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Evidence of Phosphonium-Carbenium Dication Formation in a Superacid: Precursor to Fluorinated Phosphine Oxides

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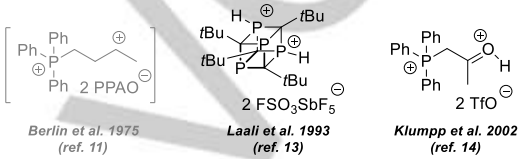
Abstract: Unambiguously confirmed by low-temperature *in situ* NMR experiments, X-ray diffraction and vibrational spectroscopy, phosphonium-carbenium superelectrophiles are shown to be generated in strong acidic conditions. Representing crucial intermediates, their exploitation allows for the synthesis of unprecedented fluorinated (cyclic) phosphine oxides.

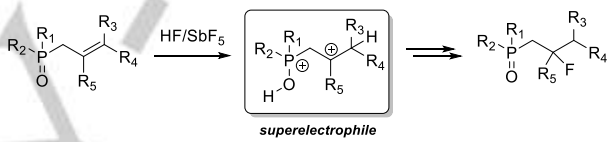
Fluorinated compounds[1] are undeniably associated with the development of catalysis,[2] agrochemicals and drugs.[3] Organophosphorus compounds have found wide application in various fields such as catalysis, medicinal chemistry, material science and inorganic chemistry.[4] To the best of our knowledge, the formation of fluorinated phosphines and their derivatives *via* direct addition is limited to a few reactions: the trifluoromethylfluorosulfonylation[5], the bromodifluoromethylation[6] of allyldiphenyl phosphine oxide, the nucleophile mediated reaction of Ruppert-Prakash reagent (or perfluoroalkyltrimethylsilanes) with phosphites, or LiC_2F_5 to chlorinated phosphine[7] and the unimolecular radical nucleophilic substitution reaction.[8] Although the addition of an element-hydrogen pair to an unsaturated C-C bond is a standard direct strategy to functionalize a molecular skeleton, hydro-(hetero)element addition to allylic or propargylic phosphorus containing derivatives is rather limited.[9] The pH dependent stability and the prototropic isomerization of the corresponding phosphonium derivatives may be the reason for the difficulty to selectively add any species to these derivatives under acidic conditions.[10] To avoid undesired rearrangement, Berlin used polyphosphoric acid (115 %) at elevated temperatures to perform the intramolecular Friedel-Crafts reaction of allyltriphenyl phosphonium salts.[11] *In situ* formation of a dication was postulated in this seminal contribution, whose hypothesis was recently reformulated by Vasilyev and Stankevic (Scheme 1a).[12] Laali[13] and Klumpp[14] went a step beyond by respectively showing the protonation of tetraphosphocubane and ketophosphonium salts in superacids.[15] On this basis, we postulated that the generation of a superelectrophile from an unsaturated organophosphorus compound can be expected under super acidic conditions and further exploited to produce valuable and innovative (P,F)-derivatives. We report here the first example of a hydrofluorination[16] and cyclization/fluorination of unsaturated phosphine oxides. The involvement of phosphonium-carbenium superelectrophiles is evidenced by X-ray crystallography, low-temperature NMR spectroscopy and DFT calculations (Scheme 1b).

a. *Postulated and observed phosphorus containing polycations*



Berlin et al. 1975 (ref. 11) — *Laali et al. 1993 (ref. 13)* — *Klumpp et al. 2002 (ref. 14)*

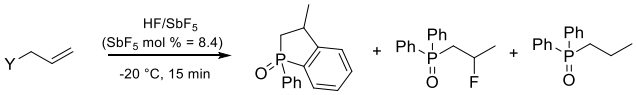
b. ***This work:*** *Generation, characterization and exploitation of phosphonium-carbenium superelectrophiles for the synthesis of fluorinated phosphine oxides*



superelectrophile

Scheme 1. a. Postulated and reported phosphorus containing polycations formation in acidic conditions (literature); **b.** Exploitation of phosphonium-carbenium superelectrophiles for the synthesis of fluorinated phosphine oxides (this work).

