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**Author(s)**  
Byrne, Peter A.; Rajendran, Kamalraj V.; Muldoon, Jimmy; Gilheany, Declan G.

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A Convenient & Mild Chromatography-Free Method for the Purification of the Products of Wittig and Appel Reactions

Peter A. Byrne, Kamalraj V. Rajendran, Jimmy Muldoon and Declan G. Gilheany

A mild method for the facile removal of phosphine oxide from the crude products of Wittig and Appel reactions is described. Work-up with oxalyl chloride to generate insoluble chlorophosphonium salt (CPS) yields phosphorus-free products for a wide variety of these reactions. The CPS product can be further converted into phosphine.

Phosphines and reagents derived from them are ubiquitous reagents in organic chemistry used, for example, in the Wittig reaction, in Appel and Mitsunobu conditions and in the azas-Wittig reaction. However the phosphine oxide by-product of these reactions poses significant problems, both of separation and disposal, leading to poor atom efficiency and requiring complex procedures, particularly for large-scale reactions.

Disposal of phosphine oxide may be achieved by incineration to phosphorus pentoxide and hence calcium phosphate but more desirable is regeneration of the phosphine. The BASF process for carotenoid synthesis provides a good illustration of the issues. In it, the alkene product from a Wittig reaction is separated first from the bulk of the phosphine oxide by extraction with hydrocarbon solvents, and then scrubbed of remaining oxide in a second extractive column with aqueous alcohol. Regeneration of phosphine is achieved by reaction of oxide with phosgene to give triphenylphosphine dichloride (vide infra), which is then treated with elemental phosphorus to give triphenylphosphine and phosphorus trichloride, the latter being also a starting material for the former. Triphenylphosphine dichloride can also be converted to triphenylphosphine by mixing with finely divided aluminium metal in chlorobenzene, which forms a triphenylphosphine-aluminium trichloride complex that can be decomposed hydrolytically. Phase separation allows isolation of triphenylphosphine from the water-soluble aluminium-containing product, Al(OH)Cl₃. These processes involve the handling of hazardous reagents and products, and are far from straightforward. Other methods for phosphine oxide removal include the addition of a hydrocarbon solvent and a carboxylic acid to the crude product, allowing separation of alkene (in organic phase) and phosphine oxide (in acid phase) by phase separation. In some cases, the alkene can be crystallised, thus facilitating its separation from the other materials in the crude product.

On a laboratory scale, phosphine oxide removal generally necessitates the use of column chromatography. This presents problems if the product is sensitive to decomposition or isomerisation through contact with the stationary phase or by light, or if it is sensitive to decomposition in air. For example, certain alkenes produced in Wittig reactions have been shown to be sensitive to isomerisation by light, or by contact with silica or alumina. Thus, there is a strong imperative for the development of chromatography-free phosphine oxide removal. Reported methods addressing this need include modification of phosphonium ylides to furnish a phosphine oxide by-product that may be removed by aqueous work-up and the use of water-soluble and hydrolytically stable ylides to allow reactions to be conducted in water, giving water-soluble phosphine oxide and insoluble alkene product, which precipitates and can be isolated by filtration. An alternative approach involves polymer-supported ylides such as those of Westman and Leung et al., in which the ylide is generated in situ from a polymer supported phosphine. These reactions often have long reaction times and in some cases poor yield due to problems with polymer swelling. Some measure of success has been achieved for one-pot Wittig reactions involving in situ generation of stabilised ylides by the use of a bifunctional polymer containing phosphine and amine groups. In all of the foregoing, the starting phosphine (free or polymer-bound) is either more expensive than triphenylphosphine, and/or must be synthesised by non-trivial routes. More seriously, the modified phosphonium entity may not have the same reactivity profile (e.g. may give different stereoselectivity in the Wittig), and the phosphorus substituents cannot easily be tuned to counter this without the undertaking of further onerous synthetic procedures.

