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To cite this version:

Jianjun Wang, Heng-Ying Xiong, Emilie Petit, Laëtitia Bailly, Xavier Pannecoucke, et al.. BiCl 3 -Mediated direct functionalization of unsaturated C–C bonds with an electrophilic SCF 2 PO(OEt) 2 reagent. Chemical Communications, 2019, 55 (60), pp.8784-8787. 10.1039/c9cc01851d . hal-02121245

HAL Id: hal-02121245

https://normandie-univ.hal.science/hal-02121245v1

Submitted on 16 May 2019

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$BiCl_3$-Mediated Direct Functionalization of Unsaturated C–C Bonds with an Electrophilic $SCF_2PO(OEt)_2$ Reagent

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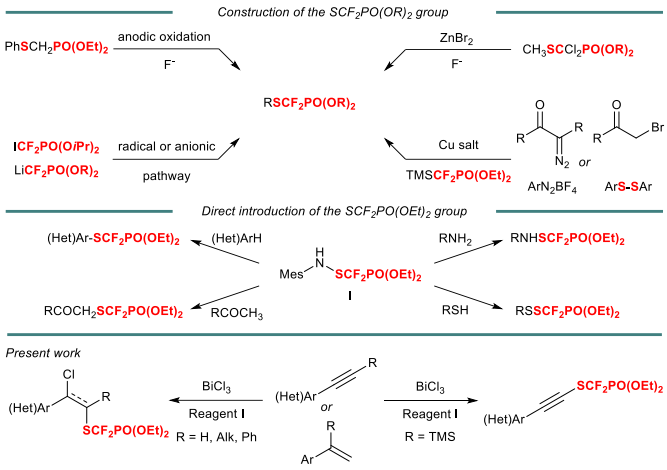
Abstract: A transition metal free approach was developped to the direct difunctionalization of disubstituted alkynes and terminal alkenes with concomittant formation of C-$SCF_2PO(OEt)_2$ and C-Cl bonds. The $BiCl_3$-mediated reaction offered an access to highly value-added functionalized scaffolds in a single operation under mild conditions. Extention to $SCF_2PO(OEt)_2$-containing alkynes was also studied.

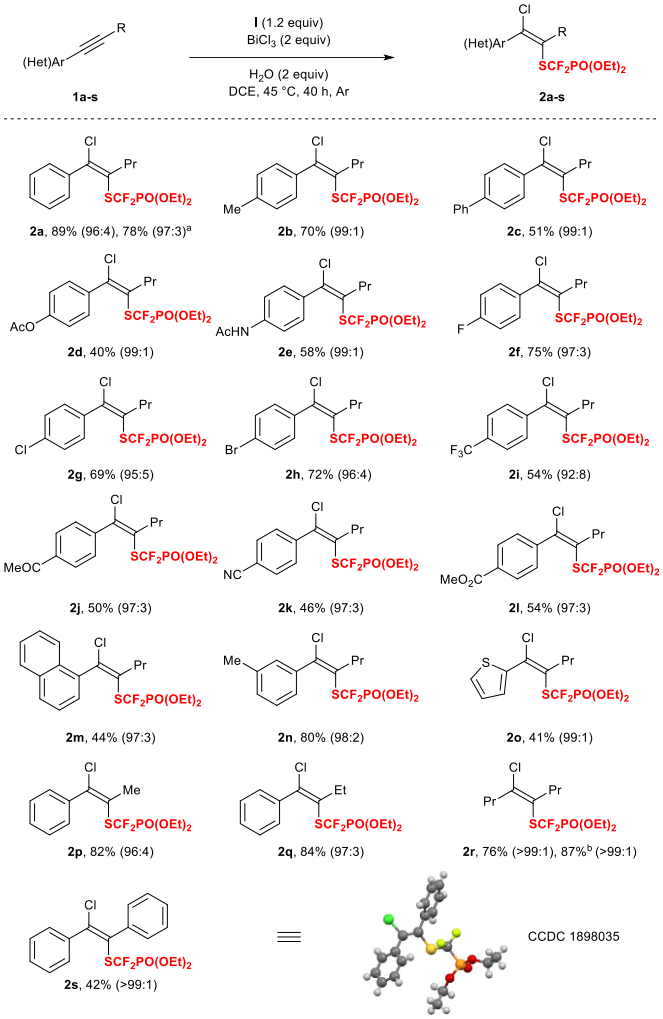
Present in pharmaceuticals and agrochemicals,[1] fluorinated products represent an important class of compounds thanks to the unique properties of the fluorine atom.[2] Although, the introduction of a fluorine atom or a CF_3 group onto molecules was widely studied,[3] the incorporation of a SR_f group (SCF_3, SCF_2H, SCF_2FG) remained in comparison rather limited.[4] Therefore, major advances were achieved over the last years by Hu,[5] Goossen,[6] Billard,[7] Shen,[8] Shibata[9] and our group,[10] among others. As part of these SR_f residues, we turned our attention to the $SCF_2PO(OR)_2$ group. Indeed, this fluorinated group is of interest due to its unique features: 1) combining the properties of both sulfur-containing molecules and the $CF_2PO(OEt)_2$ group,[11] 2) its easy transformation into other fluorinated groups (*eg*. SCF_2H, SO_2CF_2H and $SO_nCF_2PO(OEt)_2$ groups) and 3) a Hansch-Leo parameter of π = 0.76,[12] a lower value than the one obtained for the SCF_3 group (π = 1.44).[13] Hence, this group provides a new tool to modulate the lipophilicity of molecules of interest, in which it is incorporated.

