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P-Stereogenic Phosphorus Compounds: Effect of Aryl Substituents on the Oxidation of Arylmethylphenylphosphanes under Asymmetric Appel Conditions

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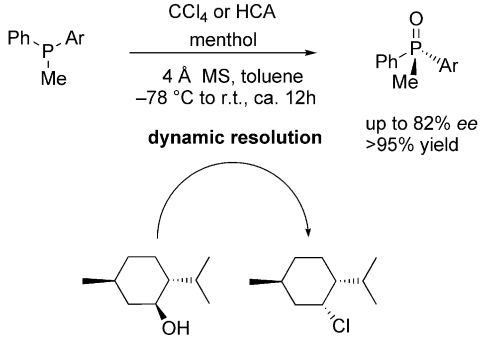
The effects of aryl ring substitution on the dynamic resolution of aryl(methyl)phenylphosphanes under asymmetric Appel reaction conditions have been studied. As expected, substitution at the *ortho* position strongly affects the degree of stereoselection that can be achieved. Unexpectedly, however, there was no variation of stereoselectivity with the electronic nature of the *para* substituents, which suggests that there are two selection processes in operation. An unusual halogen-exchange process was observed in the arylphenylphosphinous chlorides on route to the required tertiary phosphane substrates.

Introduction

The asymmetric synthesis of non-symmetrically substituted phosphorus compounds (variously referred to as *P*-stereogenic, *P*-chiral or *P*-chirogenic) is a venerable topic.[1] Its history is rich and varied with many well-known phosphorus chemists making important contributions down through the years.[2–7] Early methods were based on resolution (for which there is no general method) or on the generation and separation of diastereomers.[3–5] Better progress was made when methods for the generation of unequal amounts of diastereomers were developed. Among others,[8–14] it is reasonable to single out Mislow and co-workers whose method, based on menthyl phosphinates,[15] has been used widely.[4,16] Later, the method of Jugé, Genet and co-workers,[17,18] based on cyclic phosphoramidate precursors, came to prominence and has been used extensively.[19] Both these methods were used to good effect by Imamoto and co-workers.[20–23] More recent strategies include desymmetrisation, enzymatic resolution and catalytic asymmetric synthesis.[7,24–31] Most recently, the method via optically pure H-phosphinates, also pioneered by Mislow and co-workers,[32] has benefited from a recent, very significant improvement in methodology.[33–35]

Despite all this progress in the asymmetric synthesis of *P*-stereogenic phosphanes, the successful synthesis of any particular example is not assured. It is still the case that relatively few *P*-stereogenic ligands for transition-metal catalysis have been studied because they are difficult to synthesise.[4,7] For this reason we began to explore the possibility of kinetic resolution of phosphanes and their oxides. We previously reported success in the dynamic resolution of a variety of *P*-stereogenic aryl(methyl)phenylphosphanes under asymmetric Appel conditions (Scheme 1).[36] This is an oxidation/reduction/dehydration system[37] in which a racemic tertiary phosphane interacts with a source of positively charged chlorine, for example, hexachloroacetone (HCA), and a chiral non-racemic alcohol.



Scheme 1. Asymmetric oxidation under Appel conditions.

The dynamic nature of the resolution allows high enantiomeric excesses to be obtained at full conversion. Previously, there have been very few reported successes of kinetic resolution (KR) or dynamic kinetic resolution (DKR) in such systems,[38–40] one of the few reported cases being that of Perlikowska et. al.[38] who reported up to 39 % *ee* in the KR of *P*-stereogenic tertiary phosphanes and 70 % *ee* for a single example of the first DKR of a chlorophosphane. In our case, enantiomeric excesses of up to 82 % were achieved (Scheme 2) and some indications were obtained of the factors that influence the stereoselectivity of the reaction. It was clear that the presence of an *ortho* substituent in the aryl group was necessary for enantioselectivity. Also, certain indications were obtained relating to the choice of suitable chiral alcohol, with cyclic second-

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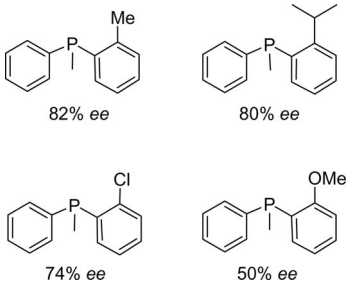
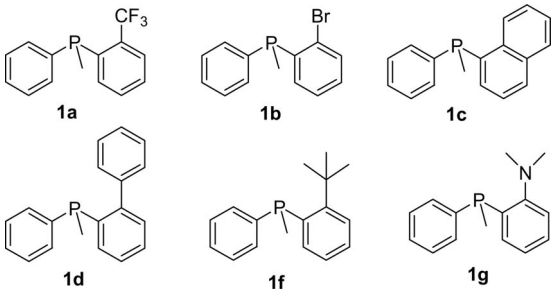
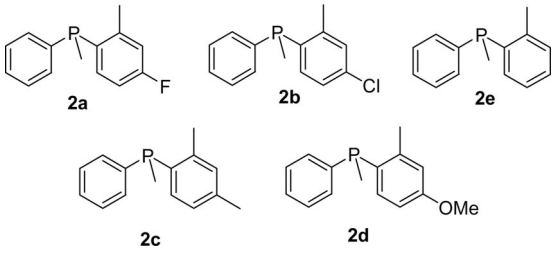
ary alcohols such as menthol being found to be the most effective. To take this study further we have synthesised a set of new phosphanes with different *ortho* and *para* substituents (see Schemes 3 and 4) and subjected them to asymmetric oxidation under Appel conditions.



Scheme 2. Some enantioselectivities previously obtained under the asymmetric Appel conditions shown in Scheme 1.



Scheme 3. Phosphanes studied with varying *ortho* substituents.

