warm to room temperature. Formation of solely the mono addition product was confirmed by ^{31}P NMR following removal of a sample *via* syringe and work up by filtration after quench with addition of $CDCl_3$. Following this the solution was cooled using in an ice water bath and vinylmagnesium bromide solution (14 mL, 14 mmol, 1 M, 1.2 eq.) in THF was added *via* a dropping funnel over 20 min, allowed to

warm to room temperature and stirred over night. The mixture was concentrated under reduced pressure to a slurry. To this degassed DCM (100 mL) was added and reaction was quenched using degassed sat. NH_4Cl solution (100 mL). This was concentrated to give a yellow oil. Acetonitrile (50 mL) was added and the mixture was cooled in an ice water bath. To the mixture H_2O_2 (3 eq., 30 %w/v) was added dropwise *via* syringe over 10 min and stirred for 1 hour. To this H_2O (20 mL) was added and acetonitrile was removed under reduced pressure leaving a cloudy aqueous solution. **CARE** - do not evaporate to dryness. This was extracted with DCM (100 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield a yellow solid. (crude yield, 2.38 g, >90 %). ^{1}H NMR ($CDCl_3$, 600 MHz) δ = 7.67-7.62 (m, 4H, Ar**H**), 7.54-7.49 (m, 2H, Ar**H**), 7.47-7.42 (m, 2H, Ar**H**), 7.36-7.32 (tdd, 1H, Ar**H**), 7.24 (dd, J_{trans} = 17.2, J_{cis} 10.9, 1H Ar-C**H**), 6.71 (m, 1H P-C**H**), 6.37-6.25 (m, 2H, P-CH-C**H$_2$**), 5.60 (dd, J_{trans} = 17.2, J_{gem} = 1 Hz, 1H, Ar-CH-C**H$_a$**), 5.20 (dd, J_{cis} = 10.9 Hz, J_{gem} = 1 Hz 1H, Ar-CH-C**H$_b$**). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 142.2 (d, $^2J_{PC}$ = 7.5 Hz, Ar**C**$_{ortho}$), 135.3 (d, $^3J_{PC}$ = 5.8 Hz, Ar-**C**H-CH_2), 134.8 (P-CH-**C**H_2), 133.1 (d, $^1J_{PC}$ = 103 Hz, Ph**C**$_{ipso}$) 132.9 (d, J_{PC} = 11.5 Hz, PhC$_{para}$), 131.9 (d, $^2J_{PC}$ = 3 Hz, ArCH$_{ortho}$), 132.4 (d, $^3J_{PC}$ = 3 Hz, ArCH$_{meta}$), 131.3 (Ph**C**$_{meta}$), 131.5 (d, $^1J_{PC}$ = 99 Hz, P-**C**H-CH_2), 129.5 (d, $^1J_{PC}$ = 99 Hz Ar**C**$_{ipso}$) 128.6 (d, $^2J_{PC}$ = 12.2, Ph**C**$_{ortho}$) , 127.3 (d, $^4J_{PC}$ = 12.3, Ar**C**H$_{para}$), 127 (d, $^3J_{PC}$ = 10.1, Ar**C**H$_{meta}$), 117.2 (Ar-CH-**C**H_2). ^{31}P NMR ($CDCl_3$ 121 MHz) δ = 25.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}OPNa$ 277.0753; Found 277.0761. IR δ 3081, 3058, 1656, 1261 (P=O) $cm^{-1.}$ Used in next step without further purification.

1-Phenyl-benzo[b]phosphole-1-oxide (8): To a dry flask charged with nitrogen the solid from the previous procedure was added (2.38 g, 10 mmol, 1 eq.) followed by dry toluene (150 mL). This was heated to 60 °C and Hoveyda-Grubbs 2nd generation catalyst was added (0.15 g, 2.5 mol %) as a solid. This was stirred at 60 °C under nitrogen and monitored by ^{31}P

NMR by removal of 1 mL portions which were filtered through a pad of celite and concentrated. Once starting material had been consumed after 24 h the mixture was concentrated under reduced pressure to yield a green solid (>90 %, 2.85 g). ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.73-7.69 (m, 2H, Ar**H**), 7.62-7.59 (m, 1H, Ar**H),** 7.34-7.53 (m, 6H Ar**H**, 1H Ar-C**H**), 6.45 (dd 1H, $^{2}J_{PH}$ = 25 Hz, J_{HH} = 8 Hz P-C**H**). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.34 (d, $^{2}J_{PC}$ = 13 Hz), 141 (d, J_{PC} = 30 Hz), 132 (d, $^{1}J_{PC}$ = 2.0), 131.3 (d, $^{1}J_{PC}$ = 3), 129.7, 129.8, 128.6 (d, J_{PC} = 10.4), 127.9 (d J_{PC} = 10 Hz) 127.8, 128.94, 126.8 (d $^{1}J_{PC}$ = 99 Hz, P-C**H**), 124.9 (d, $^{3}J_{PC}$ = 13 Hz,), ^{31}P NMR ($CDCl_3$ 121 MHz) δ = 41.2, HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}OPH$ 227.0626; Found 227.0622. IR δ 3056, 2963, 1630, 1262 (P=O) cm^{-1}. Used in next step without further purification.