This work aims to address two important challenges: 1) The deactivation of the unsaturation after protonation of the P-containing function, which could prevent substrates from any reaction, needs to be outweighed by the high acidity of the media; 2) the impact of the protonated function on the electrophilicity of the cation if a dication is formed. The reactivity of model allylic derivatives **1a**, **2a** and **3a** was evaluated (Scheme 2). After a reaction at –20°C in HF/SbF_5, phosphine oxide **1a** was shown to cyclize to phosphindoline **4a** as a 2/3 mixture of *syn/anti* diastereoisomers. The same substrate submitted to anhydrous superacid HF (H_0 = –15) or CF_3SO_3H (H_0 = –14.1) remained unreactive at -20°C.[17] This confirmed that the activation of the substrate is strongly dependent on the acidity of the respective medium; a result that is consistent with a superelectrophilic activation process. Starting from allyldiphenylphosphine **2a**, similar results were obtained. With phosphine-borane analogue **3a**, traces of the *β*-fluorinated phosphine oxide **5a**[18] and the reduced product **6a** were formed beside the expected product **4a** under the determined reaction conditions. These results confirmed that the phosphorus containing function strongly influenced the reaction course.



		4a	5a	6a
Y= Ph_2PO	**1a**	100%		
Y= Ph_2P	**2a**	100%		
Y= Ph_2PBH_3	**3a**	66%	1%	33%

Scheme 2. Allylic derivatives reactions in HF/SbF_5.

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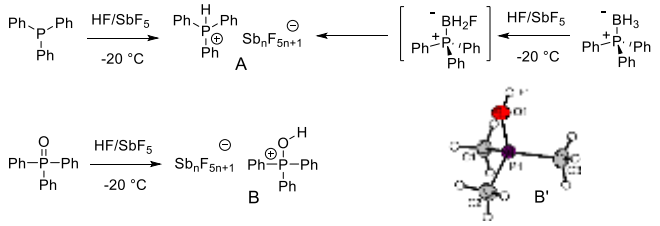
To further explore this impact, the protonation of triphenylphosphine, triphenylphosphine oxide and triphenylphosphine borane in superacid was studied by *in situ* low-temperature NMR experiments. Triphenylphosphine was first added to the superacid HF/SbF_5 at -40°C and the reaction was followed by ^{31}P NMR spectroscopy, revealing the unique formation of phosphonium ion A (signal at 6.4 ppm to be compared to signals at 3.89 ppm and 5.28 ppm for corresponding triflate and triflimidate salts, Scheme 3).[19] Under the same conditions, triphenylphosphine borane also led to A, alongside with a vigorous gas evolution which is likely to arise from a fluoride/hydride exchange followed by P-B bond cleavage. [20-21] Under the same conditions, triphenylphosphine oxide led to the single cationic species B with a ^{31}P NMR signal at 58.97 ppm, more deshielded that analogous triflate and triflimidate salts[19] (25.0 ppm for the neutral substrate).



Scheme 3. Phosphonium ions A and B generated from triphenylphosphine, triphenylphosphine borane, and triphenylphosphine oxide in HF/SbF_5 and observed by low-temperature ^{31}P NMR spectroscopy. Illustration of the B' cation (thermal ellipsoids with 50% probability) depicted according to the single crystal X-ray structure analysis of $[(CH_3)_3POH]^+[Sb_2F_{11}]^-$ (generated from trimethylphosphine oxide in superacid HF/SbF_5). [22-23]

Single crystals grown from a solution of trimethylphosphine oxide in HF/SbF_5 were investigated by X-ray crystallography.[23-24] An elongation of the P-O bond length (1.574(5) Å) of the monoprotonated cation B' was observed by means of a comparison with the P-O bond in trimethylphosphinoxide (1.489(6) Å) (Scheme 3). The P-O bond length is comparable with that of phosphoric acid (1.548(4) Å),[25-26] but shorter than a typical single P-O bond.[27-28] A possible explanation is that the highly polarized P-O sigma-bond and the two p-type orbitals of the oxygen atom undergo a negative hyperconjugation with the P-C antibonding orbital.[29] The P-C bond length remains approximately unchanged compared to that of the neutral compound.[27] The infrared spectra of $(CH_3)_3PO$(a), $[(CH_3)_3POD]^+[AsF_6]^-$(b), obtained in DF/AsF_5 solution, and $[(CH_3)_3POH]^+[Sb_2F_{11}]^-$(c), obtained in HF/$SbF_5$ solution, are illustrated in Figure 1. According to the C_s-symmetry of the cation, 39 fundamentals (22 A' + 17 A'') are expected, which all are active in the Raman and IR spectra. The ν(OH) mode detected at 3618 cm^{-1} and the corresponding ν_{as}(OD) observed at 2565 cm^{-1} are in good agreement with the Teller-Redlich rule for an H/D isotopic effect.[30] The broad band shapes are typical of the OH stretching modes that are involved in hydrogen bonds.[31] The PO stretching mode is red-shifted from 1160 cm^{-1} in the oxide to 995 cm^{-1} in the protonated cation. This is in accordance with the PO bond elongation due to the protonation, as observed in the crystal structure. The vibrational data are comparable with quantum chemically calculated frequencies (for details see Appendix 1 in the Supporting information).[23] The P-O bond elongation further confirmed the P-cationic character of the protonated phosphine oxide. After a second protonation, ion B'' is expected to generate the phosphonium-carbenium dication C (Scheme 4a). The electron withdrawing effect of the P-centered cation on the generated carbenium ion increases its electrophilic character, allowing its internal trapping with a weak nucleophilic aryl group (substituted with a protonated phosphine oxide) or external trapping with the "non-nucleophilic" solvated fluoride ions.[32]