A promising potential solution to the problem of phosphine oxide removal has been the development of processes that are catalytic in the phosphorus-containing entity. O’Brien, Chass and co-workers have recently reported the first catalytic Wittig reaction by using diphenylsilane to reduce the phosphine oxide, importantly leaving the carbonyl compound unaffected. The reaction requires the use of a cyclic phosphate but, being catalytic, this is less problematic. Two protocols for carrying out Appel reactions that are catalytic in phosphine oxide have been reported recently. In the process of Denton and co-workers, oxalyl chloride reacts with the oxide to give chlorophosphonium.
salt (vide infra), which in turn reacts with alcohol to give alkoxophosphonium salt, resulting in alkyl chloride and regenerating phosphate oxide. Denton et al. have also developed a catalytic phosphate oxide-mediated dichlorination of epoxides using oxalyl chloride, and an aza-Wittig reaction that is catalytic in phosphate oxide has also been reported. A recent report focuses on utilising the phosphate oxide by-product of the Wittig reaction as a catalyst or co-catalyst (produced in situ) in a subsequent step of a tandem reaction sequence, thus improving the atom economy of the overall process. The conversion of phosphate oxide to phosphate has also been realised by treatment with oxalyl chloride followed either by reaction of the resulting CPS (vide infra) with aluminium metal combined with a catalytic metal salt, or by electrochemical reduction of the CPS.

Finally, we note that it is not uncommon that the method used to remove phosphate oxide may result in isomerisation of a Z-alkene product of a Wittig reaction. This is the case, for example, in the catalytic version referred to above. Isomerisation can be induced by the presence of acids, strong bases, the chromatographic stationary phase used, the solvent, heat and sunlight. The Z-enones synthesised during this project were found to be extremely sensitive to isomerisation, such that samples containing only Z-enone isomerised to the E-isomer when simply allowed to stand, probably induced by light. For cases such as these, where the alkene cannot be stored or even exposed to chromatographic stationary phase, the development of a quick and easy chromatography-free method of separation of alkene and phosphate oxide is particularly important.

We now report a convenient work-up procedure for both Wittig and Appel reactions that allows such a rapid separation of the reaction product from phosphate oxide, and facilitates the reduction of the latter to phosphate. In the case of the Wittig reaction, the method is also successful in removing the aldehyde starting material and the conjugate acid of the ylide-generating base from the alkene and phosphate products of the process.

Our method is based on the aforementioned reaction of phosphate oxide with oxalyl chloride to generate chlorophosphonium chloride. We were already interested in such salts because of their involvement in other chemistry in our laboratory. They can also be generated by the reactions of phosphate with chlorine (in various solvents), and phosphate oxide with sulfuryl chloride, methanesulfonyl chloride, thionyl chloride or trichloromethyl chlorofomate. The structure of the entity produced seems to depend heavily on the solvent. It adopts a chlorophosphonium chloride structure in acetonitrile and chlorinated solvents, and a dichlorotriphenylphosphorane structure in benzene and diethyl ether. During its hydrolysis in CH₂O, both the ionic and covalent phosphorane forms co-exist. A crystal structure of the compound produced by the reaction of Ph₃P and Cl₂ in dichloromethane showed it to have a dinuclear structure [Ph₃P-Cl-Cl-PPh₃Cl-CH₂Cl₂]. The compound has been observed by us and others to have limited solubility in diethyl ether (at room temperature) and THF (with the small quantity that is soluble being in phosphorane form), and very low solubility in alkane solvents and cold diethyl ether. This last point provides the basis of the new work-up procedure.

For the production of phosphorus-free alkene by the Wittig reaction, the reaction itself may be carried out using whatever starting materials and reaction conditions are required to give the desired product with the desired stereochemistry. For the reactions in this study, the phosphonium ylide was generated in situ from dry precursor phosphonium salt in dry THF using NaHMDS or KHMS as base, followed by addition of aldehyde, which in general was carried out at 20 °C (in some cases the aldehyde was added at –20 °C or –78 °C). The crude product can then be treated in any of the following four ways to result in the separation of phosphate oxide and aldehyde from the alkene product:

(i) The solvent is removed in vacuo and oxalyl chloride is added resulting in the evolution of CO and CO₂ gas and, depending on the case, the formation of a pale yellow solid or oil. When bubbling has ceased, cyclohexane is added, and the upper phase formed is decanted off and then filtered.

(ii) Oxalyl chloride is added directly to the reaction mixture (THF solvent) and stirred, causing the evolution of CO and CO₂. When effervescence ceases, the solvent is removed in vacuo, cyclohexane is added, and the upper phase formed is decanted off and then filtered.

