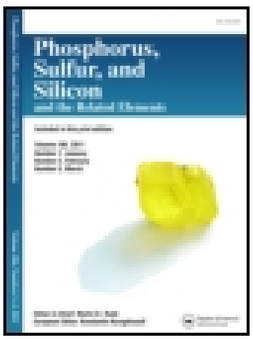

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Exploring an Umpolung strategy for quaternization of phosphorus

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ABSTRACT

We propose a new, potentially widely-applicable, Umpolung approach for the synthesis of quaternary phosphonium salts R_3PR^1 X (X = Cl, Br) from phosphine oxides R_3PO. The new organic group R^1 is introduced via nucleophilic attack on an intermediate halophosphonium salt using a Grignard reagent R^1MgX and replaces the traditional phosphine quaternization approach. Consequently, the new method does not suffer from the limited availability of many parent phosphines and is much faster than standard quaternization.

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Nucleophilic substitution; quaternary phosphonium salts; Wittig reagents; Umpolung

GRAPHICAL ABSTRACT

1. Introduction

The Wittig reaction enables alkene preparation by reaction of an aldehyde or a ketone with a phosphonium ylide generated from quaternary phosphonium salts (QPS) which, in their own right, have a multitude of applications in various fields of chemistry. These include their use as ionic liquids[1], phase-transfer[2] and organocatalysts.[3] However, the most common use of QPS is likely as starting material in the Wittig reaction. Shortly after its discovery in 1954,[4] its significance for synthesis was shown by its application to the industrial synthesis of vitamin A and β-carotene and it has continued its usefulness to this day.[5] However, modern economical use of the Wittig reaction requires a fundamental revision, considering economics and safety.[6] Currently, the entry point of phosphorus in the Wittig reaction manifold is phosphine – most commonly triphenylphosphine due to safety hazards associated with the more reactive (albeit synthetically appealing) trialkylphosphines. After conversion to QPS and exiting the Wittig reaction, phosphorus, in the form of phosphine oxide (PO), is a widely acknowledged nuisance by-product. This stoichiometric by-product, commonly Ph_3PO, and its disposal remain the major economic and environmental drawbacks of the Wittig reaction, as well as making it a prime example of poor atom economy.[7] The QPS starting material for any Wittig reaction is traditionally prepared by utilizing phosphine nucleophilicity in quaternization-type reactions. However, while currently being the method of choice, this approach bears a significant disadvantage: despite phosphines being effective nucleophiles, these processes are typically slow[8–10] thereby limiting the choice of reagents to active electrophiles and sterically-innocent phosphines. This is particularly true for arylation of parent phosphine structures, unless forcing conditions and/or transition metal catalysis is employed.[11]

Let us suppose one desired to acquire a simple reagent, for example $MePh_3PCl$ salt[12] to run a standard Wittig olefination reaction. Currently, the choice of reagents is extremely narrow: use Ph_3P, excess of hazardous MeCl gas at elevated temperate and high pressure. While an alternative all-in-one olefination reagent has recently been proposed,[13] this strategy is limited to just one example and, too, relies on quaternization under fairly harsh conditions. Conversely, we decided to develop a totally different route to QPS by employing an Umpolung approach, which utilizes the *electrophilic* character of a suitable accessible phosphorus-species. While nucleophilic P-C bond formation (Scheme 1, Umpolung approach) is a common strategy for other types of organophosphorus compounds (e.g. phosphines),[14] it was not commonly applied for the direct synthesis of QPS **5** or **6**. Phosphine oxides **1** and **2** depict an attractive starting material for this approach, however, due to the lack of the suitable

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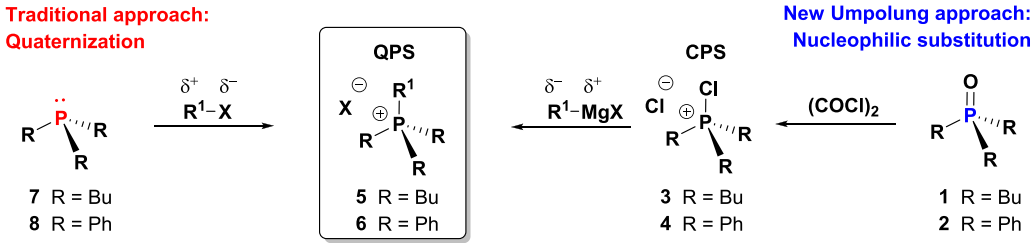
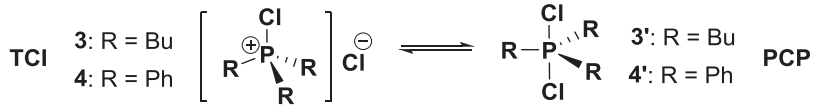


Scheme 1. Quaternization vs Umpolung approaches for the synthesis of QPS.

