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A Direct Synthesis of Vinylphosphonium Salts from α-Trimethylsilyl Ylides and Non-Enolizable Aldehydes

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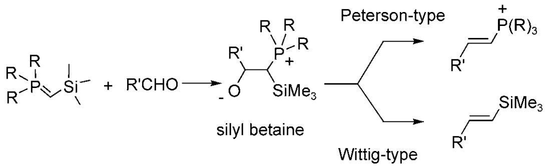
Although the first reported synthesis of a vinylphosphonium salt **4** appeared almost 1.5 centuries ago,[1] their utility as synthetic intermediates awaited a flurry of publications in the mid-1960s.[2–4] The electrophilic nature of the olefin in such species was demonstrated through the conjugate addition of phenyllithium[2] and a range of simple nucleophiles derived from enolizable precursors and amines.[3] Conjugate addition to vinylphosphonium salts leads to an initial phosphorane (ylide) which may be subsequently trapped through an intra- or intermolecular olefination reaction. Schweizer and co-workers expanded the scope of vinylphosphonium salts to a range of conjugate addition-trapping reactions.[4] The use of this electron deficient olefin as a dienophile in Diels–Alder and other cycloaddition reactions has also been demonstrated.[3] Surprisingly, few reports on synthetic applications of vinylphosphonium salts have appeared in the literature since.[5] The synthesis of vinylphosphonium salts is usually accomplished through quaternization of a trialkyl- or triarylphosphane with a bromoethane derivative containing a β-leaving group, the olefin being introduced through a subsequent elimination step. The tetravinylphosphonium[6] cation was recently reported through a similar pathway from phosphine (PH_3). Triarylvinylphosphonium salts have also been reported via Pd-mediated phosphination of vinyl bromides and triflates,[7] Pd-mediated alkyne addition[8] and via an electrochemical oxidation process.[9] Thus, synthesis of vinylphosphonium salts requires the prior assembly of a corresponding vinyl bromide or vinyl triflate, an alkylating agent containing an appropriate β-leaving group or a functionalized alkyne. The limitation in routes available for the synthesis of vinylphosphonium salts is arguably the major hindrance to their more widespread use, given the range of valuable synthetic interconversions that have been demonstrated.

We have recently become interested in the synthesis and reactivity of 1,1-bis-heteroatom substituted methylenes[10] and methines[11] as a route to useful synthetic intermediates through olefination reactions with readily available carbonyl compounds. An alternative route towards the synthesis of vinylphosphonium salts might potentially be the reaction between an α-silylated ylide and carbonyl compound, as outlined in Scheme 1. The intermediate, here shown as the silyl betaine, could potentially eliminate in Peterson fashion through *O*-silyl migration yielding a vinylphosphonium salt, or alternatively through Wittig-type elimination of phosphane oxide from the betaine (or oxaphosphetane) yielding a vinylsilane. While α-trimethylsilyl ylides are well known,[12] their reactions with carbonyl compounds are reported to be complex,[13] yielding allenes[12a,13b] and many side products. Furthermore, the one example[13a] of a straightforward olefination with an α-silyl ylide reacting with benzaldehyde is reported to give the vinylsilane product in good yield, a result that has been claimed to be general.[13c] On the basis of these reports, the direct synthesis of vinylphosphonium salts from α-silyl ylides and carbonyl compounds would not appear promising. Nonetheless, these results appeared unusual to us for several reasons. First of all, high chemoselectivity has previously been documented favouring Peterson-type elimination over Horner–Emmons phosphonate elimination with α-silyl phosphonate/aldehyde intermediates.[11] Secondly, Gilman initially postulated a vinylphosphonium intermediate in such a reaction (although it was not isolated) and showed that vinylphosphonium salts



Scheme 1. Synthesis of vinylsilanes and/or vinylphosphonium salts via the reaction of an aldehyde with an α-silyl ylide.

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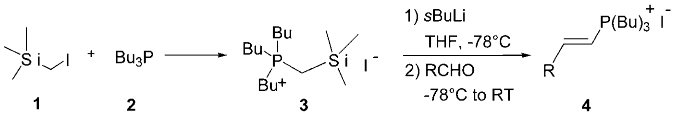
could independently be converted to allenes, the main products of Gilman's investigation.[12a] We have reinvestigated this chemistry, as shown in Scheme 2. Herein we report the finding that α-silyl ylides react with aldehydes to provide vinylphosphonium salts in high yield. Commercially available[14] iodomethyltrimethylsilane (**1**) selectively reacts with tributylphosphane (**2**) yielding the α-trimethylsilylphosphonium salt **3**. The ylide derived from **3** enters into Peterson-type olefination reactions with aldehydes with high selectivity providing a direct, general synthesis of tributyl(vinyl)phosphonium salts **4**.