To date, two main synthetic approaches were used to access $SCF_2PO(OEt)_2$-containing molecules (Scheme 1). The construction of the $SCF_2PO(OEt)_2$ moiety was developed based on electrochemical fluorination, halex-type process as well as radical and anionic processes.[14] However, this strategy only offered an access to a handful of $RSCF_2PO(OEt)_2$-containing compounds (R = Me, Ph or Py). Since 2016, a renewal of interest was shown and copper mediated transformations using $TMSCF_2PO(OEt)_2$ were developed for the formation of C(sp^3)-$SCF_2PO(OEt)_2$ bond from α-diazo carbonyl compounds[15a] and α-bromoketones.[15b] More recently, the synthesis of [(diethylphosphono)difluoromethyl]thiolated arenes starting from either diphenyl disulfides or aromatic diazonium salts was independently reported by Poisson[16a] and Goossen.[16b] A complementary strategy relied on the direct introduction of the $SCF_2PO(OEt)_2$ group onto molecules. In a previous study,[10] our group reported the synthesis and application of the newly-designed electrophilic $SCF_2PO(OEt)_2$ reagent **I** for the functionalization of various nucleophiles (C(sp^3)-, N- and S-$SCF_2PO(OEt)_2$ bonds formation). Convinced about the synthetic utility to develop efficient and general tools for the introduction of this emergent fluorinated group, we sought to explore the possibility to make challenging C(sp)-, C(sp^2)- and C(sp^3)-$SCF_2PO(OEt)_2$ bonds, using **I**, starting from alkynes and alkenes. Herein, we report a general approach based on a $BiCl_3$-mediated direct functionalization of unsaturated C–C bonds with the electrophilic $SCF_2PO(OEt)_2$ reagent **I**.



