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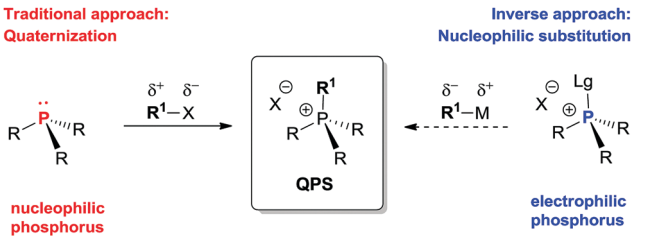
Long sought synthesis of quaternary phosphonium salts from phosphine oxides: inverse reactivity approach†

Anna C. Vetter, Kirill Nikitin and Declan G. Gilheany *

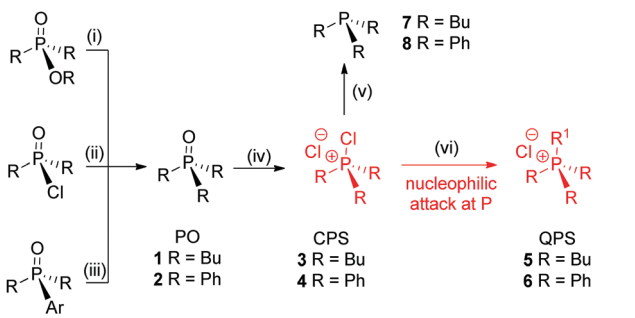
Quaternary phosphonium salts (QPS), a key class of organophosphorus compounds, have previously only been available by routes involving nucleophilic phosphorus. We report the realisation of the opposite approach to QPS utilising phosphine oxides as the electrophilic partner and Grignard reagents as nucleophiles. The process is enabled through the crucial intermediacy of the derived halophosphonium salts. The route does not suffer from the slow kinetics and limited availability of many parent phosphines and a broad range of QPS were prepared in excellent yields.

Quaternary phosphonium salts[1] are a versatile class of organophosphorus compounds having applications in many areas of chemistry. As well as the celebrated Wittig olefination,[2,3] more recent uses include organocatalysis,[4] chiral phase transfer catalysis,[5] drug delivery[6] and as ionic liquids.[7] It is therefore striking that, without exception, all of the known synthetic strategies towards QPS involve phosphorus as a nucleophilic species: whether this is by traditional quaternizations (Scheme 1, left), or by additions to a great variety of other types of electrophiles.[8] However, while widely used, there are two significant disadvantages of these routes. First, although phosphines are effective nucleophiles, many of their quaternization-like processes are slow,[9–11] limiting efficient QPS syntheses to active alkylating reagents and sterically-innocent phosphines. This is especially so for arylation reactions, unless high temperature and/or a transition metal catalyst is used.[12] Second, many of the required parent tertiary phosphines have limited availability and are dangerous to handle, especially the more nucleophilic electron rich cases (*e.g.* trialkylphosphines). These combined limitations become critical in cases where an unsymmetric (R_2PR^1) or asymmetric phosphine ($R^1R^2R^3P$) is needed, since stepwise introduction of two or three different organic groups into a PX_3 unit lacks sufficient selectivity.[13] A striking illustration of these limitations on QPS synthesis is the near universal use of triphenylphosphine-derivatives for Wittig reactions, even though it is well known that other parent phosphines can be beneficial.[3,14]



Scheme 1 Nucleophilic (red) and electrophilic (blue) approaches to QPS formation (Lg: leaving group).

We were aware that these long-known problems of QPS synthesis[1,15] could be averted by applying an inverse reactivity strategy, whereby the new group, *e.g.* R^1, is introduced using an organometallic reagent R^1–M (Scheme 1, right). Such nucleophilic P–C bond formation (Scheme 2) is a common strategy for other types of organophosphorus compounds.[16] This is especially so for tertiary phosphine oxides (PO, Scheme 2) for whose syntheses organometallic reagents have been widely used through displacement in the P(v) series of alkoxy,[17] halo[18,19] or, very recently, even certain aromatic groups[20] (Scheme 2(i–iii)).