(iii) The solvent is removed in vacuo, cyclohexane is added to the crude product, and oxalyl chloride is added, causing CO and CO₂ to be produced. When effervescence ceases, the upper phase formed is decanted off and then filtered.

(iv) As in (i), the solvent is removed in vacuo and oxalyl chloride is added resulting in the evolution of CO and CO₂ gas. When effervescence ceases, the mixture is cooled to -78 °C, dry degassed Et₂O is added and the supernatant solution is removed by cannula filtration. To ensure isolation of phosphorus-free alkene, only ca. 85% of the supernatant is removed, and the residue is washed three times with dry degassed Et₂O.

In all four methods, the oxalyl chloride reacts with phosphate oxide to form chlorophosphonium salt and release CO and CO₂. The cyclohexane used was not purified, dried or degassed in any way prior to use. The biphasic mixture that forms in the presence of cyclohexane consists of an upper phase of alkene and residual oxalyl chloride dissolved in cyclohexane (this is typically clear or pale yellow), and a solid or viscous oil that sits at the bottom of the vessel. We found, for Wittig reactions that we studied (shown in Table 1), that remaining aldehyde starting material usually does not dissolve in the cyclohexane phase, but stays in the residue along with the chlorophosphonium salt. Washing of the organic solution (after filtration) with aqueous base and then aqueous acid results in the removal of residual oxalyl chloride and also the conjugate acid of the base used to generate the phosphonium ylide (hexamethyldisilylamine in this case), furnishing a high yield of alkene that is free of both phosphorus and aldehyde (Table 1). The use of certain other bases to generate the phosphonium ylide (or indeed using a pre-generated stabilised ylide) would obviate the need for this acid wash.
From Table 1, it can be seen that this procedure was successful for the removal of triphenylphosphine oxide, iso-butyldiphenylphosphine oxide, and methyldiphenylphosphine oxide from Wittig reaction crude products, and is applicable to the crude products of the reactions of all phosphonium ylide types (non-stabilised, semi-stabilised and stabilised) with both aromatic and aliphatic aldehydes, and with ketones. In all cases, comparison of the Z/E ratio of the crude alkene product with that of the product after treatment with oxalyl chloride showed it to be unaffected by the procedure. This is particularly striking for the cases of Z-2,2′-difluorostilbene (entry 9) and 1-cyclopentyl-3-methylbut-1-ene (entries 5 & 6). The former is known to be extremely sensitive to isomerisation to the E-isomer, especially if subjected to column chromatography. The latter alkene (both isomers) spontaneously degrades under ambient conditions simply if allowed to stand. Thus neither alkene is readily accessible in pure form by methods that demand chromatography. The use of our procedure enabled the isolation of each compound in sufficiently pure form for full NMR characterisation, and in particular allowed the very challenging task of establishing the stereochemistry of the isomers of 1-cyclopentyl-3-methylbut-1-ene to be accomplished by the 1D DPFGSE-NOE NMR technique (see ESI for details). In triphenylphosphine derived cases, the residue remaining after filtration of the cyclohexane solution of alkene was shown to contain the derived CPS by NMR (δP = 65 ppm) and frequently also a small amount of aldehyde. On exposure to air this residue was usually found to gradually convert to phosphine oxide over time. The applicability of this method of purification was also investigated for the product of reactions under Appel and Appel-type conditions. Denton and co-workers have used a sequence based on the treatment of phosphine oxide with oxalyl chloride as the basis for their catalytic Appel reactions. They reported that their protocol was less efficient for reactions involving secondary alcohols. Therefore we chose to use menthol in Appel processes to see if our work-up procedure might provide a complementary methodology to theirs (Table 2).

Chlorotriphenylphosphonium salt was generated in three ways: reaction of phosphine with CCl₄ (Table 2 entry 1) or hexachloroacetone (HCA, Table 2, entry 2), and reaction of phosphine oxide with oxalyl chloride (Table 2 entry 3), all in toluene solvent. The salt so formed was treated with menthol and worked up by evaporation of toluene and addition of cyclohexane followed by oxalyl chloride (method (iii) above). After effervescence had ceased, the supernatant liquid was filtered by cannula from the white CPS-containing solid and, after aqueous work-up and evaporation of the cyclohexane, was found to contain neomenthyl chloride in good yield (see Table 2). The absence of any phosphorus-containing material was confirmed by 31P NMR of the product. In the case of Table 2 entry 2, in which HCA was used as the chlorinating agent, the neomenthyl chloride was contaminated with pentachloroacetone.