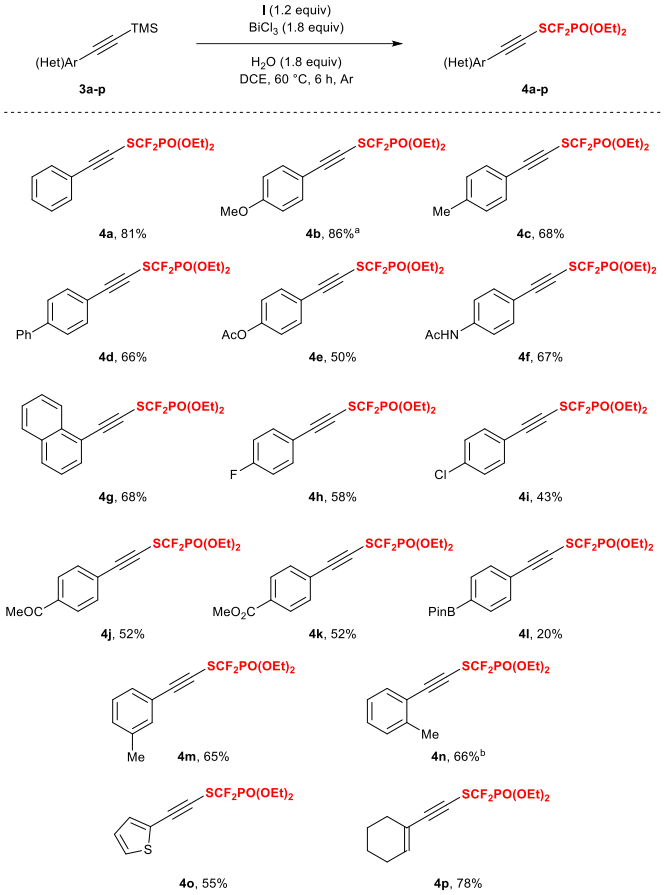
Scheme 1. State of the art and present work to access (diethyl phosphono)difluoromethylthiolated molecules.

At the outset of this study, we explored the reactivity of the reagent **I** with alkynes under transition metal free conditions. A quick screening of the reaction conditions revealed that the reaction of **1a** and **I** proceeded smoothly under mild conditions (45 °C) using $BiCl_3$ as a promoter[17] in the presence of 2 equivalents of water (Scheme 2). Indeed, the concomitant formation of C-$SCF_2PO(OEt)_2$ and C-Cl bonds occurred and **2a** was isolated in 89% yield with a good diastereoisomeric ratio (*E/Z* ratio of 96:4) in favour of the *E* isomer having a *cis* relationship between the aryl and the fluorinated group.[12] Worth mentioning that the presence of a chlorine atom on the resulting alkene **2** constituted a real asset, offering possibilities for post-functionalization reactions. The difunctionalization[1b,g,h,18] reaction was easily scaled up, giving **2a** in 78% yield with a similar diastereoisomeric ratio. Then, a myriad of disubstituted alkynes was functionalized and the challenging *tetra*substituted alkenes were isolated in good to high yields with high diastereoselectivities in favour of the *E* isomer (19 examples, up to 89% yield and *E/Z* ratio from 95:5 to 99:1). Unsymmetrical alkynes **1a-q** were first studied and electron-rich (**1b-e**) and electron-deficient (**1f-l**) 1-arylpentyne derivatives were functionalized. The transformation turned out to be tolerant to various functional groups such as OAc, NHAc, halogens, CF_3, COMe, CN and CO_2Me. Pleasingly, the reaction was also compatible with heteroaryl groups such as the 3-thienyl and the corresponding compound **2o** was obtained in 41% yield with a complete diastereoselectivity (99:1). 1-Phenyl-1-propyne **1p** and 1-phenyl-1-butyne **1q** were also suitable substrates leading to the corresponding fluorinated molecules **2p** and **2q** in 82% and 84% yields, respectively. Note that despite all our efforts, the functionalization of terminal alkynes failed and complex reaction mixtures were obtained. Finally, symmetrical alkynes with either aliphatic or aromatic substituents (**1r** and **1s**) were functionalized leading to **2r** and **2s** in somehow lower yields (76% and 42%, respectively), although an increase of the temperature to 60 °C increased the yield to 87% yield.



