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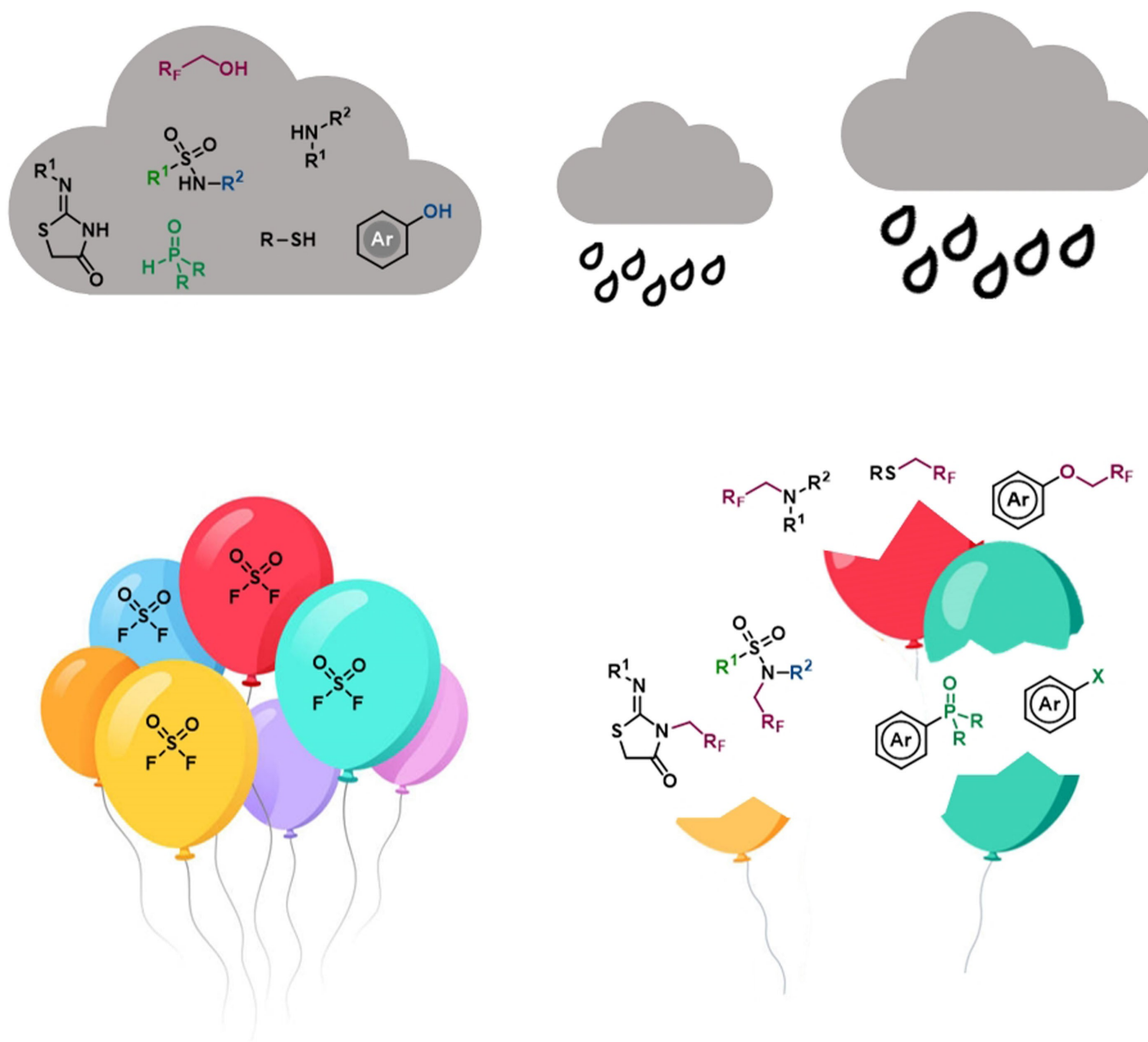
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New Chemical Transformations Involving SO_2F_2 -Mediated Alcohol Activation

