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Synthesis and application of crown ether tagged triarylphosphines

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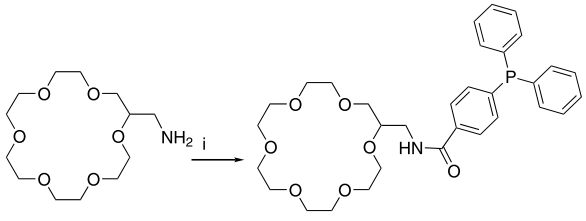
Abstract—Crown ether tagged triarylphosphines **1** and **2** were synthesised and applied in Mitsunobu and Heck reactions, their reactivity being evaluated against triphenylphosphine- and polymer-bound triphenylphosphine. Purification of the reactions was effected by post-reaction sequestration onto an ammonium functionalised solid-phase.

The synthesis of chemical libraries is still a burgeoning area of research for both industry and academia. Early library syntheses were generally performed on the solid-phase[1] but recently there has been a paradigm shift towards solution-phase synthesis.[2] This has introduced new enabling technologies such as scavenger resins,[3] fluorous-phase synthesis,[4] polymer-supported[5] and tagged reagents.[6]

In this letter we describe our preliminary results towards a novel approach to tagged reagents exemplified by the synthesis and application of crown ether tagged triarylphosphines **1** and **2**. Triarylphosphines have been synthesised on both soluble[7] and insoluble[8] polymer supports and with a masked carboxylic acid as a sequestering tag.[9] Here we have used the crown ether as an inert 'phase label' to allow selective solid-phase sequestration of the reagent and/or byproducts from reaction mixtures. A recent paper has described affinity purification using crown ether–ammonium ion interaction to isolate compounds that contained a large crown ether moiety (dibenzo-32-crown-10).[10] This was, in effect, using the crown ether as the 'support' on which synthesis was undertaken. Similarly the use of aminomethyl-18-crown-6 as an ionisable phase label has been reported.[11]

The crown tagged triarylphosphine **1** was synthesised in excellent yield in a one-step reaction from commercially available 2-aminomethyl 18-crown-6 and triphenylphosphine carboxylic acid as shown in Scheme 1. 15-Crown-5 tagged triarylphosphine **2** was synthesised from triphenylphosphine alcohol[7] and mesylated hydroxymethyl 15-crown-5 as shown in Scheme 2.



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Scheme 1. *Reagents and conditions*: (i) DCC, DMAP (cat.), HOBt, DCM, ambient temperature, 18 h, 94%.

In order to demonstrate the application of these reagents as triphenylphosphine substitutes, both crown tagged triarylphosphines **1** and **2** were used in the Mitsunobu synthesis of 7-benzyloxycoumarin **4** from 7-hydroxycoumarin **3** (Scheme 3). The results were compared to triphenylphosphine and cross-linked polystyrene supported triphenylphosphine (Novabiochem 1.10 mmol g^{-1}) (Table 1). In the reaction, 15-crown 5-tagged triarylphosphine **2** proved as effective as both triphenylphosphine and polymer-supported triphenylphosphine in converting **3** into **4**.

The reaction mixture from the 18-crown-6-tagged triarylphosphine-mediated Mitsunobu reaction was loaded onto an ammonium trifluoroacetate ArgoPore™ column[12] then eluted with dichloromethane. No phosphine derived adducts passed through the column as determined by ^{31}P NMR spectroscopy (Fig. 1). Elution

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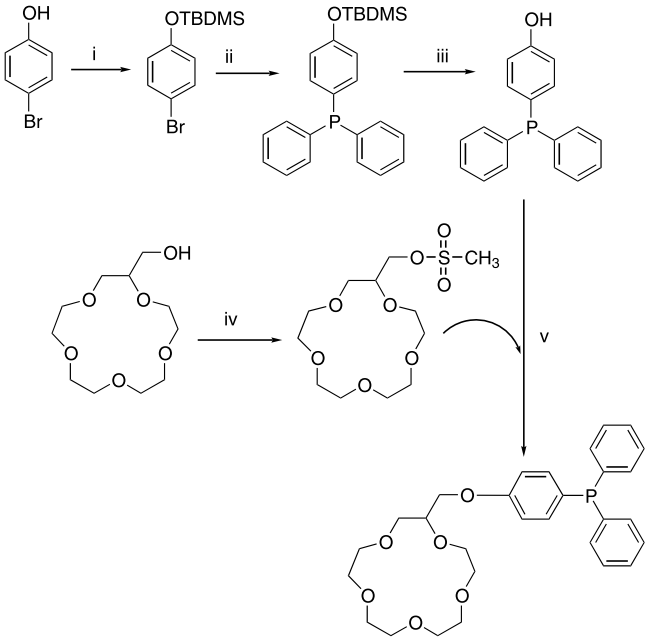
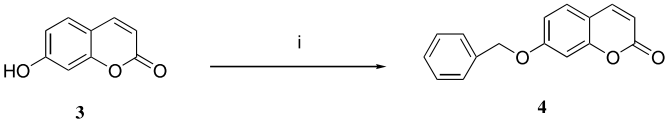


2

Scheme 2. *Reagents and conditions*: (i) TBDMS-Cl, imidazole, DCM, 24 h, 98%. (ii) BuLi (2.39 M in hexane), chlorodiphenylphosphine, THF −78°C, 0.5 h to 20°C, 24 h, 22%. (iii) TBAF (1 M in THF) (2 equiv.), 20°C, 3 h, 75%. (iv) MsCl (3 equiv.), Et_3N (3 equiv.), DCM, 20°C, 18 h, 55%. (v) Cs_2CO_3 (2 equiv.), THF, 20°C, 48 h, 70%.