Table 1. Interconversion of tetracoordinate ionic (TCI) and pentacoordinate phosphorane (PCP) form of R_3PCl_2: Experimental ^{31}P NMR chemical shifts and DFT computed parameters of R_3PCl_2 (**3**, **4**, **3′** and **4′**).



Solvent	3	4	3′	4′
Benzene, δ ppm	–	–	8.5	−44.4
Toluene, δ ppm	–	–	−5.0	−46.1
THF, δ ppm	–	–	−3.4	−43.1
DCM, δ ppm	105.3	61	–	–
TCM, δ ppm	107.2	60	–	–
MeCN, δ ppm	103.8	59.9	–	–
D(P-Cl), A	2.05[a]	2.04[a]	2.35[b]	2.34[b]
E_{rel}, kcal/mol[c]	+5.3	+6.8	0	0

[a]DFT B3LYP calculation in DCM.
[b]DFT B3LYP calculation in toluene.
[c]relative to the PCP form in toluene.

leaving group required, they cannot be directly converted into QPS. We found a solution to this in intermediate chlorophosphonium salts (CPS) **3** and **4** as shown in Scheme 1. In our method, the non-reactive phosphine oxides **1** and **2** are straightforwardly converted to the highly versatile **3** and **4** via deoxychlorination with oxalyl chloride. The presence of the Cl-substituent in CPS greatly augments the electrophilic character of phosphorus while providing for a good leaving group. Consequently, we postulated that the combination of CPS and a suitable organometallic reagent, e.g. Grignard reagents, should yield QPS.[15]

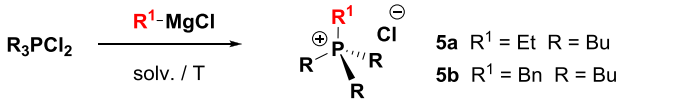
While this desirable transformation has been tried in the past, the aim was not the synthesis of QPS. Almost a century ago, in 1931, Grignard and Savard reported on the synthesis of "pentasubstituted phosphines", the formation of which involved the reaction of CPS with Grignard reagents.[16] In the same year, Blount recognized the vital role these compounds could have in understanding issues associated with "valency and stereochemistry", which were of great interest at the time.[17] However, Blount failed to isolate the products proclaimed by Grignard and Savard, attributing the lack of success to an aqueous wash post formation of Ph_3PCl_2 when he followed their method, which led to the conversion Ph_3PCl_2 to Ph_3PO. Realizing that CPS were acutely moisture-sensitive, Blount repeated the experiment yet another time using an authentic sample of Ph_3PCl_2. Still, not even then was he able to isolate the penta-substituted phosphine. Although he suspected that QPS were formed instead, he was not yet able to substantiate this. It was not until three decades later, that Denney and Gross[18] were finally able to confirm Blount's hypothesis. Cursorily, they acknowledged that in principle QPS could be the product of a standard quaternization (*vide infra*). Accordingly, the sole *bona fide* product of nucleophilic attack on P, was Ph_4PCl, which was obtained in poor yield.

2. Results and discussion

A likely reason for the lack of success in the past may be the complex interplay of factors that affect the structure of the R_3PCl_2, adopting either an ionic or pentacoordinate form. We found that, in line with earlier findings,[19] the ionic form is present in polar solvents. For example, in MeCN, chloroform and dichloromethane (DCM), it is clearly tetracoordinate, as can be observed by ^1H, ^{13}C and ^{31}P NMR spectroscopy (see Table 1). In solvents of lower polarity, R_3PCl_2 exists as pentacoordinate form, e.g. in THF, benzene and toluene, as can be seen again spectroscopically. Computational study of this equilibrium[20] also clearly demonstrated that the pentacoordinate X-X-biaxial orientation of halides is the energetically preferred geometry in vacuum, and low-polar solvents, while tetracoordinate ion-pairs possess lower energy in the polar media, as also can be seen in Table 1.

Table 2 shows selected results of our initial survey of reaction conditions for the reaction of **3** and **3'** with Grignard reagents. It can be seen that QPS **5a** is obtained in excellent yields in DCM and THF (entries 1–2), while a decrease in yield is observed in case of less polar benzene (entry 3). The reaction of **3** with BnMgCl was strongly affected by temperature, giving, perhaps somewhat

Table 2. Reaction conditions for QPS synthesis from dichlorides R_3PCl_2 and Grignard reagents.