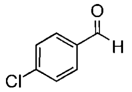
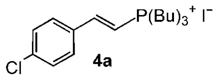
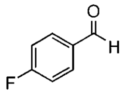
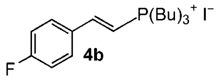
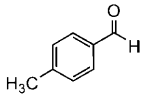
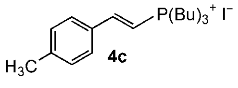
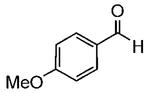
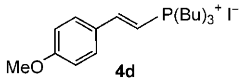
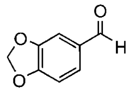
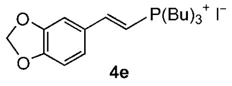
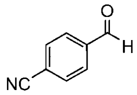
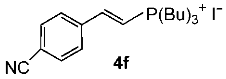
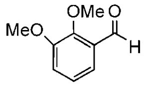
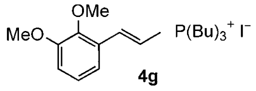
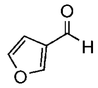
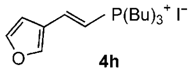
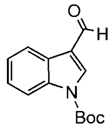
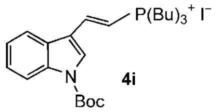
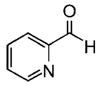
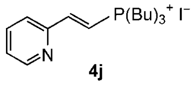
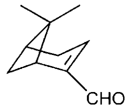
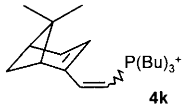
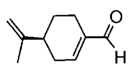
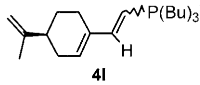
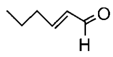
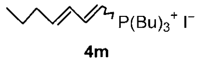


Scheme 2. Synthesis of vinylphosphonium salts via the ylide derived from **3**.

The reaction of chloromethyltrimethylsilane with triphenylphosphane or tributylphosphane **2** proceeded in THF to provide a mixture of the phosphonium chloride corresponding to **3** and triphenyl- or tributyl(methyl)phosphonium chloride.[15] Desilylation reactions are characteristic in many of the α-silyl ylide preparations described above,[12a,b,d] produced via chloride mediated desilylation and protonation of the intermediate ylide. We first found that the corresponding iodide salt **3** can be formed (ICH_2TMS, Bu_3P, THF, 20 °C, 13 h) and that this salt is stable in solid form and in $CDCl_3$ solution for at least two months. The stability of the iodide salt is most likely due to the lesser propensity for Si–I bond formation in comparison to the chloride analogue. A general procedure was then developed for the selective Peterson reaction through ylide formation from **3**, generated under kinetically controlled conditions, reacting with a range of aldehydes. Thus, a THF solution of **3** was cooled to −78 °C and one equivalent of *s*BuLi added providing a yellow solution of the ylide to which was added one equivalent of 4-chlorobenzaldehyde. The dry-ice bath was removed after 2 h and the reaction allowed to warm to room temperature. The desired vinylphosphonium salt **4a** was isolated in 90 % yield and with high stereoselectivity favouring the (*E*)-olefin.

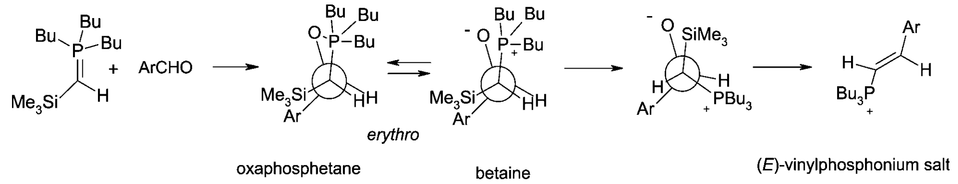
The reaction proved to be very general for a range of both electron-rich and electron-deficient aromatic aldehydes, all of which yielded the desired phosphonium salts in excellent yield and high stereoselectivity (Table 1, entries 1 to 7). In addition, heterocyclic derivatives could be prepared from 3-substituted furan, indole and pyridine derivatives in high yields but with slightly lower stereocontrol (Table 1, entries 8 to 10).

Table 1. Reaction of $(TMS)CHPBu_3$ with aldehydes.