1-Phenyl-2,3-dihydrobenzo[b]phosphole-1-oxide (oxo-1) (Route B): The green solid from the previous procedure (2.20 g, 11 mmol, 1 eq.) was added to a round bottom flask followed by MeOH (150 mL). To this 5 mol % Pd/C (10 % w/w) was added. The flask was degassed by applying a brief vacuum and was charged with hydrogen *via* a balloon and stirred vigorously for 48 hours. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure to give a dark solid (2.3 g, quantitative). To this DCM (100 mL) was added and was washed with 2 N nitric acid (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to yield a pale brown oil (1.9 g). Recrystallisation from hot cyclohexane and acetone afforded pale brown crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.61-7.67 (m, 9H, Ar**H**), 3.36-3.50 (m, 1H, C$\mathbf{H_b}$), 3.12-3.25 (m, 1H, P-C$\mathbf{H_a}$), 2.33-2.53 (m, 2H, Ar-C$\mathbf{H_2}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 147.7 (d, J_{PC} = 31Hz, ArC_{ortho}), 132.9 (d, $^{1}J_{PC}$= 98 Hz, ArC_{ipso}), 132.9 (d, $^{3}J_{PC}$= 3 Hz, ArC_{para}), 132.4 (d, $^{1}J_{PC}$ = 103 Hz, PhC_{ipso}), 131.8 (d, $^{3}J_{PC}$= 3 Hz, Ar_{meta}), 130.7 (d, $^{3}J_{PC}$ = 10.4 Hz, Ar_{meta}), 129.2 (d, $^{2}J_{PC}$= 9.5 Hz, ArC_{peri}), 128.7 (d, $^{2}J_{PC}$ = 12 Hz, Ph_{ortho}), 128 (d, $^{3}J_{PC}$ = 10 Hz, Ph_{para}), 126.6

(d, $^{3}J_{PC}$ = 11.3 Hz, Ph**C**$_{meta}$), 28.4 (d, $^{2}J_{PC}$= 4 Hz, Ar-**C**H$_2$), 28.2 (d, $^{1}J_{PC}$ = 70 Hz, P-**C**H$_2$),; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 53.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}OPH$ 229.0782; Found 229.0779.

1-Phenyl-2,3,dihydrobenzo[b]phosphole (1) (*via* oxalyl chloride/hydride reduction). To a dry nitrogen-flushed flask a solution of **oxo-1** (0.60 g, 2.6 mmol, 1 eq.) in dry DCM (10 mL) was prepared under nitrogen and cooled in an ice water bath. To this oxalyl chloride (0.27 mL, 3.2 mmol, 1.25 eq.) was added dropwise *via* syringe over 5 min. Bubbling was noted and the mixture turned a light orange and allowed to warm to room temperature. A sample was taken via syringe, added to a dry nitrogen-flushed flask, solvent removed under reduced pressure and the resulting solid was dissolved in dry $CDCl_3$. Sample was prepared under nitrogen for NMR and complete formation of chlorophosphonium salt was confirmed by ^{31}P NMR (δ = 89.8). The mixture was cooled in an ice water bath and to this $LiAlH_4$ (1.3 mL, 4 M in diethyl ether, 4 hydride eq.) was added dropwise *via* syringe over 15 min. A suspension was noted. Following this the mixture was allowed to warm to room temperature and stirred for 2 hours. Solvent was removed under reduced pressure and the mixture was quenched by addition of 20 mL of degassed ethyl acetate followed by slow addition of aq. HCl (1M) via syringe over 5 min. The aqueous layer was further extracted with degassed ethyl acetate (20 mL) and the combined organic layer was dried over $MgSO_4$ and passed through a short silica plug and concentrated under reduced pressure to yield a yellow oil (0.45 g, 80 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.65 (apparent t, J_{HH} = 8.5 Hz 1H, Ar-**H**$_{peri}$) 7.61-7.35 (m, 8H Ar), 3.22-3.07 (m, 2H, Ar-C**H**$_2$), 2.36-2.26 (m, 1H, P-C**H**), 2.02-2.12 (m, 1H, P-C**H**). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.5 (d, $^{2}J_{PC}$ = 3 Hz , Ar**C2**$_{ortho}$), 139.9 (d, $^{1}J_{PC}$ = 44 Hz , Ar**C**$_{ipso}$), 139.8 (d, $^{1}J_{PC}$ = 60 Hz , Ph**C**$_{ipso}$), 131.48 (d, $^{2}J_{PC}$ = 17 Hz PhC$_{ortho}$), 131.46 (d, $^{2}J_{PC}$ = 25 Hz Ar**CH**$_{peri}$), 129.1 (s, Ar**C4**$_{meta}$), 128.3 (d, $^{4}J_{PC}$ = 6.3 Hz Ph**C**$_{para}$), 128.1 (s, PhC$_{meta}$), 126.8 (d,

