ChemComm

This article can be cited before page numbers have been issued, to do this please use: V. Fasano, J. LaFortune, J. Bayne, M. J. Ingleson and D. W. Stephan, *Chem. Commun.*, 2017, DOI: 10.1039/C7CC09128A.

Volume 52 | Number 1 | 4 January 2016 | Pages 1–216

ChemComm

Chemical Communications
www.rsc.org/chemcomm

ISSN 1359-7345

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION
Marilyn M. Olmstead, Alan L. Balch, Josep M. Poblet, Luis Echegoyen *et al.*
Reactivity differences of $Sc_3N@C_{2n}$ (2*n* = 68 and 80). Synthesis of the first methanofullerene derivatives of $Sc_3N@D_{5h}$-C_{80}

175 YEARS

View Article Online
DOI: 10.1039/C7CC09128A

Journal Name

COMMUNICATION

Air- and water-stable Lewis acids: synthesis and reactivity of *P*-trifluoromethyl electrophilic phosphonium cations

Received 00th January 20xx,
Accepted 00th January 20xx

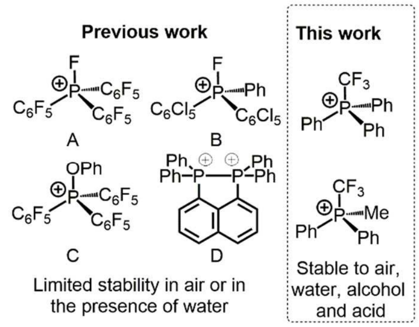
DOI: 10.1039/x0xx00000x

www.rsc.org/

V. Fasano,[a,b] J. H. W. LaFortune,[b] J. M. Bayne,[b] M. J. Ingleson*[a] and D. W. Stephan*[b]

A new class of electrophilic phosphonium cations (EPCs) containing a -CF_3 group attached to the phosphorus (V) center is readily accessible in high yields, via a scalable process. These species are stable to air, water, alcohol and strong Brønsted acid, even at raised temperatures. Thus, *P-CF$_3$* EPCs are more robust than previously reported EPCs containing *P-X* moieties (X = F, Cl, OR), and despite their reduced Lewis acidity they function as Lewis acid catalysts without requiring anhydrous reaction conditions.

Since the first report on metal-free reversible dihydrogen activation,[1] frustrated Lewis pair (FLP) chemistry has gained attention from the chemical community due to the potential for applications in important transformations (e.g. reductions). This strategy, exploiting the combined action of sterically encumbered Lewis acids and Lewis bases has been used to activate a variety of small molecules (e.g. H_2, R_3SiH, CO_2).[2] Most typically, the Lewis acids employed are tri(fluoroaryl)boranes (and derivatives), although other elements have been reported as the locus of the electrophilic character (e.g. Al, Si, Ga, C),[3] including phosphorus. While Wittig reagents[4] are perhaps the most notable example of P (V) Lewis acids, in the past decade other examples of phosphorus-based electrophiles have been reported.[5] In 2013 the synthesis and the catalytic applications of a new class of P (V) Lewis acids was reported.[6] The first example of such electrophilic phosphonium cations (EPCs) $[(C_6F_5)_3PF]^+$ (Scheme 1, A) was employed as a catalyst in a variety of transformations including hydrodefluorination,[6] dehydrocoupling,[7] hydrosilylation of unsaturated compounds,[8] hydrodeoxygenation of ketones,[9] amides,[10] and phosphine-oxides,[11] FLP-hydrogenations,[12] Friedel-Crafts arylations of fluoro-alkanes[13] and hydroarylation of alkynes.[14]



Scheme 1. Examples of EPCs and their relative stability.