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Table 1. Wittig reactions for which oxalyl chloride treatment of the crude product followed by filtration yields alkene product free of aldehyde and phosphorus. See ESI for full details of the reactions, work-up procedures and analyses.

<table>
<thead>
<tr>
<th>#</th>
<th>Phosphonium salt</th>
<th>Carbonyl compound</th>
<th>Yield (%)</th>
<th>Alkene Z/E Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1’</td>
<td>Ph</td>
<td>i-Pr</td>
<td>H</td>
<td>92</td>
</tr>
<tr>
<td>2’</td>
<td>i-Bu</td>
<td>i-Pr</td>
<td>H</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>CO₂Et</td>
<td>H</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>i-Bu</td>
<td>i-Pr</td>
<td>H</td>
<td>96</td>
</tr>
<tr>
<td>6’</td>
<td>Ph</td>
<td>i-Pr</td>
<td>H</td>
<td>96</td>
</tr>
<tr>
<td>7’</td>
<td>Me</td>
<td>2-OMeC₆H₄</td>
<td>H</td>
<td>CH₃</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>2-OMeC₆H₄</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>2-FC₆H₄</td>
<td>H</td>
<td>2-FC₆H₄</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>2-FC₆H₄</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>11</td>
<td>Ph</td>
<td>i-Pr</td>
<td>H</td>
<td>2-BrC₆H₄</td>
</tr>
<tr>
<td>12</td>
<td>Ph</td>
<td>CO₂Bu</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>CO₂Bu</td>
<td>H</td>
<td>2-MeC₆H₄</td>
</tr>
<tr>
<td>14’</td>
<td>Ph</td>
<td>C(O)Me</td>
<td>H</td>
<td>Ph</td>
</tr>
<tr>
<td>15</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>CF₃</td>
</tr>
<tr>
<td>16</td>
<td>Ph</td>
<td>CO₂Bu</td>
<td>Ph</td>
<td>CF₃</td>
</tr>
</tbody>
</table>

* Reaction temperature (at which addition of aldehyde occurred) was 20 °C, and the solvent used for the filtration step was cyclohexane, unless otherwise specified.
* Based on isolated yield of alkene.
* Z/E ratio determined by ¹H NMR and ¹⁹F NMR (where applicable) analysis of the crude product after aqueous work-up.
* Reaction (addition of alkylene) carried out at -78 °C.
* Filtration was carried out using dry degassed Et₂O at -78 °C.
* Stated yield takes account of residual alkene.
* This product could not be completely purified due to decomposition, and was contaminated with a small amount of starting aldehyde. Complete conversion (based on consumption of phosphonium salt) was confirmed by ¹H and ³¹P NMR of the crude product.
* Reaction (addition of aldehyde) carried out at -20 °C.
* Parent phosphine was regenerated from the chlorophosphonium salt contained in the residue after filtration of the alkene solution by dissolving the residue in dry THF and treating with LiAlH₄. For entry 7, Me₂PPh was isolated in a yield of 98%. For entries 11, 12, 13, and 16, Ph₂P was isolated in yields of 80%, 88%, 95%, and 88% respectively.
* Phosphonium chloride salt was used as the ylide pre-cursor.
* Z/E ratio determined exclusively by ¹⁹F NMR analysis of the crude product obtained after aqueous work-up.
* Pre-formed commercial ylide acetylidene-triphenylphosphorane (Aldrich) was used.