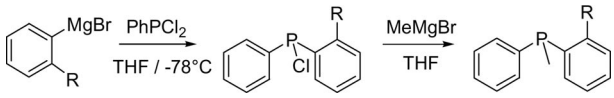


Scheme 4. Phosphanes studied with varying *para* substituents.

Results and Discussion

Synthesis of Phosphane Precursors

Previously the method of Mislow and co-workers[15] had been the most common procedure for the synthesis of racemic phosphanes in our laboratory. This route gives the phosphane oxide, which then has to be reduced to the desired phosphane. However, we found[41] that methyl(phenyl)(*o*-tolyl)phosphane could be prepared directly from dichloro(phenyl)phosphane in by two Grignard reactions at low temperatures and we have now applied, with proper care, this methodology to the synthesis of many of the phosphanes required in this work. The aryl Grignard reagent is added first and its double addition can be minimised by control of stoichiometry, a low temperature and slow addition to minimise significant exothermicity (Scheme 5). This is reasonably successful if the aryl group is somewhat bulky and so is suitable for most *ortho*-substituted cases. However a balance has to be struck such that the reaction of the aryl Grignard with dichloro(phenyl)phosphane is not too slow, otherwise certain exchange reactions can occur. Also, if the starting material [dichloro(phenyl)phosphane] is not used up in the reaction, it may react with the methylmagnesium chloride giving dimethyl(phenyl)phosphane.

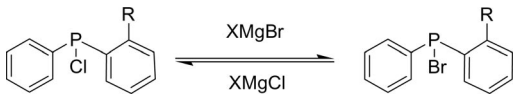


Scheme 5. Synthesis of the required phosphanes.

In one case, **2d**, this methodology could not be used and the older method of Mislow and co-workers was applied. Samples of all the phosphanes synthesised were then oxidised to the corresponding racemic oxides with hydrogen peroxide and CSP-HPLC conditions developed to allow the separation of the enantiomers of each oxide.

Halogen Exchange in Halophosphanes

In all cases, during the synthesis of the phosphanes we observed two signals in the ^{31}P NMR spectrum of the reaction mixture[42] at the intermediate stage but after the addition of methylmagnesium chloride only a single signal corresponding to the expected tertiary phosphane was observed. We investigated this further in the case of the *o*-CF_3 derivative, which shows the two signals in a 1:2 ratio at δ = 75.4 and 66.2 ppm, respectively. The reaction mixture from the initial Grignard addition was filtered from excess salts, which were further extracted with diethyl ether. After evaporation of the combined extracts, the residue was purified by vacuum distillation. The ^{31}P NMR spectrum still showed the same two peaks (but now in a 2:1 ratio) and the ^{1}H and ^{13}C NMR spectra showed only aromatic protons and carbons, respectively. Most significantly, electron ionisation mass spectra showed peaks at 287.9886 and 289.9854 in a 1:3 ratio and at 331.935 and 333.935 in a 1:1 ratio. From these results we concluded that the compounds are probably as shown in Scheme 6, formed by a halogen-exchange reaction. A similar observation was previously made by Wehmschulte and co-workers.[43]

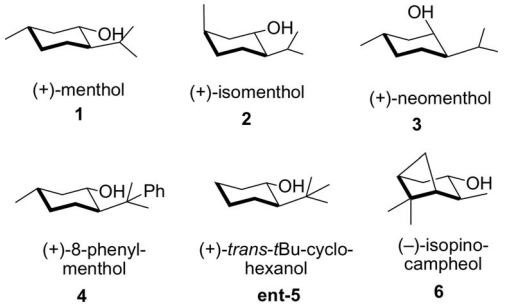


Scheme 6. Products of the halogen-exchange reaction.

Asymmetric Appel Reaction

The asymmetric Appel reaction was performed with a set of chiral alcohols similar to those used previously. The

reactions have to be performed carefully, especially with regard to the low temperatures used, the exclusion of moisture and to the order and rate of addition of the reagents. The reaction was successful if phosphane and alcohol were mixed initially with the subsequent addition of HCA at –78 °C. Alternatively, the selectivity was almost the same if the alcohol and HCA were mixed first followed by the addition of phosphane at –78 °C. However, phosphane and HCA may not be premixed. The enantiomeric excesses obtained from the oxidation of the phosphanes with the different chiral alcohols (Scheme 7) are given in Tables 1 and 2.



Scheme 7. Chiral alcohols reported in Tables 1 and 2 drawn in such a way that the enantiomers shown all give the same sense of selection in the asymmetric Appel reaction.

Table 1. Enantiomeric excesses[a] obtained in the asymmetric Appel reaction[b] (Scheme 1) of *ortho*-substituted phosphanes (Scheme 3).

Alcohol	*ortho* substituent						
	CF_3	Br	2,3-Benzo[c]	Ph	Me	*t*Bu	NMe_2
1[d]	–71	72	–59	64	82 (*S*)	–57	–71
2	–67	60	–51	64	71 (*S*)	–40	–46
3	–58	57	–54	55	65 (*S*)	–36	–43
4	–06		–36	50	69 (*S*)	–19	–55
5		–67	45	–41	–67 (*R*)		
6	13					16	

[a] Obtained by CSP-HPLC; the absolute configurations were not determined except where noted. A negative *ee* indicates that the major enantiomer was eluted second. [b] Phosphane (0.11 mmol), alcohol (1.2 equiv.), HCA (1 equiv.) at –78 °C. All yields are >95 % (as judged by ^{31}P NMR). [c] Refers to compound **1c** in Scheme 3. [d] All the reactions with (+)-menthol were repeated with (–)-menthol. Comparable results were obtained but with opposite configuration.