Entry	Aldehyde	4	*E*/*Z*	Yield [%]
1		 **4a**	49:1	90
2		 **4b**	49:1	95
3		 **4c**	49:1	92
4		 **4d**	49:1	91
5		 **4e**	49:1	85
6		 **4f**	49:1	90
7		 **4g**	49:1	90
8		 **4h**	5:1	85
9		 **4i**	3:1	99
10		 **4j**	3:1	90
11		 **4k**	1:3	78
12		 **4l**	1:3	75
13		 **4m**	1.1:1	77

The synthetic utility of this novel reaction as a route to conjugated 1,3-dienylphosphonium salts was also investigated with a range of unsaturated aldehydes (Table 1, entries 11–13). The isolated yields were invariably good in all of the cases investigated, however, the reactions proceeded with lower stereoselectivity. The reaction was also investigated with hexanal, which provided a 60 % yield of a 3:1 *Z*/*E* mixture of the corresponding vinyl phosphonium salts. In this case a significant amount (35 %) of the tributyl(methyl)phosphonium salt was also formed which we attribute to protonation and enolate-induced desilylation of the ylide derivative of **3**. High stereoselectivity appears to be restricted to non-enolizable aldehydes at present, although the chemoselectivity favouring vinylphosphonium over vinylsilane formation remains completely dominant.

The high chemoselectivity observed favouring Peterson elimination over Wittig-type elimination and general stereoselectivity favouring (*E*)-vinylphosphonium salts also offers some interesting insights into the mechanism of the Wittig reaction itself. Although the initial formation of oxaphosphetanes is now accepted,[16] a clear, stepwise account of the reaction mechanism is still debated[16a] and much discussion has been made over the relative importance of oxaphosphetane versus betaine intermediates in the Wittig reaction.[16b] In the present case, the observed Peterson elimination is revealing as it requires free-rotation about the central C–C bond of a betaine intermediate, prior to *O*-silyl transfer and elimination. If an oxaphosphetane is the kinetic intermediate in the present case, this is evidence that it readily ionizes to the betaine intermediate, under kinetically controlled conditions, in contrast to a direct elimination of tributylphosphane oxide, which would yield the corresponding vinylsilane.



Scheme 3. Stereoselectivity favouring (*E*)-vinylphosphonium salts via the kinetic *erythro* betaine.

It is difficult to rationalize the prior report on the synthesis of a vinylsilane from an α-silyl ylide,[13a] although this previous result employed an entirely salt-free ylide. The reaction of silylated ylides is reported to be complex, however, we note that many of the earlier methods[12,13] employ an excess of base or carbonyl component, use less reactive ketones such as benzophenone and often contain excess of coordinating halide, particularly chloride, which is prone to desilylate the necessary intermediates.[12] The clean synthesis of the stable silylphosphonium iodide salt **3**, subsequent generation of its ylide derivative and stoichiometric reaction with aldehydes at low temperature nonethelss allows highly selective vinylphosphonium salt formation. The present reaction may of course proceed kinetically via the betaine-type intermediate, and proceed to an oxaphosphetane only in the complete absence of lithium salts,[13a] followed by Wittig-type elimination providing the vinylsilane. Thus, we have also investigated the reaction of the ylide derived from **3** with piperonal (Table 1, entry 5) under salt-free conditions. The original process gave high yield of essentially the pure (*E*)-vinylphosphonium salt. When a solution of the ylide was prepared under identical conditions and the resulting lithium iodide (93 % calculated mass of LiI recovered) filtered off through canula, addition to piperonal gave the vinylphosphonium salt with lower stereoselectivity (3:2 *E*/*Z*). Importantly, no vinylsilane formation or phosphane oxide was formed, indicating that the preferred mode of reaction remains Peterson-like. This result may indicate that a catalytic amount of lithium salt may be all that is required to favour the Peterson elimination via oxaphosphetane opening.

Although speculative, stereochemical arguments can also be made for the intermediacy of oxaphosphetane intermediates in the reaction. The high (*E*)-stereoselectivity observed can be rationalized in terms of the currently accepted transition states leading to the oxaphosphetane intermediates.[16a] Relief of torsional and 1,2-non-bonding interactions between the TMS group and aldehyde substituents and of 1,3-steric effects between the alkyl groups on phosphorus and the aryl substituent of the aldehyde are both expected to favour the puckered *cis* transition state, leading to the *erythro* oxaphosphetane, as shown in Scheme 3. Oxaphosphetane opening, bond rotation and Peterson-type elimination then provides the (*E*)-vinylphosphonium salt. The overall results appear to indicate that the predominantly (*E*)-vinylphosphonium stereoselectivity is due to kinetic control involving Peterson *syn*-elimination from the *erythro* betaine. The transition state leading to the diastereomeric oxaphosphetane (and hence *threo* betaine) intermediate may be slightly more favourable on the basis of electronic effects. 1,3-Secondary orbital interactions between the electron rich π-molecular orbital system in entry 8 or 9, or the lone pair in the case of entry 10, and empty d orbital on phosphorus would be expected to stabilize the planar *trans* transition state and explaining the lower stereoselectivities that are observed in those cases.

