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Phosphorous(v) Lewis acids: water/base tolerant P_3-trimethylated trications†

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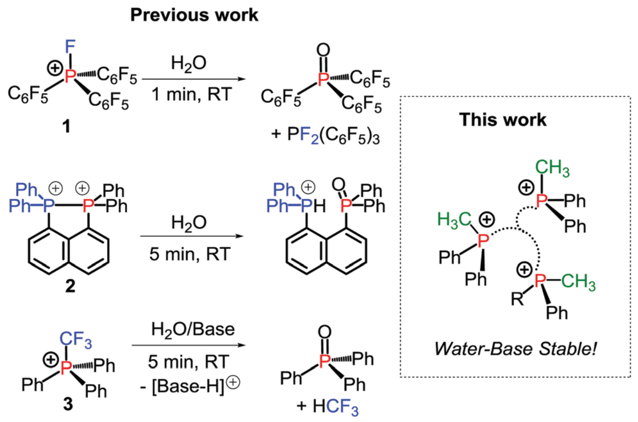
The water/base intolerance of the previously reported electrophilic phosphonium cations has been overcome by replacing the labile electron-withdrawing groups generally attached to phosphorus (*e.g.* –F, –OAr, –CF_3) with methyl groups. Tri-phosphorus(v) tricationic species, accessible in one-pot from commercially available materials, are air and water/base tolerant, yet are sufficiently Lewis acidic for catalysis.

In the past decade, frustrated Lewis pair (FLP) chemistry has emerged as a metal-free alternative to transition metal-catalysed reductions. In these systems, sterically-encumbered Lewis acids and Lewis bases in combination enable the activation of sigma bonds of H_2 and R_3SiH, to generate useful reducing agents.[1,2] However, water coordination to the Lewis acid and irreversible O–H activation represents a limitation in FLP chemistry using highly electrophilic Lewis acids (*e.g.* $B(C_6F_5)_3$). This is due to deprotonation forming a hydroxyl-Lewis acid species (*e.g.* $[HOB(C_6F_5)_3]^-$) and a protonated Lewis base which are a catalytically inactive combination.[3] For boranes, the intolerance to water/base combinations has been tackled by decreasing the Lewis acidity of the borane or by designing Lewis acids with increased steric bulk around the boron centre thus reducing the propensity for irreversible water-binding/activation.[3] Another approach to overcome water intolerance in FLP and Lewis acid chemistry is the use of non-boron based Lewis acids. In this regard, carbenium and tin(iv) cations, isoelectronic with boranes, are examples of Lewis acids that are more compatible with water/base combinations.[4–8]

Moreover, while highly electrophilic phosphonium cations (EPCs) such as $[(C_6F_5)_3PF]^+$ (**1**) have demonstrated reactivity in a wide variety of Lewis-acid catalyzed transformations,[9–13] trace water remains problematic as rapid P–F cleavage was observed.[14] Analogous results were observed by increasing the steric bulk around the phosphorus(v) centre[15] or replacing the P–F moiety with P-OAryl,[16] or P-alkyl groups.[17] In a related system, the 1,8-naphthyldiphosphonium dication $[(C_{10}H_6)(Ph_2P)_2]^{2+}$ (**2**), can be stored in air for up to 24 hours without significant decomposition, addition of H_2O to a solution of **2** results in rapid degradation.[18] On the other hand, $[Ph_3PCF_3]^+$ (**3**) is stable in the presence of water even at elevated temperature,[19] but undergoes rapid reaction at room temperature in the presence of a combination of water and a moderate organic base affording the corresponding phosphine oxide (Scheme 1).[19] Thus, developing EPCs that are active for sigma bond activation but stable in the presence of water/base combinations remains a challenge in main group Lewis acid chemistry. In this regard, we envisaged that replacing the –CF_3 group in EPCs with a methyl would disfavour hydrolysis and R_3PO formation, as tetraorgano phosphonium ions are stable in water. For example, $[Bu_4P][Cl]$ has been employed in silane activation *via* a distinct anion coordination mechanism.[20,21] However, such a replacement



Scheme 1 Examples of EPCs and their relative stability towards water/base.