The Lewis acidity of $[(C_6F_5)_3PF]^+$ is derived from the energetically low-lying σ* orbital oriented opposite to the polar P–F bond. While the fluorine atom and the C_6F_5 ring(s) boost the Lewis acidity of EPCs, the presence of the P-F moiety results in limited stability, particularly with respect to water and alcohols. This limitation has prompted the search for more robust EPCs. In FLP chemistry, a number of different approaches have been pursued to provide water and alcohol compatibility, for example, the utility of Sn cations or less Lewis acidic boranes have been explored.[3b, 15] However, to date air and water stable EPCs that are still active for σ-bond activation remains an open problem. One approach that has mimicked efforts to enhance the chemical robustness of electrophilic boranes, has been the replacement of C_6F_5 with C_6Cl_5 rings.[16] While this increases the steric bulk around the Lewis acidic phosphorus center, the P-F bond remains prone to hydrolysis (Scheme 1, B).[17] An alternative strategy has been the replacement of fluoride with aryloxy groups. With $[(C_6F_5)_3POPh]^+$ for example this achieved a modest increase in stability to ROH, although these species degrade in CH_2Cl_2 solution on exposure to atmospheric moisture after 1.5 h (Scheme 1, C).[18] In a related effort, the 1,2-diphosphonium dication $[(C_{10}H_6)(Ph_2P)_2]^{2+}$ was shown to be stable for 24 h to air in the solid state, although rapid hydrolysis occurred in non-purified (wet) solvents (Scheme 1, D).[19]

---

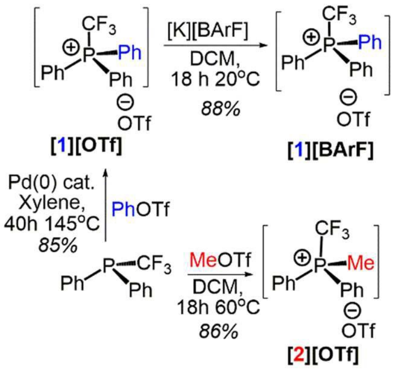
[a] *School of Chemistry, University of Manchester, M13 9PL (UK)*
email: michael.ingleson@manchester.ac.uk
[b] *Department of Chemistry, University of Toronto, M5S3H6 (Canada)*
email: dstephan@chem.utoronto.ca

Electronic Supplementary Information (ESI) available: Synthetic and spectral details are deposited. X-ray data has been deposited. CCDC 1586279-1586281. For ESI and crystallographic data in CIF or other electronic format see

View Article Online
DOI: 10.1039/C7CC09128A

While the above data illustrate that enhanced water tolerance of EPCs requires replacement of the P-halogen bond, high electronegativity of the substituent is essential to produce a low energy σ* orbital required for strong Lewis acidity. Thus the synthesis of CF_3 (electronegativity: 3.5)[20] derived phosphonium cations was targeted. Synthetic protocols to this new class of EPCs are presented herein. Despite a modest reduction in Lewis acidity, these species are shown to be effective in a variety of Lewis acid catalysis while exhibiting a significant increase in tolerance to ROH relative to other EPCs.

To the best of our knowledge, $[Ph_3PCF_3]^+$, **[1]**$^+$ is the only known example of a *P-CF₃* EPC. Umemoto and co-workers[21] synthesized this species *in-situ* via direct electrophilic trifluoromethylation of Ph_3P using a highly reactive trifluoromethylsulfonium cation. In our hands, all efforts to prepare **[1]**$^+$ (and related *P-CF₃* EPCs) by use of Umemoto's or Togni's reagents,[22] by radical trifluoromethylation or by nucleophilic reactions of $[R_3P\text{-}X]$ with CF_3-anions, failed. Seeking an alternative strategy, installation of the CF_3-group prior to quaternization of the phosphine was undertaken. Using the method of Caffyn and co-workers,[23] Ph_2PCF_3 was synthesized in high yield from Ph_2POPh and Me_3SiCF_3 in the presence of half an equivalent of CsF. Subsequent quaternization of phosphorus was achieved via reaction with MeOTf or a Pd(0)-catalyzed reaction with PhOTf yielding $[Ph_2PCF_3(Me)][OTf]$ (**[2][OTf]**) and $[Ph_3PCF_3][OTf]$ (**[1][OTf]**) in high yield, respectively (Scheme 2). Subsequent treatment of **[1][OTf]** with $[K][B(C_6F_5)_4]$ afforded **[1][BArF]** via anion metathesis.