From Table 1, it can be seen that this procedure was successful for the removal of triphenylphosphine oxide, iso-butyldiphenylphosphine oxide, and methyldiphenylphosphine oxide from Wittig reaction crude products, and is applicable to the crude products of the reactions of all phosphonium ylide types (non-stabilised, semi-stabilised and stabilised) with both aromatic and aliphatic aldehydes, and with ketones. In all cases, comparison of the Z/E ratio of the crude alkene product with that of the product after treatment with oxalyl chloride showed it to be unaffected by the procedure. This is particularly striking for the cases of Z-2,2′-difluorostilbene (entry 9) and 1-cyclopentyl-3-methylbut-1-ene (entries 5 & 6). The former is known to be extremely sensitive to isomerisation to the E-isomer, especially if subjected to column chromatography. The latter alkene (both isomers) spontaneously degrades under ambient conditions simply if allowed to stand. Thus neither alkene is readily accessible in pure form by methods that demand chromatography. The use of our procedure enabled the isolation of each compound in sufficiently pure form for full NMR characterisation, and in particular allowed the very challenging task of establishing the stereochemistry of the isomers of 1-cyclopentyl-3-methylbut-1-ene to be accomplished by the 1D DPFGSE-NOE NMR technique (see ESI for details).
The use of an alkane solvent or cold Et₂O for the filtration step after chlorophosphonium salt generation is important for the success of the separations achieved in both the Wittig and Appel reactions. We have found that the entity generated by treatment of phosphine oxide with oxalyl chloride is at least sparingly soluble in toluene, THF and Et₂O (at 20 °C), perhaps due to isomerisation between chlorophosphonium salt and dichlorophosphorane. The procedures described above were tested with dry degassed THF (20 °C) and dry degassed Et₂O (20 °C) in place of cyclohexane as the filtration solvent. Using these conditions, most of the phosphorus-containing material is successfully removed, but a small quantity of phosphine oxide is invariably present in the product. It may be possible to extend the applicability of the protocol to purification of compounds that are not soluble in cyclohexane by using mixed solvents such as cyclohexane/Et₂O at room temperature.

Table 2. Appel-type reactions for which oxalyl chloride treatment of the crude product followed by filtration yields alkyl chloride product free of phosphorus. See ESI for full details of the reaction, work-up and analyses.

<table>
<thead>
<tr>
<th>#</th>
<th>CPS Generation</th>
<th>Yield (%) n-octyl chloride</th>
<th>Yield (%) Ph₃P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃P + CCl₄</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Ph₃P + HCA</td>
<td>86</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Ph₃PO + (COCl)₂</td>
<td>80</td>
<td>86</td>
</tr>
</tbody>
</table>

Yields based on isolated material unless otherwise indicated.

HCA = hexachloroacetone

Yield estimated from ¹H NMR of crude product after filtration to remove chlorophosphonium salt. This crude product contains pentachloroacetone (by-product from chlorinating agent).

With a method for isolation of the alkene in hand, we turned our attention to the possibility of reduction of the CPS to phosphine. We were encouraged in this because we had recently discovered that both chlorophosphonium salts and alkoxyphosphonium salts could be subjected to reduction and in-situ boranation using NaBH₄, thus providing facile conversion from phosphine oxide to phosphine-borane. Drawing on this work and the work of Imamoto and co-workers, we investigated LiAlH₄ as reductant, and found it to be successful for the overall reduction of the phosphine chalcogenides shown in Chart 1.

Finally, the separation and phosphine regeneration procedures were combined for a number of Wittig and Appel reactions. Thus the residue remaining after separation of the cyclohexane phase from the insoluble material was dissolved in THF and treated with LiAlH₄ at low temperature. The reaction mixture was quenched either by addition of degassed ethyl acetate followed by addition of degassed NH₄Cl solution or by quickly pouring the reaction mixture into a separatory funnel containing a degassed mixture of dichloromethane and aqueous NH₄Cl under inert atmosphere. Standard aqueous work-up (under an oxygen-free atmosphere) followed by solvent removal in vacuo furnished the phosphine product.

Chart 1. Phosphine chalcogenides that could be reduced by sequential treatment with oxalyl chloride and LiAlH₄.

In cases where a small amount of phosphine oxide contaminant was shown to be present in the sample of phosphine, elution through a short plug of silica using cyclohexane, ethyl acetate or dichloromethane removed the phosphine oxide and furnished clean phosphine. In general, it was observed that the yield of phosphine was higher and that side-product formation was suppressed if the degassed dichloromethane/NH₄Cl solution work-up was employed. If ordinary bench solvents containing dissolved oxygen are used for the work-up then a very significant amount of phosphine oxide is formed. The high yields of regenerated phosphine from the Wittig and Appel-type reactions (where applicable) are shown in Table 1 (entries 7, 11, 12, 13, and 16 – see footnote i) and Table 2 (all entries) respectively. For phosphine regeneration from Wittig reactions, the best results were obtained if the initial crude product was subjected to aqueous work-up (before any oxalyl chloride addition) using dichloromethane as the organic solvent. This removed inorganic salts and products derived from the hexamethyldisilazide base, while ensuring that all phosphine oxide (much of it derived from

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Experimental

Representative experimental procedures for the Wittig Appel reactions, phosphine oxide removal and phosphine regeneration are given below. For details of the other reactions in Tables 1 and 2 and Chart 1 see the ESI.