Scheme 2 Phosphine oxide/chlorophosphonium salt reaction manifold: (i) RMgX, ether, 20 °C; (ii) RMgX, ether, −20 °C; (iii) RMgX, THF, 60 °C; (iv) $(COCl)_2$, DCM, 20 °C; (v) $LiAlH_4$, −80 °C; (vi) this work: R^1MgX.

Centre for Synthesis and Chemical Biology, School of Chemistry, University College Dublin, Belfield, Dublin 4, Ireland. E-mail: declan.gilheany@ucd.ie

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As well as being readily available, tertiary phosphine oxides are relatively innocuous to handle, making them desirable starting materials for QPS synthesis. However, they lack the suitable leaving group required (Scheme 1, right). We identified a solution to this in the easily derived intermediate chlorophosphonium salts (CPS, Scheme 2), the chemistry of which we have reported on extensively.[21] They are readily prepared from the parent phosphine oxides (Scheme 2(iv)) and are versatile electrophilic intermediates in the synthesis of both alkoxyphosphonium salts[21a–c] and the parent phosphines (Scheme 2(v)).[21d,e] We reasoned, therefore, that combining CPS and a suitable organometallic reagent should lead to QPS structures (Scheme 2(vi)). We chose Grignard reagents owing to their wide diversity, accessibility, relative ease of handling and environmental friendliness in reaction with tributyl- **1** and triphenylphosphine oxide **2**.

This desirable reaction has been tried in the past,[22] although only in one case with QPS synthesis in mind.[23,24] Both Grignard and Savard[22a] and Blount[22b] had targeted pentacoordinate phosphorus and the latter isolated a single example of QPS. This was much later confirmed by Denny and Gross,[23] who however also pointed out that the QPS in question could, in principle, have resulted from standard quaternization (*vide infra*). Their only *bona fide* product of attack at P, Ph_4PCl, was obtained in poor yield (7%).[23] A lifetime later, we present now the realisation of this long-sought approach to QPS synthesis.

One of the reasons for earlier failures of this approach could lie in the complex interplay of factors affecting the structure of R_3PCl_2, which can adopt ionic (**3**/**4**, Fig. 1) or pentacoordinate molecular forms (**3′**/**4′**).[25] In line with our earlier findings,[26,27] ionic **3**/**4** are formed in chloroform, dichloromethane (DCM) and MeCN, whereas molecular **3′**/**4′** strongly prevail in less polar solvents (THF, benzene, toluene) as can be seen spectroscopically (see ESI†). Another likely factor is that clean formation of halophosphonium salts had to await the introduction of oxalyl halides as reagents[28] and this took a long time to be taken up to full advantage.[21a,d,29,30]

Table 1 shows selected results of our preliminary exploration of the reaction of **3**, **3′** and **4** with Grignard reagents. It can be seen that, in the case of ethyl magnesium chloride and tri-*n*-butyl derivatives **3** and **3′**, a high yield of QPS (**5b**) is obtained in both DCM and THF as solvent (entries 1–3, 5), falling off somewhat in less polar solvents (entries 6 and 7). As well as solvent polarity, this lower reaction rate probably also reflects the differing halide structures (ionic **3** *vs.* molecular **3′**). That the rate of QPS formation is rapid can be inferred from entry 4, which shows that it could compete for Grignard reagent in reaction with MeCN present as solvent.[31]

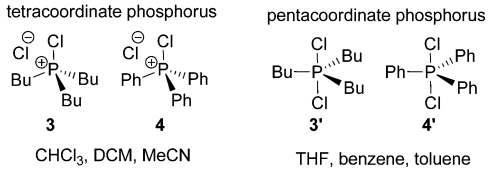
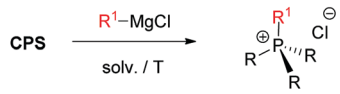


Fig. 1 Solvent dependent structures of R_3PCl_2 from R_3PO and oxalyl chloride.