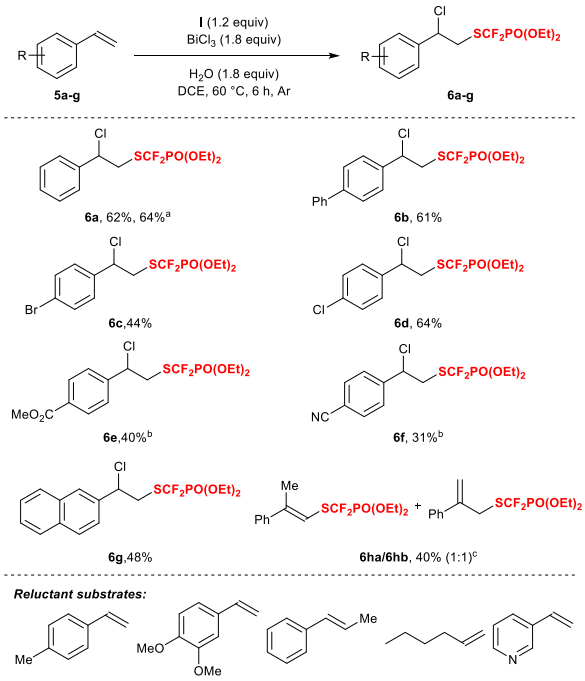
Scheme 2. (Diethyl phosphono)difluoromethylthiolation of internal alkynes. Reaction performed on 0.25 mmol scale. Isolated yields are given. The major isomer was represented. *E*/*Z* ratio was given in parenthesis and was determined by ^{19}F NMR on the crude reaction mixture. [a] on 1 mmol scale. [b] Reaction performed at 60 °C.

Surprisingly, when 1-phenyl-2-trimethylsilylacetylene was used as a substrate, the $SCF_2PO(OEt)_2$-containing alkyne **4a** was obtained as the main product (Scheme 3). Taking benefit from the opportunity to selectively get the high value-added $SCF_2PO(OEt)_2$-containing alkynes, further investigations were conducted. Using slightly modified reaction conditions, **4a** was isolated in high yield (81%). Next, a panel of trimethylsilyl(hetero)aromatic acetylene derivatives (**1b-o**) was functionalized. The introduction of the $SCF_2PO(OEt)_2$ residue on alkynes having an aromatic ring bearing both electron-donating (**1b-g**) and electron-withdrawing groups (**1h-l**) at the *para* position was realized, the transformation being more efficient with electron rich arenes. The substitution pattern on the aryl part did not have an impact on the reaction outcome since **4c**, **4m** and **4n** were obtained in similar yields. Various functional groups were tolerated, even halogen and BPin (**4h**, **4i** and **4l**). Alkynes bearing a thienyl group (**3o**) and the 1-[(trimethylsilyl)ethynyl]cyclohexene **3p** were functionalized in good to high yields.



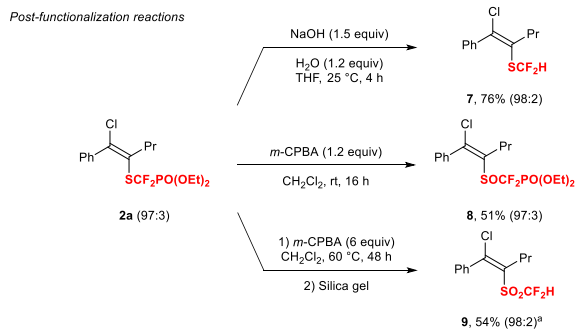
Scheme 3. Synthesis of $SCF_2PO(OEt)_2$-containing alkynes. Reaction performed on 0.25 mmol scale under Argon. Isolated yields are given. [a] Reaction performed at 45 °C. [b] **4n** was contaminated with an inseparable impurity. TMS = trimethylsilyl.