The data in Table 1 strongly suggest that there is no electronic effect of *ortho* substitution. For example, both the electron-rich NMe_2 and the electron-deficient CF_3 substituents give very similar selectivity with menthol. It might be that they give the opposite configurations but the fact that they have the same magnitude of selection is highly suggestive. However, this conclusion still must remain provisional because we were not able to determine the absolute configurations of the products. In addition, the electronic effects of *ortho* substituents are always compromised by steric effects and it is apparent that steric effects have a significant role in the stereochemical outcome of this reaction. The trends are not clear cut and, again, we are lacking absolute configurations, but it is certainly the case that the least bulky substituent (methyl) gives the best selectivity with most of the alcohols studied, whereas the most bulky (*tert*-butyl) gives the poorest selectivity in most cases.

Table 2. Enantiomeric excesses[a] obtained in the asymmetric Appel reaction[b] (Scheme 1) with *para*-substituted phosphanes (Scheme 4).

Alcohol	*para* substituent				
	F	Cl	H	Me	OMe
1[c]	73	72	82 (*S*)	–76	69
2	60	60	71 (*S*)	–68	64
3	51	57	65 (*S*)	–54	52
4	38		69 (*S*)	–57	56
5		–67	–67 (*R*)		–59

[a] Obtained by CSP-HPLC; the absolute configurations were not determined except where noted. A negative *ee* indicates that the major enantiomer was eluted second. [b] Phosphane (0.11 mmol), alcohol (1.2 equiv.), HCA (1 equiv.) at –78 °C. All yields are >95 % (as judged by ^{31}P NMR). [c] All the reactions with (+)-menthol were repeated with (–)-menthol. Comparable results were obtained but with opposite configuration.

To try to separate the electronic and steric effects we turned to *para* substitution. To ensure consistency and reasonable degrees of enantioselectivity, it was necessary to study a series of compounds having a constant substituent at the *ortho* position and we chose the methyl series. The results, given in Table 2, unexpectedly and disappointingly showed that the stereoselectivity could not be improved by variation of the electronic nature of the *para* substituent. Thus, in almost all cases lower selectivity (sometimes significantly so) was obtained with both electron-withdrawing and -donating substituents relative to the unsubstituted case. It is difficult to envisage how a selection process could be affected in the same direction by both EWGs and EDGs. We therefore believe that there is another process occurring that affects the selectivity. One possibility would be a racemisation process, for example, involving the chloride ion that is present. Assuming that one of these selectivity-affecting processes is promoted by an EDG and the other by an EWG then explains the observed trends in selectivity.

Conclusions

The synthesis and asymmetric oxidation of a series of novel *ortho*- and *para*-substituted aryl(methyl)phenylphosphanes has been carried out. During the syntheses we found that there are two intermediate diarylhalophosphane species present as a result of halogen exchange between chloro and bromo substituents. Asymmetric oxidation under Appel conditions with different chiral alcohols clearly shows that substitution at the *ortho* position in aryl(methyl)phenylphosphanes strongly affects the degree of stereoselection. Unexpectedly, selectivity was reduced by *para* substitution with both electron-withdrawing and -donating groups, which suggests that there are at least two selection processes in operation. Among several alternatives it is possible that there is a racemisation process involving the chloride ion. We will address this issue in subsequent studies. Finally, we

note that it is the *P*-stereogenic phosphanes themselves that are the more desirable products. These can be obtained from the oxides made in this work by known stereoselective reduction techniques (e.g., with silanes[3]) but these are sometimes capricious when substituents are changed and we will also address this issue in subsequent work.

Experimental Section

General: Melting points were determined with a Reichert Thermovar melting-point apparatus. Elemental analyses were carried out at the Microanalytical Laboratory, University College Dublin. Routine electrospray mass spectra were obtained with a Micromass Quattro spectrometer. High-resolution mass spectra were recorded with a Waters Micromass GCT system either by chemical ionisation (CI) or electron ionisation (EI) also at UCD. The NMR spectra were recorded at 25 °C with Varian VNMRS 300, 400, 500 MHz spectrometers. ^{13}C NMR spectra (^{31}P-decoupled) were recorded with a VNMRS 600 MHz spectrometer. All NMR spectra of potentially air-sensitive compounds were recorded under nitrogen. High-performance liquid chromatography was performed on a Shimadzu LC 10AT system with an autosampler coupled to a Shimadzu SPD 10A UV/Vis detector. HPLC grade solvents, purchased from Aldrich and Lennox Supplies, Ireland, were used as supplied. All samples were filtered through an Acrodisc CR 13 mm syringe filter with 0.2 μm PTFE prior to injection. IR spectra were recorded with a Varian 3100 FTIR Excalibur series spectrometer.

Unless otherwise stated all the reactions were carried out under N_2 in dry glassware using Schlenk-line techniques, All "dry" solvents were dried and distilled by standard procedures[44] or were processed through a Grubbs-type still, a Pure Solv-400-3-MD solvent purification system, supplied by Innovative Technology Inc.

General Method for the Synthesis of the Required Phosphanes by Direct Substitution at Phosphorus