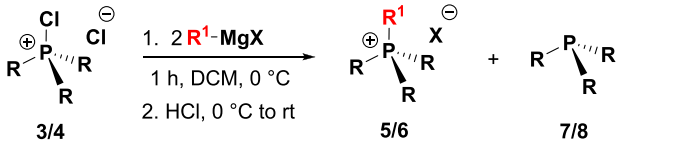


Entry	R_3PCl_2	R^1	Solvent	T, °C	QPS	Yield
1	3	Et	DCM	0	5a	100
2	3′	Et	THF	r.t.	5a	95
3	3′	Et	Benzene	r.t.	5a	79
4	3	Bn	DCM	r.t.	5b	55
5	3	Bn	DCM	0	5b	74
6	3	Bn	DCM	−83	5b	94

counterintuitively, better yields of QPS **5b** at lower temperatures (entries 4–6). Having optimized reaction conditions, we explored the scope of Grignard reagents. From Table 3 it can be seen that reactions of tributyl and triphenyl CPS **3** and **4** with MeMgCl afforded the respective QPS **5c** and **6a** in excellent yields (entries 1–2). On switching to MeMgBr (entries 3–4), the yield of **5c** remained virtually unaffected, however, reaction of CPS **4** with MeMgBr led to the formation of phosphine **8** at the expense of QPS **6a**. Increasing the steric bulk in R^1-MgCl was generally tolerated better by tributyl CPS **3** (entries 5/6 vs 7/8), affording QPS **5d** in excellent yield (entry 5), while on moving the branching point adjacent to the reaction center a decrease in yield of **5e** due to formation of **7** was observed (entry 6). This trend is even more pronounced for the reactions of CPS **4** (entries 7 and 8) with use of secondary *sec*-BuMgCl completely suppressing QPS formation. Most importantly, reaction of **3** with PhMgCl gave QPS **5f** almost quantitatively (entry 9), a drastic improvement compared to the virtually impossible traditional quaternization of **7** with chlorobenzene.

Formation of QPS (Scheme 2, red) is viewed as fast nucleophilic attack (termed here the P-attack) of the R^1-group of the Grignard reagent on the phosphonium center via an axial transition state (**10-TS**) or an alternative far less likely equatorial route (not shown). The formation of phosphine by-product is attributed to a different nucleophilic pathway (Scheme 2, blue) 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, Table 3 entry 9). 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** was also isolated strongly supports our mechanistic hypothesis. Aside from the principal mechanistic pathways (Scheme 2, red & blue), a multitude of other processes can be contemplated (Scheme 2, gray), resulting partly from the introduction of adventitious water/air into the reaction manifold. Although in the examples above most of the side processes have been avoided, work is underway on establishing the conditions for successful preparation of the desired QPS in more challenging cases.

Table 3. Preparation of QPS from CPS and Grignard reagents (R^1-MgX) vs formation of phosphine.



			Products[b]			
Entry	CPS	R^1-MgX[a]	QPS	%	Phosphine	%
1	3	MeMgCl	5c	97	7	0
2	4	MeMgCl	6a	>99	8	0
3	3	MeMgBr	5c	95	7	0
4	4	MeMgBr	6a	58	8	42
5	3	iso-BuMgCl	5d	95	7	0
6	3	sec-BuMgCl	5e	62	7	30
7	4	iso-BuMgCl	6b	48	8	46
8	4	sec-BuMgCl	6c	0	8	96
9[c]	4	Neophyl-MgCl	6d	0	8	75
10	3	PhMgCl	5f	>99	7	0