Scheme 2. Synthesis of **[1][OTf]**, **[2][OTf]** and **[1][BArF]**.

Single crystals of each of these salts, **[1][OTf]**, **[2][OTf]** and **[2][BArF]** were obtained and characterized by X-Ray diffraction studies (Figure 1) confirming the formulation. This revealed no significant contacts between the cations and anions in each case. Replacement of the methyl group of **[2]**$^+$ with a phenyl ring in **[1]**$^+$ resulted in an increase of the steric environment around the phosphorus centre, with **[1]**$^+$ assuming a more propeller-like shape (lowest torsion angles – involving the F_3**C**-**P**-**C**-**C**H- fragment – were -105° and -113° for **[2][OTf]** and **[1][OTf]**, respectively).

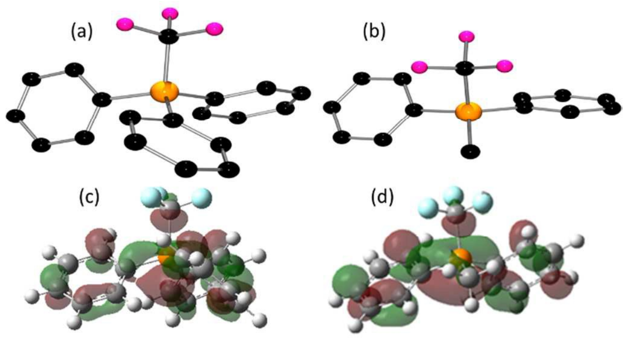


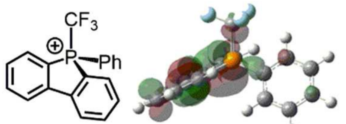
Figure 1. POV-ray depictions of the cations of (a) **[1]**$^+$ and (b) **[2]**$^+$; H atoms and anions are omitted for clarity. C: black, P: orange, F: pink. (c) LUMO of **[1]**$^+$, (d) LUMO of **[2]**$^+$ (isovalues at 0.04).

These salts could be stored as solids under ambient conditions for months with no observable degradation. Moreover, even in non-purified solvents at temperatures up to 100°C, or in the presence of excess water, alcohol, phenol / aniline combinations, or stoichiometric HCl, no degradation was evident by ^1H, ^{31}P or ^{19}F NMR spectroscopy. However, in the presence of water and base (e.g. aniline), rapid formation of Ph_3PO and HCF_3 resulted. Apart from this reactivity, the resistance to strong Brønsted acids is notable as boranes utilized in FLP chemistry either bind these Lewis bases or degrade via protodeboronation under acidic conditions.[24]

DFT calculations at the M06-2X/6-311G(d,p) level with DCM solvation (by polarizable continuum model) were used to probe the Lewis acidity of these salts. The optimized structures showed the lower torsion angles for the aryl rings in **[2]**$^+$ (-118°) in comparison to **[1]**$^+$ (-126°) consistent with the increased steric congestion in **[1]**$^+$ prompting the increased torsion angle and reduced conjugation of the phenyl rings with the σ* orbital. The hydride ion affinity (HIA) of **[1]**$^+$ and **[2]**$^+$ (relative to BEt_3) was computed at the same level of theory. HIA values of -19.2 and -19.5 kcal mol^{-1} were obtained for **[1]**$^+$ and **[2]**$^+$, respectively. These values are notably larger than that found for the catalytically active borane BPh_3 (HIA = -10.5 kcal mol^{-1}).[25] The LUMO of each of these cations is mainly comprised of the σ* orbital of the $P\text{-}CF_3$ fragment, although the LUMO of **[2]**$^+$ has a greater contribution on the phenyl rings in comparison to **[1]**$^+$ due to the lower torsion angle in the former (Figure 1(c), (d)).