Exemplar: Methyl(phenyl)(*o*-tolyl)phosphane[36] (2e): A dry 100 mL two-necked round-bottomed flask fitted with reflux condenser, nitrogen inlet and outlet and septum was charged with magnesium turnings (0.5 g, 18.7 mmol, 1.1 equiv.). 2-Bromotoluene (3.0 g, 17 mmol, 1 equiv.) was dissolved in THF (10 mL) and approx. 2 mL of this solution was added to the flask through a syringe. The mixture was heated at reflux with vigorous stirring until the reaction initiated, at which point the remainder of the solution was added over approximately 30 min, also through a syringe. After this time the reaction was heated at reflux for a further 2 h. The reaction was allowed to cool to room temperature and was then transferred through a syringe into a pressure-equalised dropping funnel attached to a flame-dried and -degassed 100 mL round-bottomed flask, which had been charged previously with dichloro(phenyl)-phosphane (3.0 g, 17 mmol, 1 equiv.) and anhydrous THF (10 mL). This solution was cooled to –78 °C using a dry ice/acetone mixture and the Grignard solution was added dropwise over 1 h. The flask was warmed to room temperature and was then stirred for 1 h. A solution of methylmagnesium bromide in THF (3.0 M, 6.2 mL, 18.7 mmol, 1.1 equiv.) was added over approximately 30 min, and the mixture was then stirred at room temperature overnight. The reaction was quenched slowly at 0 °C with degassed saturated ammonium chloride solution (100 mL) and extracted with dichloromethane (3 × 100 mL) that had been stored over anhydrous magnesium sulfate for 30 min under nitrogen. The extracts were filtered through a sintered funnel under nitrogen, the solvent removed in vacuo, the crude phosphane purified by high-vacuum distillation and the product was isolated as a colourless oil (2.3 g, 64 %); b.p. 180 °C at 1.3 Torr. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.53–7.24 (m, 9 H, Ar), 2.53 (s, 3 H, $ArCH_3$), 1.75 (d, $^2J_{PH}$ = 4.1 Hz, 3 H, CH_3) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –36.2 ppm (ref.[36] –35.2 ppm).

A similar procedure was followed to synthesise the other phosphanes.

Methyl(phenyl)(2-trifluoromethylphenyl)phosphane (1a): 2-Bromo-(trifluoromethyl)benzene (3.8 g, 17.5 mmol, 1 equiv.) was added to magnesium (0.45 g, 18.7 mmol, 1.1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (3.1 g, 17.5 mmol, 1 equiv.) and subsequently methylmagnesium chloride (6.8 mL of a 3.0 M solution in THF, 20.4 mmol, 1.2 equiv.) and the crude phosphane was purified by high-vacuum distillation and the product was isolated as a colourless oil (2.5 g, 53 %); b.p. 160 °C at 1.3 Torr. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.64–7.42 (m, 9 H, Ar), 1.76 (d, $^2J_{PH}$ = 3.6 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^1H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 139.9, 139.5, 134.3, 133.3 131.6, 128.6, 128.4, 128.2, 126.0, 125.9, 124.4 (q, J = 275.2 Hz), 12.8 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –32.8 ppm. MS (electrospray): *m*/*z* = 269 $[M + H]^+$. HRMS (EI): calcd. for $[M]^+$ 268.0629; found 268.0641.

Methyl(1-naphthyl)phenylphosphane[45] (1c): 2-Naphthyl bromide (4.02 g, 20 mmol, 1 equiv.) was added to magnesium (0.5 g, 20 mmol, 1.1 equiv.). The formed Grignard reagent was then treated with dichloro(phenyl)phosphane (3.40 g, 19 mmol) and methylmagnesium chloride (6.3 mL, 19 mmol) to yield a yellow-tinted oil. The phosphane was purified by column chromatography on silica using ethyl acetate. A white solid (4.15 g, 87 %) was obtained. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.58–8.22 (m, 1 H, Ar), 7.42–7.24 (m, 2 H, Ar), 7.17–7.00 (m, 3 H, Ar), 6.97–6.78 (m, 4 H, Ar), 6.78–6.61 (m, 2 H, Ar), 1.14 (d, $^2J_{PH}$ = 4.4 Hz, 3 H, CH_3) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –36.1 ppm (ref.[45] –37.1 ppm).

Biphenyl-2-yl(methyl)phenylphosphane[46] (1d): Biphenyl-2-yl bromide (5.22 g, 20 mmol, 1 equiv.) was added to magnesium (0.57 g, 20 mmol, 1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (3.96 g, 22 mmol, 1 equiv.) and subsequently methylmagnesium chloride (7.34 mL, 22 mmol, 1 equiv.). The product was purified by column chromatography on silica using an ethyl acetate mobile phase to yield the pure phosphane as a clear oil (4.75 g, 78 %). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.23–7.45 (m, 14 H, Ar), 1.44 (d, $^2J_{PH}$ = 3.9 Hz, 3 H, CH_3) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –32.7 ppm (ref.[46] –34.2 ppm).

(2-*tert*-Butylphenyl)(methyl)phenylphosphane (1f): 1-Bromo-2-*tert*-butylbenzene[47] (4.2 g, 20.1 mmol, 1 equiv.) was added to magnesium (0.5 g, 22.1 mmol, 1.1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (3.6 g, 20.1 mmol, 1 equiv.) and subsequently methylmagnesium chloride (8.0 mL of a 3.0 M solution in THF, 24.12 mmol, 1.2 equiv.). The crude phosphane was purified by high-vacuum distillation and the product was isolated as a colourless oil (3.3 g, 64 %); b.p. 200 °C at 1.3 Torr. ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.12–7.54 (m, 9 H, Ar), 1.73 (s, 9 H, *tert*-butyl-CH_3), 1.64 (d, $^2J_{PH}$ = 5.7 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^1H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 155.8, 143.2, 136.5, 130.8, 130.6, 128.1, 126.9, 126.5, 125.4, 125.3, 32.6, 26.9, 13.6 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –31.9 ppm. MS (electrospray): *m*/*z* = 257.1 $[M + H]^+$. HRMS (CI): calcd. for $[M + 1]^+$ 257.1459; found 257.1449.

Dimethyl-[2-(methylphenylphosphanyl)phenyl]amine (1g): 2-Bromo-*N,N*-dimethylaniline (2 g, 9.8 mmol, 1 equiv.) was added to magnesium (0.26 g, 10.8 mmol, 1.1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (1.7 g, 9.8 mmol, 1 equiv.) and subsequently methylmagnesium chloride (4.0 mL of a 3.0 M solution in THF, 11.8 mmol, 1.2 equiv.). The crude phosphane was purified by high-vacuum distillation and the product was isolated as a colourless oil (1.2 g, 50 %); b.p. 185 °C at 1.3 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.02–7.45 (m, 9 H, Ar), 2.65 [s, 6 H, $N(CH_3)_2$], 1.63 (d, $^2J_{PH}$ = 4.8 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 158.2, 141.6, 132.5, 132.3, 131.6, 129.4, 128.2, 128.0, 124.5, 120.5, 45.5, 12.6 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –35.1 ppm. MS (electrospray): *m*/*z* = 244.2 $[M + H]^+$. HRMS (EI): calcd. for $[M]^+$ 243.1177; found 243.1187.