Table 1 Preliminary survey of reaction conditions for Grignard synthesis of CPS[a]



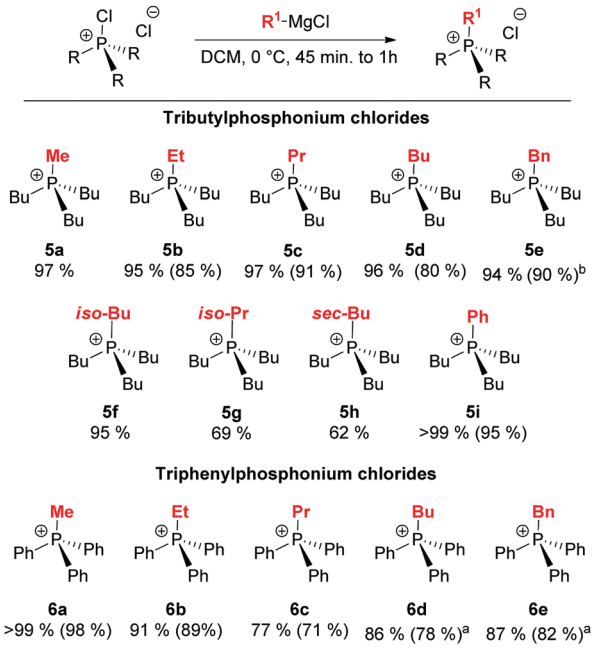
Entry	CPS[b]	R^1	Solvent	T,[c] °C	Eq.[d]	QPS[e]	Yield[f]
1	**3**	Et	DCM	r.t.	2	**5b**	96
2	**3**	Et	DCM	0	1	**5b**	94
3	**3**	Et	DCM	0	2	**5b**	100
4	**3**	Et	MeCN	r.t.	2	**5b**	27
5	**3′**	Et	THF	r.t.	2	**5b**	95
6	**3′**	Et	Benzene	r.t.	2	**5b**	79
7	**3′**	Et	Toluene	r.t.	2	**5b**	53
8	**3**	Bn	DCM	r.t.	2	**5e**	55
9	**3**	Bn	DCM	0	2	**5e**	74
10	**3**	Bn	DCM	−83	2	**5e**	94
11	**4**	Bn	DCM	0	2	**6e**	79
12	**4**	Bn	DCM	−41	1	**6e**	67
13	**4**	Bn	DCM	−41	2	**6e**	94

[a] Grignard reagent in THF (1.4–2.7 M) added to CPS solution (0.2 M), quenched after 45 min at the reaction temperature – see ESI for full details. [b] Structure known in the specified solvent. [c] For DCM cases: decremented from r.t. to −83 °C – see ESI. [d] Incremented from 1–2 equivalents – see ESI. [e] Structures in Scheme 3. [f] By ^{31}P NMR of reaction mixture: balance mostly phosphine oxide from unreacted CPS.

We settled on DCM as reaction solvent with two equivalents of the Grignard reagent. While uncommon for Grignard chemistry, DCM allowed easier generation of the CPS and convenient work-up. Although probably not strictly necessary in all cases, excess Grignard was used to ensure complete reaction on our approximately one-hour reaction timescale (entries 2 *vs.* 3 and 12 *vs.* 13). The effect of reaction temperature was examined with benzylmagnesium chloride as nucleophilic partner (entries 8–13) leading to tri-*n*-butyl- and triphenylphosphonium salts **5e** and **6e**. Both reactions were strongly affected by temperature with, perhaps unexpectedly, higher yields of QPS obtained at lower temperatures due to a fewer number of side-products. We settled on reaction at 0 °C for the subsequent studies, being relatively convenient while still allowing for moderation of any reaction exotherms.

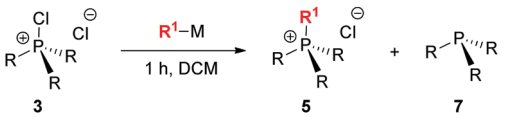
Using the optimised reaction conditions, we then explored the Grignard reagent scope. In Scheme 3 it can be seen that reactions of tributyl and triphenyl CPS (**3** and **4**) with primary alkyl magnesium chlorides uniformly afforded the QPS salts (**5a–5f**, **6a–6e**) in high yields. Most significantly, the reaction of **3** with aromatic PhMgCl gave over 99% yield of **5i** Bu_3PPhCl – a major improvement compared to the virtually impossible quaternization of Bu_3P with chlorobenzene. However, secondary Grignard reagents afforded the corresponding phosphonium salts (**5g** and **5h**) in lower yields. In these cases, the reduced yields are due to the formation of a side product, the corresponding tertiary phosphine **7**. Table 2 and Scheme 4 show our exploration of that issue.