Florian Audet,^[a] Morgan Donnard,^[a] Armen Panossian,^[a] David Bernier,^[b]
Sergii Pazenok,^[c] and Frédéric R. Leroux^{*[a]}



Abstract: Sulfuryl fluoride is a gas produced on a multi-ton scale for its use as a fumigant. In the last decades, it has gained interest in organic synthesis as a reagent with unique properties in terms of stability and reactivity when compared to other sulfur-based reagents. Sulfuryl fluoride has not only been used for sulfur-fluoride exchange (SuFEx) chemistry but also encountered applications in classic organic synthesis as an efficient activator of both alcohols and phenols, forming a triflate surrogate, namely a fluorosulfonate. A long-standing industrial collaboration in our research group drove our work on the sulfuryl fluoride-mediated transformations that will be highlighted below. We will first describe recent works on metal-catalyzed transformations from aryl fluorosulfonates while emphasizing the one-pot processes from phenol derivatives. In a second section, nucleophilic substitution reactions on polyfluoroalkyl alcohols will be discussed and the value of polyfluoroalkyl fluorosulfonates in comparison to alternative triflate and halide reagents will be brought to light.

Keywords: Alkylation, Fluorine, Fluorosulfonate, Nucleophilic substitution, Sulfuryl-fluoride

1. Introduction

Sulfuryl fluoride (SO_2F_2) is a colorless, odorless and non-flammable gas which is 3.5 times heavier than air.^[1] It was first described in 1901 by Moissan^[2] and subsequently developed by Dow Chemical in the 1950s as a pest control agent. It has been used as a fumigant for over five decades, and is a commodity chemical produced on a multi-ton scale.^[3] As a matter of fact, it is relatively inert in its gaseous form (stable up to 400 °C when dry).^[4] Nevertheless, although it hydrolyzes slowly under neutral aqueous conditions, under basic conditions the process is much more rapid, providing fluoride and fluorosulfonate anions.^[5] Besides, SO_2F_2 is a powerful neurotoxic gas that should be handled with care, in a well-ventilated fumehood.^[6]

Among sulfur (VI) compounds, fluorinated ones, such as sulfuryl fluoride or sulfonyl fluoride (i.e. RSO_2F), have unique properties. First, the S–F bond in S(VI) compounds is exclusively cleaved in an heterolytic fashion with the release of a fluoride anion while homolytic scission of the S–Cl bond in S(VI) compounds is rather common.^[7] Moreover, the meas-

ured homolytic bond dissociation energy of $\text{SO}_2\text{–F}$ is almost twice that of $\text{SO}_2\text{–Cl}$ (Figure 1).^[8,9] Hence, sulfonyl fluorides are much more stable toward nucleophilic substitution, hydrolysis and thermolysis in comparison to other sulfonyl halides.^[10,11] Finally, sulfur(VI) compounds are much more stable than other sulfur-based compounds in lower oxidation states such as the sulfur(IV) oxyhalides SOF_2 and SOCl_2 .^[12]

During this last decade, SO_2F_2 has gained interest in organic synthesis with the development of a new class of click reactions: the sulfur–fluoride exchange (SuFEx) chemistry.^[7,13,14] Due to their unique properties, sulfonyl fluorides have been widely adopted as electrophilic warheads in chemical biology.^[15]

Apart from SuFEx chemistry, different research groups, including ours, became interested in the use of sulfuryl fluoride for the *in situ* formation of fluorosulfonates from alcohols and their use as triflate surrogate. From a practical standpoint, SO_2F_2 can be used directly from a gas cylinder or can be generated *ex-situ* from SDI (1,1'-sulfonyldiimidazole) with KF, after addition of TFA.^[16] Many reactions involving an alcohol activation step have been developed and have already been reviewed recently.^[17,18] Therefore, this personal account is not