$^{4}J_{PC}$ = 8.3 Hz ArC_{para}), 125 (d, $^{3}J_{PC}$ = 3 Hz, Ar**C2**$_{meta}$), 27.7 (d, $^{1}J_{PC}$ = 9 Hz, P-**C**H_2), 34.4 (d, $^{3}J_{PC}$ = 6 Hz, Ar-**C**H_2),; ^{31}P NMR (121 MHz, $CDCl_3$) δ = -2.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}PH$ 213.0833; Found 213.0825.

Preparation of Stock Solutions:

To a dry 100 mL nitrogen-flushed flask molecular sieves (~ 25, 4Å) were added and flame dried and placed under reduced pressure and left to cool. Following this the flask was heated for 2 min concentrating on sieves and allowed to cool before being back filled with nitrogen three times *via* standard Schlenk technique. In a separate flask under flow of nitrogen reagents (menthol or HCA or phosphine) were added followed by dry toluene to prepare the desired solution. This was then transferred *via* cannula transfer under flow of nitrogen directly into flask containing sieves and left for 24 h prior to use.

Procedure for Asymmetric Appel Reaction:

A 50 mL Schlenk flask equipped with molecular sieves (~ 1g, 4Å) and a magnetic stirrer was flame dried and placed under reduced pressure and left to cool. Following this the flask was heated for 2 min concentrating on sieves and allowed to cool before being back filled with nitrogen three times *via* standard Schlenk technique. To this dry toluene (3 mL), a solution of menthol in dry toluene (3 mL, 0.396 mmol, 0.132 M, 1.2 eq.) and a solution of HCA in dry toluene (3 mL , 0.330 mmol, 0.11 M, 1 eq.) was added and left over sieves for 1 hour. This was cooled to desired temperature (dry ice/acetone, dry ice/acetonitrile or ice water bath). Following this a solution of phosphine in dry toluene (3 mL, 0.330 mmol, 0.11 M, 1 eq.) was added dropwise over 10 min. The temperature was maintained and the mixture allowed to stir for 1 hour. Following this the mixture was allowed to warm to room temperature over night. This was heated to 50 °C and stirred for 2 hours. On cooling the mixture was filtered and

concentrated under reduced pressure to give an oil which was dissolved in HPLC eluent to give a homogeneous solution, filtered through an PTFE membrane (0.2 μm) syringe filter directly into vial and analysis carried out by HPLC.

1-Phenyl-2,3-dihydrobenzo[b]phosphole-1-oxide (oxo-1) HPLC conditions:

HPLC (CHIRALPAC® IA column, 90:10 heptane:ethanol), flow rate 1 mL/min. R_t : 20.5 min for (*R*)-**oxo 1** and 22.2 min for (*S*)-**oxo 1**.

Phenyl(methyl)(*o*-tolyl)phosphine oxide (oxo-2) HPLC conditions:

HPLC (CHIRALPAC® IA column, 80:10 heptane:ethanol), flow rate 1 mL/min. R_t: 8.9 min for (*S*)-**oxo 2** and 9.8 min for (*R*)-**oxo 2**

Acknowledgment. This research was supported by the Science Foundation Ireland (Grant No. 09/IN.1/B2627. We are also very grateful to UCD Centre for Synthesis and Chemical Biology (CSCB) and the UCD School of Chemistry and Chemical Biology for access to their extensive analysis facilities.

Supporting Information Available: Data including ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra and HPLC analysis for Appel reaction procedure is available. For crystal information see supporting CIF file. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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26. Molecular sieves in the reaction are necessary to keep it dry during reaction. As discussed previously (ref 12a), water has a strong detrimental effect by hydrolysis of reactive intermediates, which results in racemic phosphine oxide formation. For the cyclic case reported here (**1**), a control was also carried out with no molecular sieves, which showed a detrimental effect on the ee, lowering it by 16%. (HPLC trace included in SI). This reduction is consistent with that obtained previously (ref 12a) for the acyclic system (**2**).

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