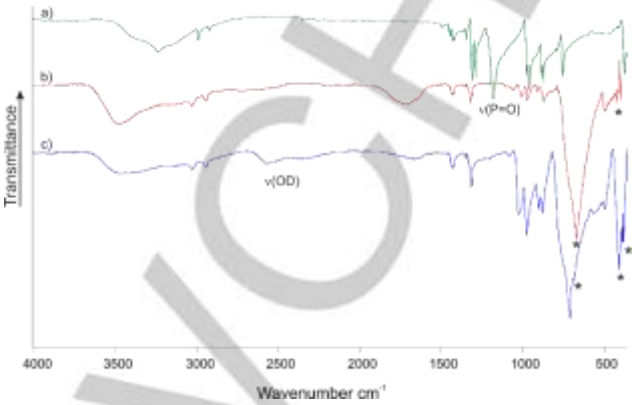
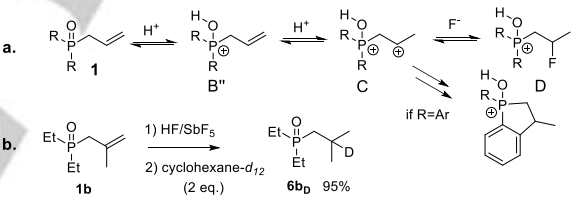


Figure 1: Low temperature Infrared spectra of a) $(CH_3)_3PO$, b) $[(CH_3)_3POH]^+[Sb_2F_{11}]^-$ and c) $[(CH_3)_3POD]^+[AsF_6]^-$ (* are marking the anions vibrations).

If a superelectrophile, such as C, is formed in the superacid, it is expected to act as a hydride abstracting agent and perform an ionic hydrogenation process in the presence of cyclohexane.[33] This was confirmed by the formation of deuterated product **6b$_D$** from diethylmethallylphosphine oxide **1b** after a reaction in HF/SbF_5 in the presence of cyclohexane-d_{12} (Scheme 4b).



Scheme 4. a. Proposed mechanism for the hydrofluorination and cyclization of alkenyl phosphine oxides. **b.** Ionic deuteration of a phosphonium-carbenium dication.

The formation of a dication after the reaction of substrate **1b** in the superacid was finally confirmed by *in situ* NMR analysis (Figure 2).

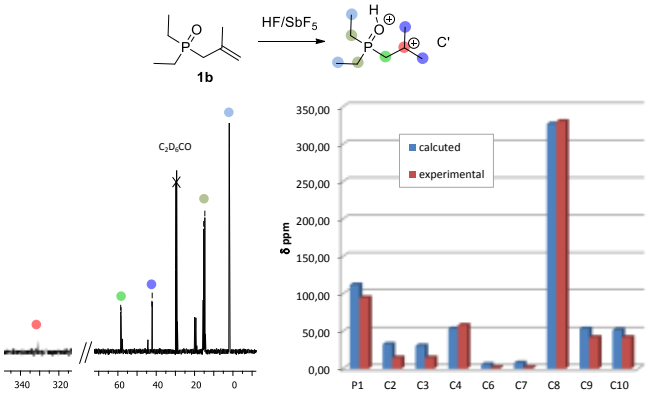


Figure 2. Generation and NMR spectra of dication C' in HF/SbF_5 (SbF_5 mol% = 21.6) at –30°C and comparison of experimental and calculated ^{13}C NMR and ^{31}P NMR shifts.