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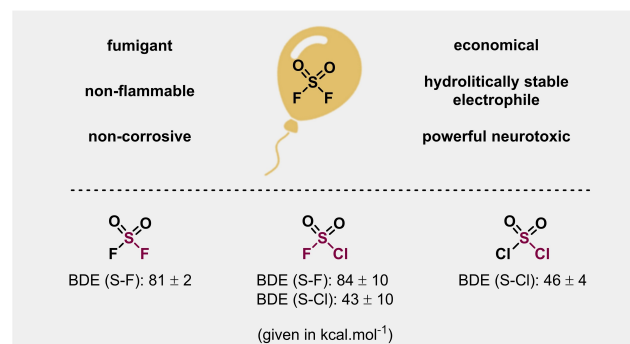


Figure 1. Key properties of sulfuryl fluoride and S–X bond dissociation energy for SO_2F_2 , SO_2ClF and SO_2Cl_2 .^[8,9]

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intended to present an extensive list of SO₂F₂-mediated transformations, but will instead focus on recent advances on

industrially relevant methodologies. A long-standing industrial collaboration led our group to work on sulfuryl fluoride-



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Morgan Donnard obtained his PhD from the École National Supérieure de Chimie de Mulhouse (France) in 2008 under the guidance of Prof. Jacques Eustache. He then joined for two years Prof. Jonathan Clayden's group as postdoctoral fellow at the University of Manchester (UK). After a second post-doctoral stay in Dr. Nicolas Blanchard's group (ENSCMu- France), he joined the CNRS as Research Associate (Chargé de Recherche) in 2012 at the University of Strasbourg (France). He obtained his Habilitation in 2019. His research interests focus on catalysis (organometallic as well as photocatalysis), domino reactions, heterocyclic chemistry (mainly N, Si, O & S) and alkyne/alkene/allene/nitrile transformations.



Armen Panossian carried out his PhD studies under the supervision of Dr. Angela Marinetti at the ICSN (Gif-sur-Yvette, France). In 2009, he moved to the ICIQ (Tarragona, Spain) for a postdoctoral position in the group of Dr. Anton Vidal-Ferran. After one year as temporary assistant professor at the Université Pierre et Marie Curie (Paris, France), he became in 2011 CNRS Research Associate (Chargé de Recherche). He obtained his Habilitation in 2019. His research interests focus on the control of chirality, heavy metal-free methods, the organic chemistry of heteroelements of the main group.



David Bernier completed his PhD in 2006, carried out at the University of Freiburg-im-Breisgau (Germany) under the guidance of Prof. Reinhard Brückner. After a postdoctoral stay with Prof. Simon Woodward at the University of Nottingham (UK) he joined Bayer CropScience in 2008. His research focuses on hit-to-lead optimization of active ingredients for crop protection.



Sergii Pazenok obtained a Ph.D. from the Institute of organic chemistry of National Academy of Science of the Ukraine in Kiewi (Ukraine) under supervision of Prof. L.M Yagupolskii in 1985. After a postdoctoral stay with Prof. D. Naumann at the University of Cologne he joined in 1994 the central research department of Hoechst AG in Frankfurt (Germany) and due to the several acquisitions worked for AgrEvo and Aventis. In 2003, after acquisition of Aventis by Bayer, he moved to Monheim (Germany) as laboratory leader. In 2010 he was nominated as expert and in 2016 became a distinguished science fellow in process research at Bayer Crop Science division. The main focus of his research is the development of chemical processes for fluorine containing intermediates and agrochemicals. He is recipient of Hoechst and Bayer Crop Science Innovation Award and Impact Award.