Synthesis & purification of tert-butyl 3-(2-methylphenyl)prop-2-enoate (Table 1 entry 13).

\[
\begin{align*}
\text{(i) KHMDS} & \quad \text{THF} \\
\text{(ii) } & \quad \text{O} \\
\text{(iii) } & \quad \text{Cl} \\
\text{(iv) Cyclohexane, filter} & \quad \text{O} \\
\end{align*}
\]

(i) KHMDS in THF
(ii) Oxalyl chloride (0.10 ml, 1.2 mmol) was added to the residue, causing the formation of a pale yellow solid. Cyclohexane (10 ml) was added, and after swirling the mixture, the liquid was decanted off. The residue was washed a further five times in this manner with cyclohexane (5 ml). The combined cyclohexane phases were filtered through a cannula using Whatman grade GFD glass micro fibre filter paper. The filtered solution was washed with saturated NaHCO₃ solution (2 x 5 ml) and aqueous HCl solution (1M, 2 x 5 ml), dried over MgSO₄ and concentrated in vacuo to yield the phosphorus-free alkene (0.15 g, 88%), as confirmed by ¹H and ³¹P NMR. The Z/E ratio of the alkene was determined to be 3:97 by comparison of the relative integrations of the signals assigned to each isomer.

[(tert-Butoxycarbonylmethyl)triphenylphosphonium bromide (328 mg, 0.794 mmol) and KHMDS (167 mg, 0.834 mmol) were added to a flame-dried Schlenk flask under an atmosphere of argon in a glove box. The Schlenk flask was attached to a Schlenk manifold and charged with nitrogen by the standard pump-and-fill technique.]

Dry THF (4 ml) was added, and the resulting mixture was stirred for one hour at 20 ºC. 2-methylbenzaldehyde (95 mg, 0.79 mmol) was added by nitrogen-flushed syringe. The reaction mixture was stirred for 12 hours. The THF solvent was removed in vacuo. A small sample was removed for analysis by NMR (Z/E ratio of alkene in crude product was 3:97). The residue was dissolved in CH₂Cl₂ (15 ml) and washed with saturated NH₄Cl solution (5 ml). The phases were separated, and the aqueous phase was washed twice with CH₂Cl₂ (10 ml each). The combined isolated CH₂Cl₂ phases were dried over MgSO₄, filtered and concentrated in vacuo.

Oxalyl chloride (0.10 ml, 1.2 mmol) was added to the residue, causing the formation of a pale yellow solid. Cyclohexane (10 ml) was added, and after swirling the mixture, the liquid was decanted off. The residue was washed a further five times in this manner with cyclohexane (5 ml). The combined cyclohexane phases were filtered through a cannula using Whatman grade GFD glass micro fibre filter paper. The filtered solution was washed with saturated NaHCO₃ solution (2 x 5 ml) and aqueous HCl solution (1M, 2 x 5 ml), dried over MgSO₄ and concentrated in vacuo to yield the phosphorus-free alkene (0.15 g, 88%), as confirmed by ¹H and ³¹P NMR. The Z/E ratio of the alkene was determined to be 3:97 by comparison of the relative integrations of the signals assigned to each isomer.

[1H NMR of purified product (integrations relative to 1 H of E-isomer):  ²³⁵H (500 MHz, CDCl₃) 7.88 (1 H, d, J 15.9, E-H-3), 7.55-7.53 (1 H, m, E-ArH), 7.27 – 7.22 (contains CHCl₃ signal, m, E-ArH), 7.21-7.16 (2 H, m, E-ArH), 7.02 (0.03 H, d, J 12.1, Z-H-3), 6.29 (1 H, d, J 15.9, E-H-2), 5.95 (0.03 H, d, J 12.1, Z-H-2), 2.43 (3 H, s, E-CH₃), 2.27 (0.1 H, s, Z-CH₃), 1.54 (9 H, s, E-C(CH₃)₃), 1.30 (0.27 H, s, Z- C(CH₃)₃).]