Finally, this reaction manifold was successfully extended to the difunctionalization of a panel of styrene derivatives **5** under same conditions (Scheme 4). Styrene **6a** was isolated in a good yield whatever the scale of the reaction (0.25 or 1 mmol). Arenes substituted with a phenyl group (**5b**) or a halogen (**5c** and **5d**) were suitable substrates. Gratifyingly, the transformation was tolerant to functional groups such as ester and nitrile groups, providing **6e** and **6f** in 40% and 31% yield, respectively. When 2-vinylnaphthalene **5g** was reacted, the corresponding product **6g** was obtained in 48% yield. α-Methylstyrene was a suitable substrate, although a 1:1 mixture of **6ha** and **6hb** was isolated, probably resulting from a fast HCl elimination. Unfortunately, electron rich styrenes, *trans*-β-methylstyrene, 1-hexene and heteroaromatic derivative were reluctant under our standard reaction conditions.



Scheme 4. Scope and limitations of the difunctionalization reaction of styrene derivatives. Reaction performed on 0.25 mmol scale. Isolated yields are given. [a] on 1 mmol scale. [b] **6e** and **6f** were contaminated with an inseparable impurity. [c] The ratio was determined on the ^{19}F NMR of the crude reaction mixture.

The potential of the compound **2a** was further explored by converting the $SCF_2PO(OEt)_2$ residue into other highly value- added fluorinated moieties (Scheme 5). Upon basic conditions, the difluoromethylthiolated *tetra*substituted alkene **7** was obtained in 76% yield, without erosion of the diastereoisomeric ratio (Scheme 5). This provided an unprecedented synthetic route to this class of polysubstituted SCF_2H alkenes.[4] In addition, the selective oxidation of **2a** into the corresponding sulfoxide **8** was possible, the olefin part remaining intact. Using, an excess of the oxidizing agent, the target sulfone derivative was not isolated. However, the SO_2CF_2H-containing alkene **9** was obtained after removal of the $PO(OEt)_2$ moiety upon purification on silica gel.



Scheme 5. Post-functionalization reactions. Reactions performed on 0.15 mmol scale under Argon. Isolated yields are given. *E/Z* ratio was determined by ^{19}F NMR on the crude mixture. The major isomer was represented. [a] *E/Z* ratio was determined by ^{19}F NMR on the product **9** after column chromatography on silica gel.

In conclusion, the $BiCl_3$-mediated difunctionalization reaction of alkynes and alkenes using the electrophilic reagent **I** was developed. This transition metal free approach offered a straightforward access to unprecedented highly functionalized aliphatic and vinylic $SCF_2PO(OEt)_2$-containing molecules. Moreover, starting from trimethylsilyl(hetero)aromatic acetylene derivatives, a selective and original access to $SCF_2PO(OEt)_2$-containing alkynes was established. Under mild conditions, these transformations turned out to be tolerant to a broad variety of functional groups (nitrile, ketone, ester, amides, halogen, BPin, …) giving the products in good to excellent yields (40 examples, up to 89% yield). Post-functionalization reactions were successfully realized, showcasing the synthetic utility of the products since other fluorinated groups of interest were readily obtained ($SOCF_2PO(OEt)_2$, SO_2CF_2H and SCF_2H groups). Using simple and practical conditions, this methodology considerably broadened the toolbox to access $SCF_2PO(OEt)_2$-containing molecules, a significant advance in organofluorine chemistry. We believe that this approach will open new avenues towards further studies related to the $SCF_2PO(OEt)_2$ residue and offer novel synthetic access to high value-added scaffolds.

This work was partially supported by INSA Rouen, Rouen University, CNRS, EFRD, Labex SynOrg (ANR-11-LABX-0029), Région Normandie (Crunch Network) and the IUF (Institut Universitaire de France). T.B. thanks the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no. 758710). J.W. thanks the UMR 6014 COBRA for a postdoctoral fellowship. H.-Y.X. thanks China Scholarship Council (CSC) for a doctoral fellowship.

Electronic Supplementary Information (ESI) available: Detailed experimental procedures, characterization data, copies of ^{1}H, ^{19}F and ^{13}C spectra of new compounds. CCDC 1898035.

Conflicts of interest

There are no conflicts to declare.

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