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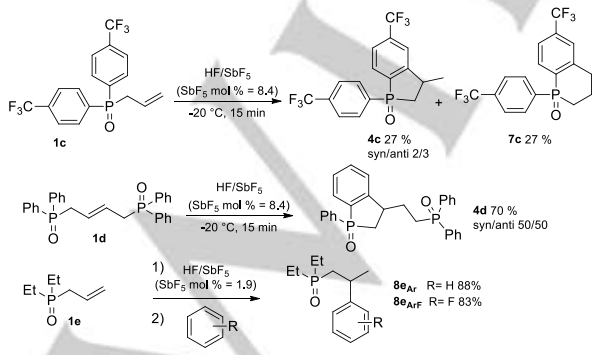
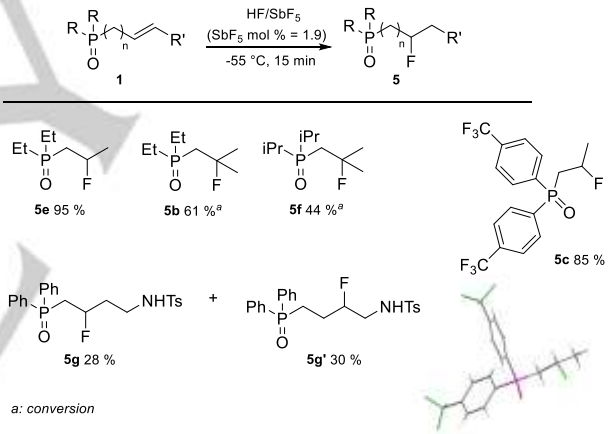
In the ^{1}H NMR spectrum, methyl groups appear deshielded at 2.80 ppm. The central methylene group signal is centered at 3.28 ppm. In addition, a singlet at 9.26 ppm, attributed to the protonation of the phosphine oxide further confirmed the formation of dication C'.[23] In the ^{13}C NMR spectrum, beside traces of a fluorinated product, the carbocation of the phosphonium-carbenium dication C' was characterized by the singlet located at 330.6 ppm. These values match the theoretical NMR parameters deduced from calculations for the most stable postulated intermediate (Figure 2). To note, the same reaction conducted in TfOH led to the formation of the corresponding O-protonated vinylphosphine oxide obtained after double bond isomerization.[23] This result further confirms that it is necessary to use strong superacid conditions to promote the reaction. To gain further insight, the same substrate was submitted to less acidic HF/SbF_5 solutions (SbF_5 mol % = 1.9) and to neat HF. No dication formation could be observed and the ratio of the observed protonated fluorinated phosphine oxide of type D over the O-protonated starting material of type B'' increased with acidity.[23] Furthermore, this ratio increased through reaction time in these conditions, confirming the mechanism depicted in scheme 4. This phenomenon is not limited to ethyl-substituted phosphine oxide, as diisopropylmethallylphosphine oxide also led to the formation of a phosphonium-carbenium dication.[23]

Having demonstrated that phosphonium-carbenium dications are generated under these conditions, the impact of the substitution of the phosphine oxide on their reactivity was evaluated (Scheme 5). Substrate **1c** was efficiently converted to its trifluoromethylated dihydrophosphindole **4c**[34] and to tetrahydrophosphinoline oxide congener **7c**, confirming the possibility to trap the superelectrophile with a weak nucleophile. The formation of a six-membered ring product involving an anti-Markovnikov addition to the olefin can be directly related to the formation of a hydrido-bridged (carbonium ion structure) containing superelectrophile, as already observed for ammonium-carbonium superelectrophilic activation process.[35] Interestingly, despite the deactivation of the unsaturation (inductive electron withdrawing effect of the second phosphine oxide function), the cyclization still occurred for substrate **1d**, making it a relevant starting reaction for the synthesis of ligand precursors.[36] Finally, we postulate that, if a dication was generated in solution, any intermolecular trapping with a weakly nucleophilic partner should occur. This was confirmed with the formation of the arylated products $\mathbf{8e_{Ar}}$ and $\mathbf{8e_{ArF}}$ after the reaction of phosphine oxide **1e** respectively with benzene and fluorobenzene.



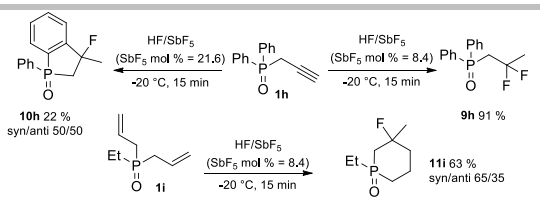
Scheme 5. Evaluation of superelectrophilic activation starting from alkenyl phosphine oxides.