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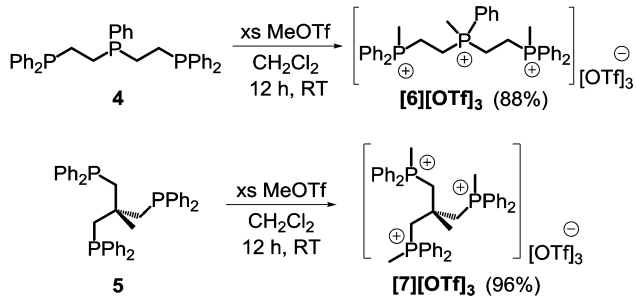
of an electron withdrawing group by methyl is also expected to reduce Lewis acidity. Thus, we proposed to compensate for this shortcoming by the inclusion of multiple positive charges. Herein, we report that P_3-trimethylated phosphonium trications are readily prepared, provide water/base stability, and are effective and highly robust Lewis acid catalysts for reduction chemistry. In this regard, while polycationic phosphonium based polymers and oligomers have found applications in material science and biology, as ionic liquids,[22] metal scavengers,[23] antibacterial agents,[24] and dendrimers,[25] their utility in FLP chemistry and Lewis acid catalysis remains unexplored.

The commercially available triphosphine ligands $PhP(CH_2CH_2PPh_2)_2$ (**4**) and $MeC(CH_2PPh_2)_3$ (**5**) were treated with an excess of MeOTf (methyl trifluoromethanesulfonate, 6–10 equiv.) in CH_2Cl_2 at room temperature (Scheme 2). In both cases, after 10–15 minutes a white solid precipitated from the solution. The reaction was left stirring at room temperature for 12 hours to ensure complete conversion, after which time solvent removal and pentane washing gave the desired P_3-trimethylated phosphonium trications $[PhPMe(CH_2CH_2PMePh_2)_2][OTf]_3$ (**[6][OTf]$_3$**) and $[MeC(CH_2PMePh_2)_3][OTf]_3$ (**[7][OTf]$_3$**) in yields of 88% and 96%, respectively. Single crystals of **[6][OTf]$_3$** and **[7][OTf]$_3$** were obtained and characterized by X-ray diffraction studies, further confirming their formulation (Fig. 1). Notably, the trication **[7]**$^{3+}$ shows an interesting arrangement in the solid state, assuming pseudo-C_3 symmetry, with all the methyl groups orientated in the same direction. One of the three triflate counterions occupies the putative electrophilic pocket. While the P–O$_{(OTf)}$ contacts are longer than the sum of the van der Waals radii, short contacts are seen between the triflate anion and the CH_2 protons of the cation. This hydrogen bonding network is reminiscent of urea-based organocatalysts, where short anion-H contacts are also observed.[26]



Scheme 2 Synthesis of P_3-trimethylated phosphonium trications.

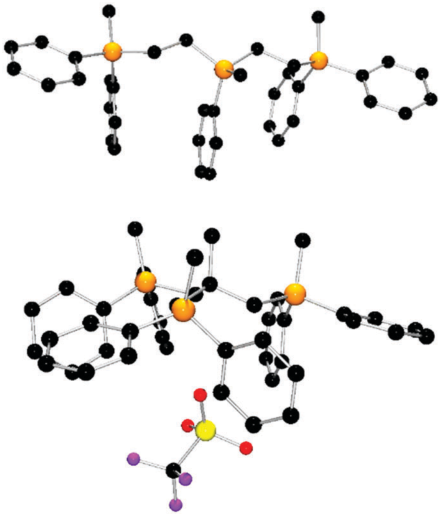
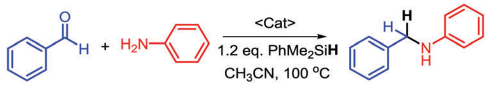


Fig. 1 POV-ray depictions of the trications of **[6]**$^{3+}$ (top, hydrogen atoms and triflate counterions omitted for clarity) and **[7]**$^{3+}$ (bottom); hydrogen atoms selected triflate counterions, and co-crystallized solvent molecules omitted for clarity C: black, P: orange, O: red, S: yellow, F: purple.

Both **[6][OTf]$_3$** and **[7][OTf]$_3$** can be synthesized on a gram scale and stored as solids for months in air and/or dissolved in non-purified MeCN without observable degradation even at elevated temperature (100 °C). These trications were also stable in the presence of an excess (10 equiv.) of water and aniline, with no phosphine oxide formation observed after 24 hours at 100 °C in MeCN.