(4-Fluoro-2-methylphenyl)(methyl)phenylphosphane (2a): 1-Bromo-4-fluoro-2-methylbenzene (4.7 g, 9.8 mmol, 1 equiv.) was added to magnesium (0.6 g, 27.5 mmol, 1.1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (4.6 g, 25 mmol, 1 equiv.) and subsequently methylmagnesium chloride (10 mL of a 3.0 M solution in THF, 30 mmol, 1.2 equiv.). The crude phosphane was purified by high-vacuum distillation and the product was isolated as a colourless oil (3.9 g, 65 %); b.p. 180 °C at 1.3 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.43–6.95 (m, 8 H, Ar), 2.48 (s, 3 H), 1.64 (d, $^2J_{PH}$ = 10.9 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 163.2 (d, *J* = 247.5 Hz), 144.9, 139.8, 133.3, 132.3, 131.9, 128.5, 128.2, 116.8, 113.0, 21.5, 12.5 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –37.4 ppm. MS (electrospray): *m*/*z* = 233.39 $[M + H]^+$. HRMS (CI): *m*/*z* calcd. for $[M + 1]^+$ 233.0895; found 233.0895.

(4-Chloro-2-methylphenyl)(methyl)phenylphosphane (2b): 2-Bromo-5-chlorotoluene (5.00 g, 24 mmol, 1 equiv.) was added to magnesium (0.60 g, 25 mmol, 1.1 equiv.). The aryl Grignard reagent was dropped onto dichloro(phenyl)phosphane (4.35 g, 24 mmol, 1 equiv.) at –78 °C over a period of 2 h and the mixture was then stirred for a further hour. Methylmagnesium chloride (8 mL, 24 mmol) was added as the temperature rose to room temperature. This reaction mixture was stirred for 2 h. The reaction was worked up as stated for **2e**. A caramel-coloured oil was recovered, which was then purified by column chromatography on silica with 100 % dichloromethane as the mobile phase. This gave a clear oil (4.77 g, 80 %). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.44–7.31 (m, 5 H, Ar), 7.30–7.18 (m, 3 H, Ar), 2.41 (s, 3 H, CH_3), 1.60 (d, $^2J_{PH}$ = 4.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 144.0, 139.5, 136.6, 134.6, 132.2, 131.7, 130.0, 128.6, 128.50, 126.2, 21.1, 12.2 ppm. ^{31}P NMR ($CDCl_3$, 241 MHz): δ = –36.8 ppm. $C_{14}H_{14}ClP$ (248.69): calcd. C 67.61, H 5.67, Cl 14.26, P 12.45; found C 67.50, H 5.82, Cl 14.50, P 12.26. HRMS (CI): calcd. for $C_{14}H_{14}ClP$ $[M + 1]^+$ 249.0600; found 249.0588.

(2,4-Dimethylphenyl)(methyl)phenylphosphane (2c): 1-Bromo-2,4-methylbenzene (4.8 g, 26 mmol, 1 equiv.) was added to magnesium (0.7 g, 28.6 mmol, 1.1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (4.7 g, 26 mmol, 1 equiv.) and subsequently methylmagnesium chloride (10.4 mL of a 3.0 M solution in THF, 31.3 mmol, 1.2 equiv.). The crude phosphane was purified by high-vacuum distillation and the product was isolated as a colourless oil (3.7 g, 61 %); b.p. 185 °C at 1.3 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45–7.09 (m, 8 H, Ar), 2.45 (s, 3 H), 2.39 (s, 3 H), 1.64 (d, $^2J_{PH}$ = 4.1 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 142.3, 140.6, 138.5, 134.2, 132.2, 131.9, 131.0, 130.5, 128.4, 126.9, 21.2, 21.0, 12.2 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = –37.4 ppm. MS (electrospray): *m*/*z* = 229.30 $[M + H]^+$. HRMS (EI): calcd. for $[M]^+$ 228.1068; found 228.1059.

Halogen Exchange in Halophosphanes

Chloro(2-trifluoromethylphenyl)phenylphosphane: 2-Bromo(trifluoromethyl)benzene (2 g, 9.2 mmol, 1 equiv.) was added to magnesium (0.2 g, 9.8 mmol, 1.1 equiv.). The aryl Grignard reagent was then treated with dichloro(phenyl)phosphane (1.6 g, 9.2 mmol, 1 equiv.). The solvent was removed in vacuo. Dry diethyl ether (100 mL) was added to the reaction mixture to precipitate the magnesium salts, which were filtered through a sintered funnel under nitrogen. The solvent was removed in vacuo, the crude phosphane was purified by high-vacuum distillation and the product was isolated as a colourless oil (1.2 g, 64 %); b.p. 135 °C at 1.3 Torr. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.86–7.18 (m, 9 H, Ar) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 139.9, 139.5, 134.3, 133.3, 131.6, 128.6, 128.4, 128.2, 126.0, 125.9, 124.4 (q, *J* = 275.2 Hz) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 75.9, 66.5 ppm. HRMS (EI): calcd. for $C_{13}H_9BrF_3P$ $[M]^+$ 331.9577, 333.9558; found 331.9356, 333.9352; calcd. for $C_{13}H_9ClF_3P$ $[M]^+$ 288.0082, 290.0053; found 287.9886, 289.9954.