3 4

Scheme 3. *Reagents and conditions*: (i) **L** (2 equiv.), benzyl alcohol (1.1 equiv.), DEAD (2 equiv.), THF, 0–20°C, 3 h.

Table 1. Synthesis of 7-benzyloxycoumarin **4**

Phosphine **L**	Percentage conversion of **3** to **4**[a] (%)
Triphenylphosphine	91
Polymer-supported triphenylphosphine	93
Tagged triarylphosphine **1**	63
Tagged triarylphosphine **2**	>95

Tagged triarylphosphine **2**ca = "D" > > >95
[a] Percentage conversion determined by HPLC analysis.

of the column with dichloromethane doped with 2% v/v triethylamine released all sequestered tagged phosphine oxide (Fig. 2). After washing to remove triethylamine, 80% of the expected triarylphosphine oxide was recovered.

Palladium-mediated carbon–carbon bond formations are extensively used in organic synthesis. In order to explore the application of crown-tagged triarylphosphine **2** in a Heck reaction it was used to synthesise the

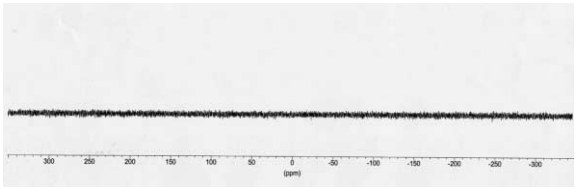


Figure 1. ^{31}P NMR spectrum of dichloromethane eluent from reaction to form **4**.

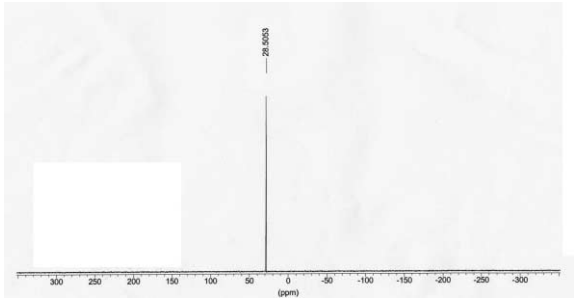
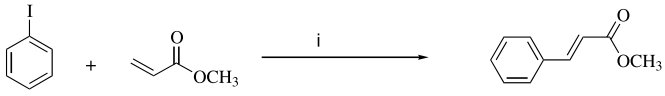


Figure 2. ^{31}P NMR spectrum of dichloromethane (+2%v/v triethylamine) elution of ammonium functionalised ArgoPore™ column.

methyl ester of 3-phenylacrylic acid **6** (Scheme 4) from iodobenzene **5** and methylacrylate. The results were compared to those obtained with triphenylphosphine (Table 2).



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Scheme 4. *Reagents and conditions*: (i) **L** (0.32 equiv.), $Pd(OAc)_2$ (0.17 equiv.), NEt_3 (2 equiv.), THF reflux, 8 h.

Table 2. Synthesis of 3-phenylacrylic acid methylester **6**

Phosphine **L**	Percentage conversion of **5** to **6**[a] (%)
Triphenylphosphine	>95
Tagged triphenylphosphine **2**	>95

[a] Percentage conversion determined by HPLC analysis.

In both cases the reaction showed quantitative conversion of iodobenzene **5** to 3-phenylacrylic acid methyl ester **6**. The reaction mixture was loaded onto an ammonium trifluoroacetate ArgoPore™ column then eluted with dichloromethane. As expected no phosphine derived adducts passed through the column as determined by ^{31}P NMR spectroscopy (Fig. 3).

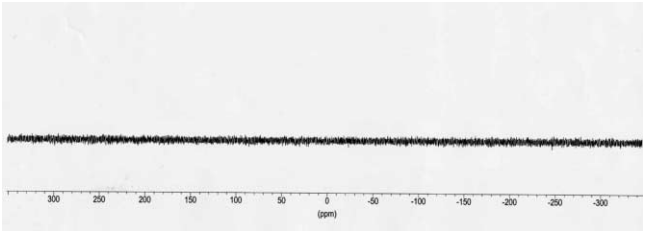

Figure 3. ^{31}P NMR spectrum of dichloromethane eluent from Heck reaction to form **6**.

In conclusion, we have demonstrated that tagged triarylphosphine reagents can be used in both Mitsunobu and Heck chemistry with removal of phosphine derived by-products achieved by elution through ammonium functionalised ArgoPore™ resin. Work is currently in progress to recycle these reagents by reduction of the triarylphosphine oxide.

Acknowledgements

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12. Ammonium functionalised ArgoPore™ resin was prepared by the methodology outlined in Ref. 10.