While the field of EPC-catalysed transformation has grown significantly in the last 5 years, transformations have been limited to reactions that do not employ strongly donating substrates or generate strongly donating products, including water. Moreover, reactions generally required strict air- and moisture-free conditions, limiting further applications. Given the tolerance of the trications to the presence of air, moisture, and moisture/base combinations, the catalytic reactivity for reductive amination of carbonyl compounds with primary amines was probed. In this strategy, the corresponding imine is formed and reduced *in situ* without purification, thus providing reactivity in the presence of water (generated as a by-product). Such reductive aminations using H_2 or hydrosilanes as reductants mediated by boranes and tin cations have been reported in the past 2 years.[27–31] However, to the best of our knowledge, there are no reports of phosphorus(V) reductive amination catalysts. To probe the reactivity of the trications as Lewis acid catalysts in reductive amination reactions, **[6][OTf]$_3$** and **[7][OTf]$_3$** were dissolved in "wet" MeCN. The reaction between benzaldehyde and aniline (1 : 1.2), in the presence of 5 mol% of **[6][OTf]$_3$** or **[7][OTf]$_3$** and 1.2 equiv. of $PhMe_2SiH$ yielded a significant amount of imine after 18 h at room temperature. This was similar to that previously reported for the borane-catalysed reaction.[32] However, heating the reaction mixtures to 100 °C in a sealed tube for 5 hours resulted in formation of the desired *N*-benzyl-aniline using both **[6][OTf]$_3$** and **[7][OTf]$_3$**. A control experiment without catalyst showed no reactivity under identical conditions (Table 1, entries 1–3). Notably, replacing the trications with $[Ph_3PMe][OTf]$ as the catalyst at 15 mol% to provide comparable $[R_4P]^+$ content, resulted in 58% conversion after 5 h. Longer reaction times were required for comparable conversion (Table 1, entry 4). Similarly, using 7.5 mol% $[Ph_2PMe(CH_2)_3MePPh_2][OTf]_2$ as the catalyst resulted in 20% conversion after 5 h and 41% after 24 h. It is worth noting that the decrease in reactivity compared to $[Ph_3PMe][OTf]$ may be a result of increased electron density around the P centre due to the alkyl linker. This reactivity highlights the

Table 1 Reductive aminations using P(V) Lewis acids catalysts[a]



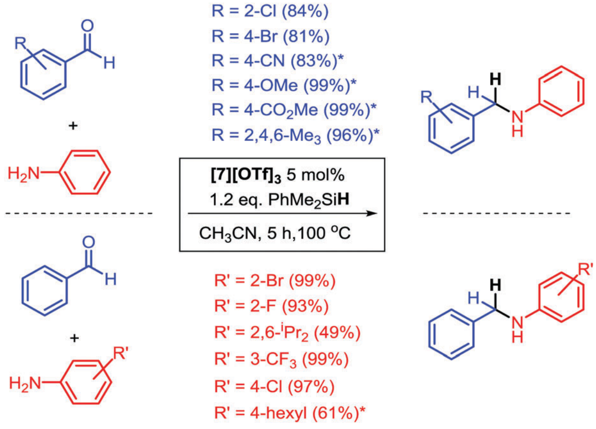
Entry	Catalyst	*T* (h)	Yield[b] (%)
1	None	18	0
2	5 mol% **[6][OTf]$_3$**	5	82
3	5 mol% **[7][OTf]$_3$**	5	93
4	15 mol% [Ph_3PMe][OTf]	5	58
5	7.5 mol% [$Ph_2PMe(CH_2)_3MePPh_2$][OTf]$_2$	5	20

[a] Reaction conditions: 1.0 equiv. of aldehyde, 1.2 equiv. of amine, 1.2 equiv. of silane and the catalyst, "wet" MeCN as the solvent. [b] Based on ^{1}H-NMR spectroscopy using mesitylene as an internal standard.

role of the three proximal P(V)-centres in enhancing Lewis acidity, as was suggested by the solid state structure of **[7][OTf]$_3$**, although conclusive evidence of silane activation (both experimentally and computationally) were not accessible. However, this phenomenon is conceptually related to the activation of carbonyl substrates using dicationic antimony-based Lewis acids reported by Gabbaï and co-workers.[33]

The Gutmann–Beckett method was used to assess the Lewis acidity of [7]$^{3+}$ ([7][OTf]$_3$: Et_3PO 1 : 1, in CD_3CN) and showed a small downfield shift of the signal of Et_3PO by ^{31}P NMR spectroscopy ($\Delta\delta$ = 4.1 ppm), suggesting a weak interaction with Et_3PO, although this is comparable to [$(C_6F_5)_3POC_6F_5$][$B(C_6F_5)_4$] (**[8][B(C_6F_5)$_4$]**) which contains strongly electron-withdrawing substituents around the phosphorus centre.[14] Moreover, the Gutmann–Beckett test with [Ph_3PMe][OTf] (in a 3 : 1 ratio of phosphonium to Et_3PO) showed a slightly smaller chemical shift change of Et_3PO by ^{31}P NMR spectroscopy ($\Delta\delta$ = 3.8 ppm).