(4-Methoxy-2-methylphenyl)(methyl)phenylphosphane (2d) by Reduction of the Oxide: (4-Methoxy-2-methylphenyl)(methyl)phenylphosphane oxide (0.37 g, 1 mmol, 1 equiv.) was added to a flame-dried round-bottomed flask under vacuum and flushed with nitrogen three times, fitted with a magnetic stirring bar, nitrogen inlet/outlet, condenser and rubber septum, and dissolved in toluene (5 mL/g approx.). Trichlorosilane (0.54 g, 4 mmol, 4 equiv.) was added dropwise through a syringe. The reaction was heated to 70 °C for 12 h using an oil bath. The reaction was allowed to cool and quenched with 20 equiv. of aqueous degassed sodium hydroxide (2 M). The organic material was extracted with dichloromethane, dried with sodium sulfate and the solvent removed in vacuo to yield a clear oil. The compound was purified by chromatography on silica with a dichloromethane (DCM) mobile phase to give a clear oil (0.31 g, 76 %). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.30–7.19 (m, 6 H, Ar), 6.82–6.72 (m, 2 H, Ar), 3.81 (s, 3 H, OCH_3), 2.42 (s, 3 H, CH_3), 1.57 (d, $^2J_{PH}$ = 4.1 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 160.1, 144.1, 140.1, 132.1, 131.8, 128.5, 128.3, 128.0, 115.6, 111.6, 55.1, 21.4, 12.4 ppm. ^{31}P NMR ($CDCl_3$, 241 MHz): δ = 38.3 ppm. HRMS (CI): calcd. for $C_{15}H_{17}OP$ $[M + 1]^+$ 245.1095; found 245.1089.

General Method for the Synthesis of Racemic Phosphane Oxides and Their Separation on Chiral HPLC Columns

Exemplar: (±)-Methyl(phenyl)(*o*-tolyl)phosphane Oxide[36] (Oxo-2e): Hydrogen peroxide (1.14 mL, 35 wt.-%, 0.4 g, 11.6 mmol, 1.5 equiv.) was added dropwise to a stirred solution of phosphane (2.2 g, 10.2 mmol, 1 equiv.) in acetone (30 mL, degassed) at 0 °C (ice bath). After the addition was complete the solution was stirred overnight. Water (60 mL) and dichloromethane (120 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 60 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to yield a white solid. Column chromatography on silica gel was carried out with dichloromethane followed by dichloromethane/methanol (95:5) to yield a white solid (1.24 g, 53 %); m.p. 113–114 °C (ref.[36] m.p. 114–115 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.71-7.61 (m, 3 H, Ar), 7.53–7.40 (m, 4 H, Ar), 7.35–7.21 (m, 2 H, Ar), 2.39 (s, 3 H, Ar-CH_3), 2.01 (d, $^2J_{PH}$ = 13.0 Hz, 3 H, CH_3) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 32.5 ppm (ref.[36] 31.8 ppm). IR: $\tilde{\nu}$ = 3379, 1593, 1474, 1180 (P=O), 1138, 1112 cm^{-1}. HPLC (CHIRALPAK® AD column, 90:10 heptane/EtOH, 1 mL/min): R_t = 13.8, 21.3 min.

A similar procedure was followed to synthesise the other phosphane oxides.

(±)-Methyl(phenyl)(2-trifluoromethylphenyl)phosphane Oxide (Oxo-1a): From the phosphane (1 g, 3.7 mmol, 1 equiv.) in a yield of 0.68 g, 65 %. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.93–7.12 (m, 9 H, Ar), 2.1 (d, $^2J_{PH}$ = 10.2, Hz, 3 H, P-CH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 134.9, 134.4, 132.1, 131.9, 131.7, 131.6, 131.4, 130.0, 128.4, 127.4, 123.5 (q, J = 274.2 Hz), 16.63 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 31.6 ppm. IR: $\tilde{\nu}$ = 3223, 1679, 1591, 1574, 1127 (P=O), 1132 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 284.0578; found 284.0582. HPLC (CHIRALPAK® OD column, 95:5 pentane/EtOH, 1 mL/min): R_t = 17.5, 20.6 min.

(±)-(2-*tert*-Butylphenyl)(methyl)phenylphosphane Oxide (Oxo-1f): From the phosphane (1 g, 3.9 mmol, 1 equiv.) in a yield of 0.62 g, 58 %; m.p. 137–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–6.40 (m, 9 H, Ar), 2.06 (d, $^2J_{PH}$ = 12.9 Hz, 3 H, PCH_3), 1.55 (s, 9 H, *tert*-butyl-CH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 156.2, 144.1, 133.3, 131.2, 130.5, 129.9, 127.5, 126.8, 124.25, 123.9, 31.06, 24.8, 13.3 ppm. ^{31}P NMR ($CDCl_3$, 300 MHz): δ = 37.4 ppm. IR: $\tilde{\nu}$ = 3329, 1635, 1591, 1455, 1167 (P=O), 1138, 1123, 1082 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 272.1330; found 272.1322. HPLC (CHIRALPAK® OD column, 98:2 pentane/EtOH, 1 mL/min): R_t = 19.6, 21.1 min.

(±)-Methyl(phenyl)[2-(dimethylamino)phenyl]phosphane Oxide (Oxo-1g): From the phosphane (1 g, 4.1 mmol, 1 equiv.) in a yield of 0.72 g, 67.9 %; m.p. 117–120 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.95–6.67 (m, 9 H, Ar), 2.23 [s, 6 H, $N(CH_3)_2$], 2.04 (d, $^2J_{PH}$ = 10.4 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 154.3, 136.7, 132.5, 131.2, 130.4, 129.9, 127.5, 127.1, 124.2, 122.1, 44.3, 12.3 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 29.5 ppm. IR: $\tilde{\nu}$ = 3342, 1663, 1585, 1522, 1169 (P=O), 1118, 1044 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 259.1126; found 259.1118. HPLC (CHIRALPAK® OD column, 95:5 pentane/EtOH, 1 mL/min): R_t = 14.1, 16.2 min.