To further probe the effect of conjugation between the σ* orbital and aryl substituent(s), computations for the EPC in which two of the phenyl rings are linked, $[(C_{12}H_8)PPh(CF_3)]^+$ **[3]**$^+$ (Figure 2) were also performed. The reduced torsion angle for the biphenyl fragment (-70°), led to more delocalization of the LUMO onto the biphenyl fragment and reduced contribution with the isolated phenyl ring where the torsion angle increases to -147°. This also results in a reduced HIA on P for **[3]**$^+$ compared to **[1]**$^+$ (-17.9 and -19.5 kcal mol^{-1}, respectively).

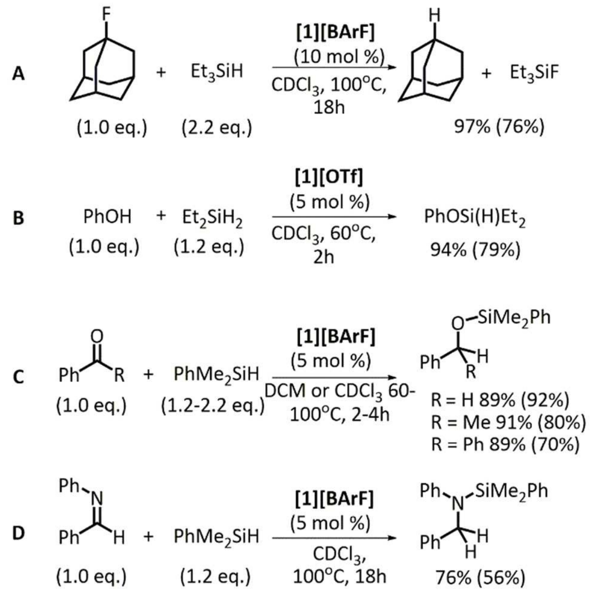
View Article Online
DOI: 10.1039/C7CC09128A



[3]

Figure 2. LUMO orbital for **[3]** (isovalues at 0.04).

The computations of the Lewis acidity of **[1]**$^+$ and **[2]**$^+$ prompted experiments targeting their use as Lewis acid catalysts. EPCs have been shown to effect catalytic hydrodefluorination.[6] Thus the EPC salts were evaluated in the reaction of 1-fluoroadamantane with Et_3SiH. While modest hydrodefluorination was observed at 60 °C, using **[1][OTf]** or **[1][BArF]** the conversions were improved at 100 °C with the latter giving excellent reactivity after 18 h (Scheme 3, A). Most notably, repeating the reaction under ambient conditions with un-purified solvent / reactants resulted only in a small diminishing of the conversion.



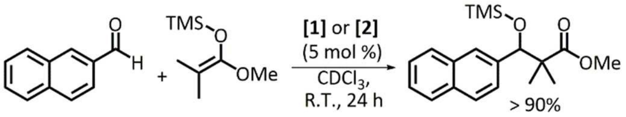
Scheme 3. Transformations catalysed by **[1]**. In brackets the conversion under ambient conditions in unpurified solvent. For A, the conversions are based on ^{19}F-NMR spectra using fluorobenzene as standard. For B-D, the conversions are based on ^{1}H-NMR using mesitylene as standard. For aldehyde / ketone reductions, the product further reacted losing siloxane, as previously reported.[9]