Encouraged by these findings, we reasoned that the superelectrophilic character of these dications should allow their efficient fluorination in HF/SbF_5. It is known that for SbF_5 concentrations lower than 10 mol %, SbF_6^- almost is the only anionic species in solution. Moreover, the nucleophilicity of the fluoride ion source is likely to increase when the HF/SbF_5 ratio increases.[37] Substrate **1e** was thus added to HF/SbF_5 (%mol SbF_5 = 1.9). Under these conditions, allyldiethylphosphine oxide **1e** led to the exclusive formation of the desired *β*-fluorinated product **5e** in 95 % yield (Scheme 6). Similarly, the hydrofluorination could be applied to methallyl substrates **1b** and **1f**. Under these "fluorinating conditions", the cyclization could be prevented, and the desired fluorinated product **5c** was gratifyingly obtained in 85 % yield from substrate **1c**. An interesting preferred *gauche* conformation in the solid state was evidenced by a single crystal X-ray structure analysis (torsion angle *Ø* P-C-C-F = 64.23°).[38] When exploiting the conformational gauche preference of *β*-fluorinated functionalized molecules[39] emerged recently as a tool of choice in medicinal chemistry SAR studies or catalysis,[40] this preferred gauche conformation of *β*-fluorinated phosphine oxides offers future perspective in the field.[41] Fluorinated *δ*-aminophosphine oxides **5g** and **5g'**, analogues of the GABAB receptor agonist,[42] could also be directly generated in reasonable yields from the unsaturated precursor **1g**.



Scheme 6. Hydrofluorination of alkenyl phosphine oxides under superacid conditions and X-ray image of **5c** crystals.

Furthermore, the direct access to the *β-gem*-difluorinated analogues was evaluated. In a one-pot process, two consecutive hydrofluorinations of propargylic phosphine oxide **1h** successfully delivered *β*-gem-difluorinated analogue **9h** in 91 % yield (Scheme 7). By increasing the acidity of the media (%mol SbF_5 = 21.6), which must favor C-F bond activation,[43] the reaction became less selective, generating a mixture of compounds with 22 % being represented by the original fluorinated phosphindoline derivative **10h**, which could be purified. The potential ability to perform a tandem cyclization/fluorination process from diallylic substrates was subsequently evaluated with substrate **1i** in the superacidic solution. Gratifyingly, after a reaction in HF/SbF_5, the fluorinated cyclic product **11i** was generated in 63 % yield, opening further perspectives for the synthesis of novel fluorinated cyclic phosphine oxides.



Scheme 7. Consecutive hydrofluorination and cyclization/fluorination of unsaturated phosphine oxides

In conclusion, using single-crystal X-ray diffraction studies, vibrational spectroscopy and *in situ* low-temperature NMR experiments, we have provided evidence for the formation of phophonium carbenium dications from unsaturated phosphine oxides protonation in superacid. The superelectrophilic character of these dications was shown to be essential for the syntheses of various novel fluorinated and cyclic phosphine oxides. Evidenced by the direct generation of fluorinated analogues of ion-channel receptors agonists and desymmetrization of prochiral dialkenyl phosphine oxides, precursors of non-heterocyclic P-stereogenic compounds, this work opens innovative directions toward the synthesis of new (fluorinated) valuable organophosphorus compounds.

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Keywords: Superacid • Superelectrophile • Fluorination • Cyclization • Phosphine oxide

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[22] For a sake of clarity, $Sb_2F_{11}^-$ anion has been omitted from this representation.

[23] See SI for more details.

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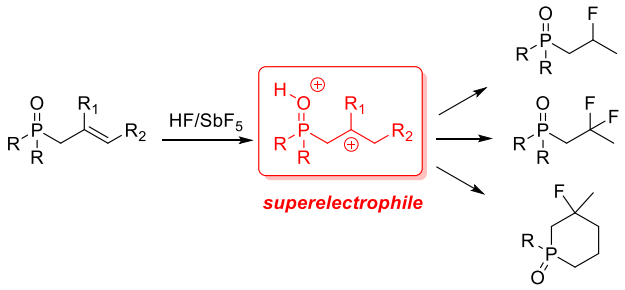

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