(±)-(4-Fluoro-2-methylphenyl)(methyl)phenylphosphane Oxide (Oxo-2a): From the phosphane (1 g, 4.3 mmol, 1 equiv.) in a yield of 0.74 g, 69.1 %; m.p. 98–102 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64–6.84 (m, 8 H, Ar), 2.29 (s, 3 H, Ar), 1.96 (d, $^2J_{PH}$ = 13.1 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 163.8 (d, J = 253.0 Hz), 144.8, 133.8, 132.6, 132.9, 130.7, 129.3, 127.7, 118.0, 111.4, 20.3, 16.6 ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 31.0 ppm. IR: $\tilde{\nu}$ = 3052, 2973, 1724, 1583, 1483, 1183 (P=O), 1107, 1072 cm^{-1}. HRMS (CI): calcd. for $[M + 1]^+$ 249.0845; found 249.0836. HPLC (CHIRALPAK® AD column, 90:10 pentane/EtOH, 1 mL/min): R_t = 19.0, 21.0 min.

(±)-(4-Chloro-2-methylphenyl)(methyl)phenylphosphane Oxide (Oxo-2b): From the phosphane (0.5 g, 2.4 mmol, 1 equiv.) in a yield of 0.54 g, 99 %. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.53–7.43 (m, 3 H, Ar), 7.34 (m, 1 H, Ar), 7.34 (m, 2 H, Ar), 7.12 (m, 1 H, Ar), 7.17 (m, 1 H, Ar), 2.2 (s, 3 H, CH_3), 1.95 (d, $^2J_{PH}$ = 13.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 143.9, 138.1, 134.1, 132.8, 131.7, 130.3, 130.2, 128.6, 21.1, 17.1 ppm. ^{31}P NMR ($CDCl_3$, 241 MHz): δ = 30.6 ppm. IR: $\tilde{\nu}$ = 3361, 2973 (w, C–H) 1585, 1437 (m, aromatic C=C) 1178 (s, P=O) cm^{-1}. HRMS (CI): calcd. for $[M + 1]^+$ 265.0543, 267.0520; found 265.0549, 267.0409. HPLC (CHIRALPAK® AS-H, 83:17 heptane/EtOH, 1 mL/min): R_t = 8.3, 15.5 min.

(±)-(2,4-Dimethylphenyl)(methyl)phenylphosphane Oxide (Oxo-2c): From the phosphane (1 g, 4.3 mmol, 1 equiv.) in a yield of 0.65 g, 61 %. M.p 125–128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.67–6.90 (m, 8 H, Ar), 2.35 (s, 3 H), 2.33 (s, 3 H), 2.04 (d, $^2J_{PH}$ = 10.9 Hz, 3 H, PCH_3) ppm. ^{13}C NMR {^{1}H, ^{31}P} ($CDCl_3$, 151 MHz): δ = 142.4, 141.8, 135.5, 134.1, 132.6, 131.3, 130.3, 130.2, 128.5, 126.1, 21.3, 21.2, 17.6 ppm. ^{31}P NMR ($CDCl_3$, 300 MHz): δ = 31.7 ppm. IR: $\tilde{\nu}$ = 3372, 1723, 160.5, 1438, 1187 (P=O), 1071, 1037 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ 244.1017; found 244.1008. HPLC (CHIRALPAK® OD column, 90:10 pentane/EtOH, 1 mL/min): R_t = 15.3, 16.9 min.

Synthesis of Phosphane Oxides via Phosphanyl Chloride

General Method: Magnesium turnings (1.1 equiv.) were placed in a flame-dried three-necked round-bottomed flask fitted with a condenser, nitrogen in/outlet, pressure-equalising dropping funnel, magnetic stirring bar and stoppers. All joints were greased and the vessel was placed under vacuum using an oil pump and then flushed with nitrogen. This procedure was repeated three times. The aryl bromide (1 equiv.) was added to the dropping funnel and dissolved in dry THF (20 mL/g approx.). Approximately one third was added to magnesium and stirred until the reaction had initiated, which could be observed in different ways depending on the substrate used, for example, the evolution of heat, a colour change and/or effervescence from the magnesium. The remainder of the aryl bromide solution was then added slowly (approx. 50 mL/h) and the reaction was heated at reflux until all the magnesium was consumed (approx. 2 h). The reaction was allowed to cool and methyl(phenyl)phosphanyl (1 equiv.) chloride was added dropwise through a syringe. The reaction was heated at reflux overnight and then allowed to cool and quenched with saturated ammonium chloride[15] (20 mL/g). The organic material was extracted with dichloromethane, dried with sodium sulfate and the solvent removed under reduced pressure.

(±)-Methyl(2-naphthyl)phenylphosphane Oxide (Oxo-1c):[48] Using magnesium (0.27 g, 10 mmol, 1 equiv.), 2-naphthyl bromide (2.34 g, 10 mmol, 1 equiv.) and methyl(phenyl)phosphanyl chloride (1.67 g, 10 mmol, 1 equiv.), a yellow soft solid was obtained. The material was purified by column chromatography on silica with a 1:1 ethyl acetate/dichloromethane mobile phase. The pure product was a white solid (1.59 g, 63 %); m.p. 151–152 °C (ref.[48] 150–152 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.44 (d, J = 8.2 Hz, 1 H, Ar), 8.03 (d, J = 8.2 Hz, 1 H, Ar), 7.91 (m, 2 H, Ar), 7.73 (dd, J = 6.7, 12.1 Hz, 2 H, Ar), 7.60–7.37 (m, 6 H, Ar), 2.17 (d, $^2J_{PH}$ = 13.1 Hz, 3 H, CH_3) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 33.1 ppm. HPLC CHIRALPAK® AS-H column, 90:10 heptane/EtOH, 1 mL/min): R_t = 9.7, 11.11 min.