Similarly, investigation of the dehydrocoupling of silanes and alcohols was probed (Scheme 3, B). Combination of phenol and Et_2SiH_2, in the presence of 5 mol% **[2][OTf]** as catalyst showed limited reactivity (19% conversion), whereas **[1][OTf]** and **[1][BArF]** afforded $PhOSi(H)Et_2$ in high yield. Once again, repeating the reaction under ambient conditions with unpurified solvent / alcohols had minor effect on the catalyst performance. When BnOH was used as alcohol and Et_2SiH_2 as silane in the presence of 5 mol% **[2][OTf]** as catalyst at 20 °C or at elevated temperatures no reaction was observed. However, using **[1][OTf]** or **[1][BArF]** as the catalyst, dehydro-coupling of silane and benzyl-alcohol at 60 °C proceeded affording $BnOSi(H)Et_2$ in 90% yield. Treatment of benzaldehyde with 1.2 equivalents of $PhMe_2SiH$ in the presence of a catalytic amount of either **[1][OTf]** or **[1][BArF]** at 60 °C led to good reduction of the carbonyl affording Bn_2O and $(PhMe_2Si)_2O$ (Scheme 3, C).

Analogously, benzophenone or acetophenone were both reduced at 100 °C with **[1][BArF]** as the catalyst in the presence of 2.2 equivalents of $PhMe_2SiH$ leading to a mixture of silyl-ether and the deoxygenated product alkane (Scheme 3, C). In contrast, the catalyst **[1][OTf]** proved inactive under these conditions, although reductive de-arylation of **[1]**$^+$ did generate Ph_2PCF_3 and PhOTf. The superior catalytic activity of **[1][BArF]** is thus attributed to the more weakly nucleophilic anion. Also in those cases, repeating the reactions under ambient conditions in non-purified solvents resulted in good reduction of the carbonyls despite the competitive dehydrosilylation of water.[3b, 26]

Treatment of *N*-benzylidene aniline with 1.2 equivalents of $PhMe_2SiH$ in the presence of a catalytic amount of **[1][BArF]** at 100 °C gave full imine reduction leading mainly to the corresponding hydrosilylated product (Scheme 3, D) and similar conversion again was observed when the reaction was performed under ambient conditions. Under non-anhydrous conditions, Brønsted acid catalysis has been observed. For example, CF_3CO_2H has been shown to activate silanes.[27] However, the low Lewis acidity of the P-CF_3 EPCs towards H_2O disfavours this possibility and the reactivity observed is more consistent with EPC activation of silane. This was supported by H/D scrambling being observed using freshly distilled Ph_2MeSiH and Et_3SiD in anhydrous DCM, under inert atmosphere, in the presence of 5 mol % of **[1][OTf]**.

Recently, EPCs were also shown to initiate the Mukaiyama aldol addition reaction[28] under strictly anhydrous, but otherwise mild conditions. Indeed, use of 5 mol% of the salts of **[1]**$^+$ and **[2]**$^+$ proved effective in initiating the aldol reaction of 2-naphthaldehyde and 1-methoxy-2-methyl-1-trimethylsiloxypropene in $CDCl_3$, affording quantitative yields of the addition product after 24 h at room temperature (Scheme 4).



Scheme 4. Mukaiyama aldol reaction with **[2][OTf]**, **[1][OTf]** and **[1][BArF]**.

In summary, the first example of an air and water-stable EPC catalyst has been reported.[29] This new class of catalyst is based on the inclusion of a more robust CF_3 substituent as the essential highly electronegative component of the EPC. This class of catalyst has shown high tolerance to ROH, including water, allowing them to be stored under ambient conditions and to be used without rigorous exclusion of water from the reaction mixture. Experimental and computational evidence demonstrate that the P-CF_3 cation decorated with three phenyl rings is sufficiently Lewis acidic to be a useful Lewis acid catalyst, with an inert anion helping to insure no decomposition at high temperature. While this new class of

DOI: 10.1039/C7CC09128A

EPCs have a lower catalytic activity compared to that of previous EPCs, **[1]**$^+$ represents a balance between air- and water-stability and catalytic activity. Furthermore, compound **[1][BArF]** is readily accessible not requiring strong oxidants (XeF_2) or highly sensitive silylium cations [Et_3Si][BArF] as reported for the more reactive fluorophosphonium EPCs.[5] On the basis of this work, the generation of other readily accessible, water-stable EPCs is under investigation.