From Table 2 it can be seen that when the reactions of tributyl CPS **3** with Grignard reagents of varying steric bulk were compared (entries 1–5) the effect of iso-branching in R^1MgCl two atoms away from the phosphorus reaction centre was negligible,



Scheme 3 Facile preparation of QPS by reaction of triphenyl- and tributyl-chlorophosphonium salts with organomagnesium reagents. Yields by ^{31}P NMR spectroscopy of the crude reaction mixture (isolated yields). [a] −41 °C, [b] −83 °C.

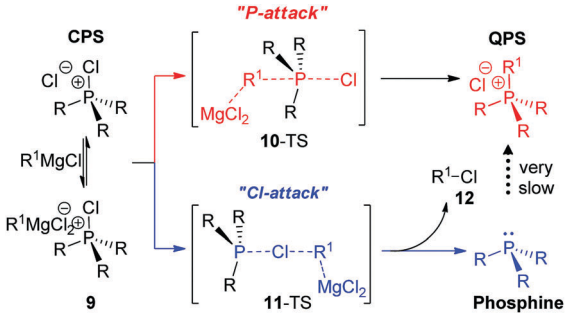
Table 2 QPS *vs.* phosphine formation in reactions of Grignard reagents with CPS[a]



				Products[b]			
Entry	CPS	R^1–M	T, °C		%		%
1	**3**	*n*-BuMgCl	0	**5d**	96	7	0
2	**3**	iso-BuMgCl	0	**5f**	95	7	0
3	**3**	iso-PrMgCl	0	**5g**	69	7	23
4	**3**	*sec*-BuMgCl	0	**5h**	62	7	30
5	**3**	*tert*-BuMgCl	30	—	0	7	86
6	**3**	PhMgCl	0	**5i**	>99	7	0
7	**4**	*n*-BuMgCl	0	**6d**	69	**8**	31
8	**4**	*n*-BuMgCl	−41	**6d**	86	**8**	9
9	**4**	iso-BuMgCl	0	**6f**	48[c]	**8**	46
10	**4**	iso-PrMgCl	0	—	0	**8**	89
11	**4**	*sec*-BuMgCl	0	—	0	**8**	96
12	**4**	*tert*-BuMgCl	0	—	0	**8**	100
13	**4**	PhMgCl	0	**6i**	15	**8**	78
14[d]	**4**	NeophylMgCl	30	—	0	**8**	75
15	**4**	*n*-BuLi	−83	**6d**	7	**8**	88
16	**4**	PhLi	−83	**6i**	9	**8**	69
17[e]	**4**	Et_2Zn	30	**6b**	67	**8**	0
18	**4**	*n*-Bu_2Mg	0	**6d**	59[f]	**8**	16

[a] As for Table 1 using 2 equiv. of organometallic reagent (see ESI for full details). [b] By ^{31}P NMR of reaction mixture: balance mostly phosphine oxide from unreacted CPS. [c] Isolated yield 38%. [d] Reaction time = 42 h. [e] Reaction time = 18 h. [f] Another phosphonium salt was also formed (17%).

with QPS **5d** and **5f** both formed essentially quantitatively (entries 1 and 2). However, moving the branching point closer to the reaction centre (entries 3 and 4) causes a significant shift



Scheme 4 Mechanistic hypothesis showing competing pathways: axial attack of Grignard reagent at P (red) leading to QPS; attack of Grignard reagent at Cl (blue) leading to phosphine and R^1–Cl **12**.

towards phosphine production so that both iso-Pr- and *sec*-BuMgCl furnished some tributylphosphine **7** at the expense of **5g** and **5h**, while use of *tert*-butylmagnesium chloride completely suppressed QPS formation (entry 5).

Side product formation also became more pronounced with the triphenyl CPS **4** (entries 7–12). Now, both primary R^1MgCl do give significant amounts of the phosphine **8** (compare entries 1 and 2 to 7–9), while secondary and tertiary R^1MgCl completely suppress QPS formation (entries 10–12). This increased suppression is further demonstrated by the very low yielding arylation reaction with PhMgCl to form Ph_4PCl **6i** (entry 13), whereas **3**, as discussed above, gives the arylation product **5i** essentially quantitatively (entry 6). It should be noted that even where a reduced amount of QPS is formed, it is still relatively easy to isolate (entry 9).