(±)-Biphenyl-2-yl(methyl)phenylphosphane Oxide[41] (Oxo-1d): Biphenyl-2-yl bromide (4.94 g, 20 mmol, 1 equiv.) was treated with magnesium (0.57 g, 20 mmol, 1 equiv.) and methyl(phenyl)phosphinyl chloride (3.05 g, 20 mmol, 1 equiv.) to yield a yellow tinted soft solid. The material was purified by column chromatography on silica with a 1:1 ethyl acetate/dichloromethane mobile phase. The pure product was a white solid (3.9 g, 63 %); m.p. 87–89 °C (ref.[41] 87–89 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84 (dd, J = 7.6, 13.1 Hz, 1 H, Ar), 7.54–6.98 (m, 13 H, Ar), 1.50 (d, $^2J_{PH}$ = 13.3 Hz, 3 H, CH_3) ppm. ^{31}P NMR ($CDCl_3$, 121 MHz): δ = 26.9 ppm. HPLC (CHIRALPAK® AS-H column, 90:10 heptane/EtOH, 1 mL/min): R_t = 12.3, 18.7 min.

(±)-(4-Methoxy-2-methylphenyl)(methyl)phenylphosphane Oxide (Oxo-2d): 4-Methoxy-2-methylphenyl bromide (1.16 g, 10 mmol, 1 equiv.) was treated with magnesium (0.17 g, 10 mmol, 1 equiv.) and methyl(phenyl)phosphanyl chloride (0.97 g, 10 mmol, 1 equiv.) to give a clear crude oil. The phosphane oxide was purified by recrystallisation from toluene to give a white solid (0.77 g, 54 %); m.p. 144–146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.83–7.32 (m, 6 H, Ar), 6.87–6.60 (m, 2 H, Ar), 3.83 (s, 3 H, OCH_3), 2.34 (s, 3 H, Ar-CH_3), 2.00 (d, $^2J_{PH}$ = 13.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR {^{1}H,^{31}P} ($CDCl_3$, 151 MHz): δ = 162.4, 144.2, 135.2, 133.4, 131.4, 130.4, 125.6, 121.1, 117.6, 110.6, 21.5, 17.4 ppm. ^{31}P NMR

($CDCl_3$, 161 MHz): δ = 31.9 ppm. $C_{15}H_{17}O_2P$ (260.27): calcd. C 69.22, H 6.58, P 11.90; found C 68.93, H 6.47, P 12.04. HRMS (CI): calcd. for $C_{15}H_{17}O_2P$ $[M + 1]^+$ 261.1033; found 261.1044. HPLC (CHIRALPAK® AS-H column, 90:10 heptane/EtOH, 1 mL/min): R_t = 15.4, 17 min.

Asymmetric Appel Reaction

Predrying of Stock Solutions: The alcohol, phosphane and HCA were dried thoroughly before preparing the stock solution as follows. The individual alcohols (1.2 equiv.) were weighed into flame-dried and degassed round-bottomed flasks with dry toluene. The toluene was removed using a rotary evaporator with a membrane pump to remove water through the azeotrope. This process was repeated three times and dry solvent (from Grubbs' system) was added to the vessels to make up to their respective concentrations (0.132 M) and the flask was capped. Molecular sieves (4 Å), which were flame-dried until red hot, were added to flame-dried Young's flasks. The flasks were heated with a heat gun focusing on the molecular sieves for 2 min each and then flushed with nitrogen. This was repeated. The vessels were then put under vacuum again and flushed with nitrogen. The Young's flask screw crown was removed with a good flow of nitrogen and replaced with a rubber septum. While both vessels were under nitrogen the stock solutions were removed by syringe from the round-bottomed flask and placed on the sieves in the Young's flask and the stock solutions were left overnight.

For HCA, molecular sieves (4 Å), which were flame-dried until red hot, were added to flame-dried Young's flasks. The flasks were heated with a heat gun focusing on the molecular sieves for 2 min each and then flushed with nitrogen. This was repeated. The vessels were then put under vacuum again flushed with nitrogen. The screw caps of the Young's flasks were removed with a good flow of nitrogen and replaced with rubber septa. Distilled HCA (1 equiv.) was weighed into the Young's flasks and dry toluene (from Grubbs' system) was added to the vessels to give 0.11 M solution of HCA, which was then left overnight.

A similar procedure was followed to make up 0.11 M stock solutions of distilled phosphane in dry toluene.

Exemplar Reaction with Methyl(phenyl)(*o*-tolyl)phosphane (2e): The phosphane (**1e**; 0.11 M, 1 equiv.) and alcohol solutions (0.132 M, 1.2 equiv.) were removed by syringe and added to the flame-dried degassed Schlenk flask fitted with a stirring bar. A rubber septum was put over the Schlenk arm and the Schlenk flask was then immersed in a dry ice/acetone bath and cooled to –78 °C. A HCA stock solution (0.11 M, 1 equiv.; 0.1 mL/min approx.) was added through the syringe. When all the HCA had been added, the reaction was stirred at –78 °C for 1 h. The reaction was then removed from the cold bath, allowed to warm to room temperature and then stirred for a further 24 h under nitrogen. Triphenylphosphane sulfide (as an internal standard, 0.11 M, 3 mL) was added to each reaction and stirred. A portion (0.5 mL) of the mixture was removed, diluted to 2 mL with HPLC solvent (HPLC grade solvents purchased from Aldrich were used as supplied) and filtered through a PTFE syringe filter into a HPLC vial. High-performance liquid chromatography was performed with a Shimadzu LC 10 AT system with an autosampler coupled to a Shimadzu SPD 10A UV/Vis detector.

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