We are grateful to the Royal Society of Chemistry for a Research Mobility Grant (V.F.) and the University of Manchester for financial support. D.W.S. acknowledges the financial support of the NSERC of Canada and the award of a Canada Research Chair. M.J.I. acknowledges the EPSRC (grant numbers EP/K03099X/1 and EP/M023346/1) for financial support. Dr. Alan Brisdon is thanked for useful discussions. Additional research data supporting this publication are available as supplementary information accompanying this publication

Conflicts of interest

The authors declare no conflict of interest.

Notes and references

1. G. C. Welch, R. R. S. Juan, J. D. Masuda and D. W. Stephan, *Science*, 2006, **314**, 1124-1126.
2. (a) D. W. Stephan, *J. Am. Chem. Soc.*, 2015, **137**, 10018-10032; (b) D. W. Stephan, *Acc. Chem. Res.*, 2015, **48**, 306-316; (c) D. Stephan and G. Erker, *Isr. J. Chem.*, 2015, **55**, 133-133; (d) D. W. Stephan and G. Erker, *Angew. Chem. Int. Ed.*, 2010, **49**, 46-76.
3. (a) S. A. Weicker and D. W. Stephan, *Bull. Chem. Soc. Jap.*, 2015, **88**, 1003-1016; (b) V. Fasano, J. E. Radcliffe, L. D. Curless and M. J. Ingleson, *Chem. Eur. J.*, 2017, **23**, 187.
4. G. Wittig and U. Schöllkopf, *Chem. Ber.*, 1954, **87**, 1318-1330.
5. D. W. Stephan, *Angew. Chem. Int . Ed.*, 2017, **56**, 5984 -5992.
6. C. B. Caputo, L. J. Hounjet, R. Dobrovetsky and D. W. Stephan, *Science*, 2013, **341**, 1374-1377.
7. M. Pérez, C. B. Caputo, R. Dobrovetsky and D. W. Stephan, *Proc. Nat. Acad. Sci.*, 2014, **111**, 10917-10921.
8. M. Pérez, L. J. Hounjet, C. B. Caputo, R. Dobrovetsky and D. W. Stephan, *J. Am. Chem. Soc.*, 2013, **135**, 18308-18310.
9. M. Mehta, M. H. Holthausen, I. Mallov, M. Pérez, Z. W. Qu, S. Grimme and D. W. Stephan, *Angew. Chem. Int . Ed.*, 2015, **54**, 8250-8254.
10. A. Augurusa, M. Mehta, M. Pérez, J. T. Zhu and D. W. Stephan, *Chem. Commun.*, 2016, **52**, 12195-12198.
11. M. Mehta, I. G. de la Arada, M. Pérez, D. Porwal, M. Oestreich and D. W. Stephan, *Organometallics*, 2016, **35**, 1030-1035.
12. T. vom Stein, M. Pérez, R. Dobrovetsky, D. Winkelhaus, C. B. Caputo and D. W. Stephan, *Angew. Chem. Int . Ed.*, 2015, **54**, 10178-10182.
13. (a) J. T. Zhu, M. Pérez and D. W. Stephan, *Angew. Chem. Int . Ed.*, 2016, **55**, 8448-8451; (b) J. Zhu, M. Pérez, C. B. Caputo and D. W. Stephan, *Angew. Chem. Int . Ed.*, 2016, **55**, 1417-1421.
14. J. H. W. LaFortune, J. M. Bayne, T. C. Johnstone, L. Fan and D. W. Stephan, *Chem. Commun.*, 2017, **53**, DOI: 10.1039/C1037CC08037A.