The Schlenk flask containing the residue from the filtration was charged with nitrogen. Dry THF (2 ml) was added, and the resulting mixture was cooled to – 78 ºC and LiAlH₄ in THF (1M,
1.2 mL, 1.2 mmol) was added dropwise, resulting in the evolution of hydrogen gas and the dissolution of all of the solid material in the THF. The reaction mixture was removed from the cold bath and stirred for 20 minutes, then quickly poured into a degassed mixture of CH₂Cl₂ (30 mL) and saturated NH₄Cl solution (15 mL) contained in a separatory funnel under an inert atmosphere. After swirling, the CH₂Cl₂ phase was allowed to drain off. The aqueous phase was extracted with further degassed CH₂Cl₂ (15 mL). The combined CH₂Cl₂ phases were dried over MgSO₄ and filtered. The solvent was removed under vacuum yielding clean Ph₃P (0.20 g, 95%). δₚ (121 MHz, CDCl₃) -5.3 (lit.13 -4.8).

**Reaction of triphenylphosphine oxide + oxalyl chloride + (-)-menthol (Table 2 entry 3).**

Triphenylphosphine oxide (1.0 g, 3.5 mmol) was dissolved in dichloromethane (10 mL) in a flame dried Schlenk tube under an atmosphere of nitrogen. Oxalyl chloride (0.30 mL, 3.5 mmol) was added dropwise to the reaction mixture resulting in the formation of a white precipitate. (³¹P NMR δ 64.5 ppm). (-)-Menthol (0.56 g, 3.5 mmol) was added to the reaction mixture through a powder funnel, causing the reaction mixture to become clear. The complete formation of alkoxyphosphonium salt was confirmed by ³¹P NMR of a small sample of the reaction mixture (³¹P NMR δ 58.9). The reaction was allowed to stir for 30 minutes. Completion of the reaction was confirmed by ³¹P NMR analysis of a small sample of the reaction mixture (³¹P NMR δ 25.2). The tolune reaction solvent was removed in vacuo and cyclohexane (10 mL) was added to the residue. Oxalyl chloride (0.30 mL, 3.5 mmol) was added dropwise to the reaction mixture which caused the formation of a white precipitate of chlorophosphonium salt. The supernatant liquid was removed by cannula filtration. The mixture was washed (2x 10 mL) twice with cyclohexane and the washings removed by cannula filtration. The combined cyclohexane filtrate was washed with cyclohexane and the washings removed by cannula filtration. The residue was washed (2x 10 mL) twice with cyclohexane and the washings removed by cannula filtration. The residue was washed (2x 10 mL) twice with cyclohexane and the washings removed by cannula filtration.

The solid residue remaining after cannula filtration of the reaction mixture was dissolved in THF (10 mL) and cooled to 0°C. A solution of LiAlH₄ in THF (1.0M, 3.5 mL, 3.5 mmol) was added dropwise to the mixture, which was then stirred for 30 minutes while warming to room temperature. Ethyl acetate (10 mL) was added to quench the LiAlH₄ followed by saturated aqueous NH₄Cl (10 mL). The reaction mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was washed twice more with ethyl acetate (10 mL each wash). The combined organic phases were dried over MgSO₄, filtered through a silica plug to remove residual phosphine oxide and concentrated in vacuo to give phosphine (0.78 g, 86%). δₚ (162 MHz): -4.5 (lit.13 -4.8).

**Notes and references**


7. See reference 3f.


37 N. C. Gonnella, C. Busacca, S. Campbell, M. Eriksson, N. Grinberg, T. Bartholomeyzik, S. Ma, D. L. Norwood, Magn. Reson. Chem., 2009, 47, 461. For cases where the Wittig reaction is performed in Et2O, it was found in practice that the reproducibility of phosphorus removal was far superior if the oxalyl chloride was added to the neat crude product rather than to the solution of the crude product in Et2O.
38 The Z/E ratio of the alkene was assigned by integration of characteristic signals in the 1H NMR and/or 19F NMR, for both the crude and the purified products.
39 DPFGSE-NOE stands for Double Pulse Field Gradient Spin Echo Nuclear Overhauser Effect NMR spectroscopy.