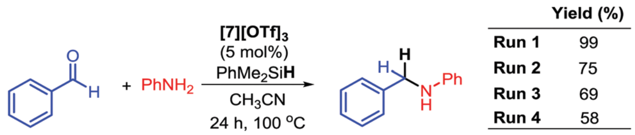
The ability to promote reductive aminations was then further explored with other substrates in the presence of 5 mol% of **[7][OTf]$_3$** (Scheme 3). It is noteworthy that all reactions were completed in air, with "wet" and untreated reagent-grade solvent. Several functional groups on the benzaldehyde were tolerated, with good conversion obtained after heating the reaction mixture for between 5 and 24 hours. Notably, ester groups were not reduced under these reaction conditions, in contrast to previous observations in the $B(C_6F_5)_3$-catalysed reductive amination of similar substrates.[15] However, aliphatic aldehydes and ketones proved to be challenging substrates for this reaction. Several functional groups on the aniline component were also compatible (Scheme 3, bottom). The tolerance to –CF_3 groups is noteworthy as previously EPCs have been shown to activate the C–F bonds of trifluorotoluene and fluoroadamantane.[9] When aniline was replaced with the more basic amine *t*-butylamine, the reductive amination with benzaldehyde and $PhMe_2SiH$ using **[7][OTf]$_3$** was unsuccessful due to catalyst decomposition. A complex ^{31}P{^{1}H} NMR spectrum was observed; among the products, the phosphine oxide was evident, however other by-products were not identified. It is interesting to note that the tricationic Lewis acids can be recycled multiple times for the reductive amination of benzaldehyde with aniline using $PhMe_2SiH$ as reductant in the presence of the initial 5 mol% of **[7][OTf]$_3$**, although gradual diminishing in reactivity is observed (Scheme 4).



Scheme 3 Reductive amination substrate scope. For reaction conditions see Table 1. Yields based on ^{1}H NMR spectroscopy using mesitylene as an internal standard. * 24 hours.

Probing the mechanism of these reductive aminations prompted a series of control experiments. Under anhydrous conditions, isolated *N*-benzylidene-aniline was reduced to some extent (~20% conversion) in the presence of $PhMe_2SiH$ in CH_3CN and 5 mol% of **[7][OTf]$_3$** upon heating to 100 °C for 5 hours. The formation of $BnN(SiMe_2Ph)Ph$ was confirmed by *in situ* ^{1}H/^{29}Si NMR spectra and GC-MS analysis. However, we note the significant decrease in reactivity (*cf.* Table 1, entry 3). This infers a role for H_2O, possibly as the nucleophile attacking the Lewis acid activated silane, R_3Si–H–[PR_4]$^+$ species. It is noteworthy that repeating the standard reaction (Table 1, entry 3) in the presence of the non-nucleophilic base $PMes_3$ (Mes = 2,4,6-trimethylphenyl, 5 mol%) slowed reductive amination, affording the desired amine in only 17% after heating for 5 hours at 100 °C. Moreover, a similar decrease in reactivity was observed for the corresponding reaction of 2-pyridinecarboxaldehyde yielding the desired product in 43% after heating for 5 hours at 100 °C. These results suggest that the presence of an exogenous base deprotonates a Lewis acid–water adduct (*e.g.* [R_4P–OH_2]$^+$ or [R_3Si–OH_2]$^+$ adducts). This suggests protonation of the imine enables more rapid reduction, although the fact that the chemistry proceeds in anhydrous solvents (albeit more slowly) indicates that reduction *via* an imine silylation process also occurs. It is noteworthy that previous reports have described mechanisms involving both Lewis acid and Brønsted acid activation of the reductant followed by silylation or protonation of the imine.[27,30,32,34–37]

The facile methylation of commercially available triphosphine ligands affords air and water tolerant EPCs with non-coordinating



Scheme 4 Recycling experiment of the reductive amination with **[7][OTf]$_3$**. For reaction conditions see Table 1. Yields based on ^{1}H-NMR spectra using mesitylene as an internal standard.

triflate anions. The unprecedented (for EPCs) water/aniline tolerance of these phosphonium trications allow them to be employed as Lewis acid catalysts for the one-pot reductive amination of benzaldehydes with arylamines using hydrosilanes as the reductant.

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Conflicts of interest

The authors declare no conflicts of interest.

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