15. (a) T. Mahdi and D. W. Stephan, *J. Am. Chem. Soc.*, 2014, **136**, 15809-15812; (b) D. J. Scott, M. J. Fuchter and A. E. Ashley, *J. Am. Chem. Soc.*, 2014, **136**, 15813-15816; (c) Á. Gyömöre, M. Bakos, T. Földes, I. Pápai, A. Domján and T. Soós, *ACS Catalysis*, 2015, DOI: 10.1021/acscatal.5b01299, 5366-5372; (d) D. J. Scott, T. R. Simmons, E. J. Lawrence, G. G. Wildgoose, M. J. Fuchter and A. E. Ashley, *ACS Catalysis*, 2015, **5**, 5540-5544; (e) D. J. Scott, N. A. Phillips, J. S. Sapsford, A. C. Deacy, M. J. Fuchter and A. E. Ashley, *Angew. Chem. Int. Ed.*, 2016, **55**, 14738; (f) V. Fasano, J. E. Radcliffe and M. J. Ingleson, *ACS Catalysis*, 2016, **6**, 1793-1798; (g) E. Dorko, M. Szabo, B. Kotai, I. Papai, A. Domjan and T. Soos, *Angew. Chem. Int . Ed.*, 2017, **56**, 9512-9516.
16. (a) A. E. Ashley, T. J. Herrington, G. G. Wildgoose, H. Zaher, A. L. Thompson, N. H. Rees, T. Kramer and D. O'Hare, *J. Am. Chem. Soc.*, 2011, **133**, 14727-14740; (b) H. Zaher, A. E. Ashley, M. Irwin, A. L. Thompson, M. J. Gutmann, T. Kramer and D. O'Hare, *Chem. Commun.*, 2013, **49**, 9755-9757.
17. S. Postle, V. Podgorny and D. W. Stephan, *Dalton Trans.*, 2016, **45**, 14651-14657.
18. J. H. W. LaFortune, T. C. Johnstone, M. Pérez, D. Winkelhaus, V. Podgorny and D. W. Stephan, *Dalton Trans.*, 2016, **45**, 18156-18162.
19. M. H. Holthausen, J. M. Bayne, I. Mallov, R. Dobrovetsky and D. W. Stephan, *J. Am. Chem. Soc.*, 2015, **137**, 7298-7301.
20. F. R. Leroux, B. Manteau, J.-P. Vors and S. Pazenok 4, *Beilstein J. Org. Chem.*, 2008, **4**, doi:10.3762/bjoc.3764.3713.
21. T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156.
22. S. Barata-Vallejo, B. Lantano and A. Postigo, *Chemistry*, 2014, **20**, 16806-16829.
23. M. B. Murphy-Jolly, L. C. Lewis and A. J. M. Caffyn, *Chem. Commun.*, 2005, 4479.
24. S. Das and S. K. Pati, *Chem. Eur. J.*, 2017, **23**, 1078.
25. (a) D. Mukherjee, DanielF.Sauer, A. Zanardi and J. Okuda, *Chem. Eur.J.*, 2016, **22**, 7730 -7733; (b) D. Mukherjee, S. Shirase, K. Mashima and J. Okuda, *Angew. Chem. Int. Ed.*, 2916, **55**, 13326.
26. V. Fasano and M. J. Ingleson, *Chem. Eur. J.*, 2017, **23**, 2217.
27. M. P. Doyle and C. T. J. West, *J. Org. Chem.*, 1975, **40**, 3835.
28. A. G. Barrado, J. M. Bayne, T. C. Johnstone, C. W. Lehmann, D. W. Stephan and M. Alcarazo, *Dalton Trans.*, 2017, DOI: 10.1039/c1037dt03197a.
29. Whilst the initial silane activation step requires the phosphorus Lewis acid we acknowledge it is feasible that subsequent catalytic cycles may be mediated by a silicon electrophile, for a related example using a strong Brønsted acid see: Q.-A. Chen, H. F. T. Klare, M. Oestreich, *J. Am. Chem. Soc.*, 2016, **138**, 7868.