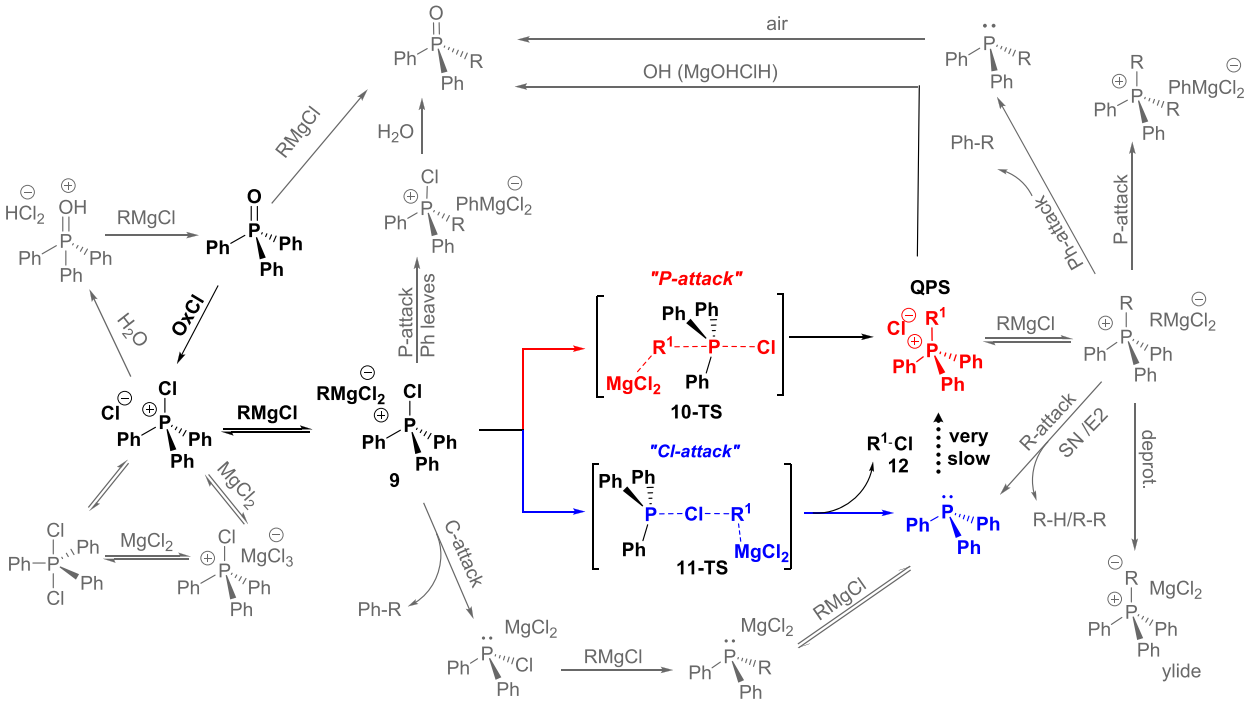
[a]using 2 equivalents of R^1MgX.
[b]by ^{31}P NMR of reaction mixture: balance largely phosphine oxide derived from unreacted CPS.
[c]reaction time 42 h, reaction temperature 30 °C.

3. Conclusions

A high-yielding nucleophilic preparation of QPS, e.g. tetraalkyl, and alkyl-aryl series from phosphine oxides is now realized. The corresponding chlorophosphonium species, CPS, are excellent intermediate synthons for this transformation. The new methodology is another implementation of a general Umpolung strategy, whereby both reacting partners have been subjected to inversion of polarity with respect to standard quaternization. Mechanistically, 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 routes to QPS based on alkylation/quaternization of highly nucleophilic, and therefore readily oxidized, phosphines because it does not require synthesis/handling of such substrates.

4. Experimental

Methyltriphenylphosphonium chloride, **6a.** To a DCM solution of **4** (0.2 M in DCM, 25.00 mL, 5.00 mmol) a solution of MeMgCl (3.0 M in THF, 3.35 mL, 10.05 mmol) was added at 0 °C and the mixture was stirred at 0 °C for 1 hour after which time it was quenched by HCl (2.0 M in Et_2O, 5.00 mmol), concentrated *in vacuo* to yield an oily residue which was treated with DCM (50 mL) and aqueous NaCl (2.0 M, 2 × 10 mL). The DCM layer was washed with an equal volume of saturated aqueous NaCl. The organic layer was eluted through sodium sulfate (10 g) and concentrated *in vacuo* to yield a clear oily residue, which crystallized on standing. Recrystallization from chloroform/ethyl acetate afforded **6a** (1.53 g, 98%) as fine white crystals: MP 219–221 °C, HRMS (ES+) m/z: calculated for $C_{19}H_{18}P^+$ 277.1146, found 277.1135.



Scheme 2. Bold/red/blue: Mechanistic hypothesis illustrating competing pathways: axial attack of R^1MgCl at P (red) leading to QPS and attack of R^1MgCl at Cl (blue) to give phosphine. Grey: Plausible mechanistic pathways (for the tetracoordinate ionic form).

Phenyltributylphosphonium chloride (**5f**) was prepared in a similar fashion from **3** and PhMgCl: transparent crystalline sheets (yield 95%): MP 138–140 °C; HRMS (ES^+): calculated for $C_{18}H_{32}P^+$ = 279.2242, found 279.2247.

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