Formation of QPS (Scheme 4) is proposed as a fast nucleophilic attack (termed here the P-attack) of the R^1-group from the Grignard reagent on the phosphonium centre *via* an axial transition state (**10**-TS) or an alternative equatorial route (not shown). The formation of phosphine by-product is attributed to a different nucleophilic pathway where the covalently bonded Cl of the chlorophosphonium cation is attacked by the R^1-group *via* a different transition state (the Cl-attack, **11**-TS). The Cl-attack can also be considered a reductive process as it yields the parent phosphine and the derived alkyl halide **12**. To confirm this latter point, we used the bulky branched Grignard reagent derived from 2-methyl-2-phenylpropyl chloride (**12a** neophyl chloride, entry 14). The reaction with **4** was very sluggish and, as expected, phosphine **8**, but not the respective QPS, was formed. The fact that the parent **12a** (see ESI†) was also isolated strongly supports our mechanistic hypothesis.

Evidently, the choice of **4** as substrate was not optimal in the earlier studies.[22,23] In trying to explain the greater propensity for Cl-attack in the reactions of **4**, we considered a number of possibilities. We have previously shown that the barriers to nucleophilic attack by halide at phosphorus in **3** and **4** are similar,[27b] so we think it is unlikely that the electronic or steric nature of the phosphorus controls the reactivity. Therefore, we conclude that it is the greater leaving group ability of Ph_3P that leads to the greater degree of Cl-attack.

Two other significant points about Scheme 4 deserve mention. First, we are showing that the actual reacting species is the

magnesium ate-complex **9**, formed through initial coordination of the Cl-anion from CPS. While not strictly necessary for the overall explanation, we believe that it is the more likely reacting species.

The second point about Scheme 4 is related to the fact that Denny and Gross[23] could not authenticate their new reaction. This is because the combination of phosphine and **12** would itself lead to QPS *via* a subsequent independent standard quaternization after Cl-attack. However, from our own kinetic studies of phosphine alkylation in conjunction with those by McEwen and co-workers,[32] we can now categorically rule this out: the standard quaternization pathway is *ca.* 10^5–10^6 times slower than inverse polarity alkylation (see ESI†).

Finally, it was intriguing, of course, to examine the use of other organometallic reagents, hoping to achieve different P-selectivity patterns. In reaction with **4**, the more reactive organolithiums strongly favoured Cl-attack regardless of the R^1Li type (entries 15/16 *vs.* 8/13). Conversely, a very pronounced shift towards P-attack was observed with the less reactive diethylzinc (entry 17). Reaction of di-*n*-butyl-magnesium (entry 18) leads to somewhat less Cl-attack than with the corresponding Grignard reagent (entries 7 *vs.* 18).

In conclusion, we have discovered a new high-yielding nucleophilic preparation of quaternary phosphonium salts, including tetraalkyl, and alkyl–aryl series from phosphine oxides *via* the corresponding chlorophosphonium species, CPS. Our new methodology can be viewed as a rather powerful implementation of an Umpolung strategy, whereby both reacting partners have been subjected to inversion of polarity with respect to standard quaternization. Mechanistically, we have shown that the ionic tetracoordinate form of CPS in the presence of strongly nucleophilic Grignard reagents undergoes two principal reactions: P-attack leading to the desired QPS or Cl-attack leading to side-product phosphine.

Our new method is a very practical alternative to the existing quaternization routes to QPS, especially involving those with highly nucleophilic, and therefore readily oxidised, phosphines because it does not require synthesis/handling of such substrates. The mechanistic complementarity also provides further operational superiority, allowing rapid alkylation and arylation offering easy access to known and new QPS structures as key materials for synthesis.

A primary driver of our study is that this new inversed reactivity methodology opens the prospect of directly accessing a variety of QPS – immediate precursors of phosphorus ylides – from phosphine oxides. This could, in principle, render fully recyclable and reusable the key phosphorus components in Wittig and Wittig-type reactions. Work is presently underway on further development of this approach to Wittig reactions avoiding use of phosphorus(III) compounds altogether and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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