In conclusion, we have shown that α-trimethylsilyl(methyl)phosphonium iodide may be prepared from the reaction of tributylphosphane and iodomethyltrimethylsilane and that its ylide derivative adds cleanly to aromatic and unsaturated aldehydes, eliminating selectively in Peterson fashion to yield vinylphosphonium salts in excellent yield and (*E*)-stereoselectivity. Further extension and application of this unprecedented and chemoselective method for vinylphosphonium salt synthesis is currently under investigation.

Experimental Section

Trimethylsilyl(methyl)tributylphosphonium iodide 3: Into a flame-dried flask, containing a magnetic stirring bar, was weighed iodomethyltrimethylsilane (200 μL, 1.346 mmol) under argon and dry THF (2.7 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min. at room temperature whereupon tributylphosphane (353 μL, 1.413 mmol) was added slowly to the reaction flask. The flask was maintained at room temperature for 13 h. Solvent was removed under vacuum to yield the title compound (0.555 g, 99 %) as colourless crystals. M.p. 101–102 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=0.30$ (s, 9H); 0.95 (m, 9H); 1.53 (m, 12H), 1.87 (d, $J_{P,H}=17.0$ Hz, 2H); 2.36 ppm (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta=1.0$, 6.9 (d, $J=42.3$ Hz), 13.6, 22.2 (d, $J=49.2$ Hz), 23.9 (d, $J=12.1$ Hz), 24.1 ppm; ^{31}P NMR (80 MHz, $CDCl_3$): $\delta=34.9$ ppm; HRES MS: *m*/*z*: calcd for $C_{16}H_{38}PSi$: 289.2468, found: 289.2480 $[M]^+$.

(*E*)-2-(3′,4′-Methylenedioxyphenyl)vinyl-1-tributylphosphonium iodide (Table 1, entry 5): Into a flame-dried flask, containing a magnetic stirring bar, was weighed trimethylsilyl(methyl)tributylphosphonium iodide

(200 mg, 0.481 mmol) under argon and dry THF (1 mL) was added to make a 0.5 M solution. The flask was stirred for 15 min. at −78 °C whereupon *s*BuLi (360 µL, 0.505 mmol, 1.4 M stock, C_6H_{12}) was added slowly. After 40 min, a 0.5 M solution (in THF) of piperonal (75.8 mg, 0.505 mmol) was added slowly to the reaction flask maintained at −78 °C. The flask was kept at −78 °C for 2 h and then slowly warmed to room temperature where it was stirred for a further 2 h. The resulting mixture was concentrated to remove solvent. Water was added (5 mL) to the residue, and the resulting mixture was extracted with dichloromethane (3× 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Hexane was added (5 mL) to the flask which was stirred, vacuum filtered and dried to yield the title compound (195 mg, 85 %) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.92$ (m, 9 H), 1.50 (m, 12 H), 2.55 (m, 6 H), 5.90 (s, 2 H); 6.71 (dd, $J_{H,H} = 17.5$, $J_{P,H} = 17.5$ Hz, 1 H), 6.84 (d, $J_{HH} = 8.5$ Hz, 2 H), 7.22 (s, 1 H), 7.59 ppm (dd, $J_{H,H} = 17.5$, $J_{P,H} = 20.9$ Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.6$, 20.1 (d, $J = 47.2$ Hz), 23.8, 23.9 (d, $J = 19.3$ Hz), 101.7 (d, $J = 64.8$ Hz), 102.0, 107.0, 108.6, 125.8, 128.6 (d, 18.8 Hz), 148.6, 150.8, 152.5 ppm (d, $J = 3$ Hz); ^{31}P NMR (80 MHz, $CDCl_3$): $\delta = 27.7$ ppm; HRES MS: *m*/*z*: calcd for $C_{21}H_{34}O_2P$: 349.2282, found: 349.2296 $[M]^+$.

Acknowledgements

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Keywords: alkenes · betaines · carbanions · vinylic compounds · ylides

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