Frederic Leroux obtained a Ph.D. from the University of Konstanz (Germany) in 1997. After a postdoctoral stay with Prof. M. Schlosser at the University of Lausanne (Switzerland) he became Assistant Professor in 1998. In 2001 he moved then to the Swiss Federal Institute of Technology in Lausanne (EPFL). He joined in 2003 the CNRS as Research Associate and was promoted CNRS Research Director in 2009. The philosophy of his research is based on a fruitful interplay of several objectives (a) the synthesis of biologically relevant molecules, (b) asymmetric methodologies using organic and organometallic chemistry, (c) organofluorine chemistry and (d) application of the objectives to industrial problems, which led to strong industrial collaborations.

mediated reactions as described below. Additionally, some methods developed by other groups and that are the most relevant to the discussion will be presented. The first part will be dedicated to metal-catalyzed transformations of aryl and alkenyl fluorosulfonates, focusing on one-pot methods through the SO_2F_2 -activation and direct transformation of phenol derivatives via metal-catalyzed reactions. In a second part, nucleophilic substitution reactions using *in situ* generated polyfluoroalkyl fluorosulfonates as electrophiles will be detailed.

2. Metal-Catalyzed Transformations of Aryl & Alkenyl Fluorosulfonates

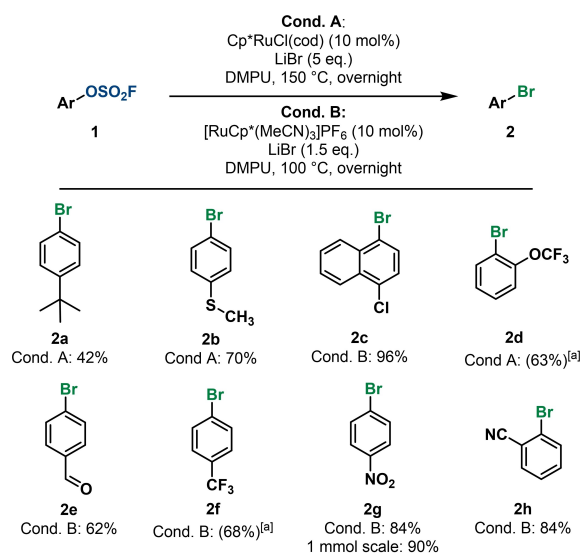
Aryl fluorosulfonates were first described in 1927 by Steinkopf and then in 1930 by Lange and Miller who synthesized them from arene diazonium fluorosulfate salts.^[19,20] Later, the reaction of phenols with sulfuryl chloride fluoride (ClSO_2F) was reported by Coffman and Cramer to access those substrates.^[21] However, these methods led to low to moderate yields and used costly starting materials and hazardous reaction conditions. As an answer to this issue, the use of SO_2F_2 to synthesize aryl fluorosulfonates from phenols was first reported in the 1970s by Firth.^[22,23] These substrates have not been investigated again before the 2010s with reports by Sharpless and Ishii,^[7,24] followed by many other groups since. Aryl fluorosulfonates have been used as aryl triflate surrogates and have been widely adopted and applied in a large variety of subsequent transformations. The synthesis of functionalized aryl moieties from aryl fluorosulfonates is particularly interesting as phenols are readily available and their conversion to fluorosulfonates only requires sulfuryl fluoride and a base with the only formed by-product being a fluoride anion.^[7] In particular, these aryl fluorosulfonates were employed in a wide range of metal-catalyzed transformations. As a matter of fact, palladium-catalyzed cross-couplings were developed, including Stille,^[25] Negishi,^[25–27] Suzuki,^[28–33] Heck,^[28] Sonogashira^[28] and Buchwald-Hartwig^[34,35] coupling reactions as well as Pd- or Ni-catalyzed cyanation.^[36,37] The Ni-catalyzed homocoupling of aryl fluorosulfonates was also reported by Sharpless and co-workers.^[28] Metal-catalyzed reactions involving a CO insertion were also developed using aryl fluorosulfonates as starting materials.^[38–44] Most of these metal-catalyzed transformations have already been discussed in precedent reviews and will not be detailed in this personal account.^[17,18,45] Here we will rather discuss three of the recent methods that have not already been included in the above-mentioned reviews. The one-pot procedures using *in situ* phenol activation and subsequent reaction in a metal-catalyzed transformation will be especially highlighted.

2.1. Synthesis of Aryl Halides

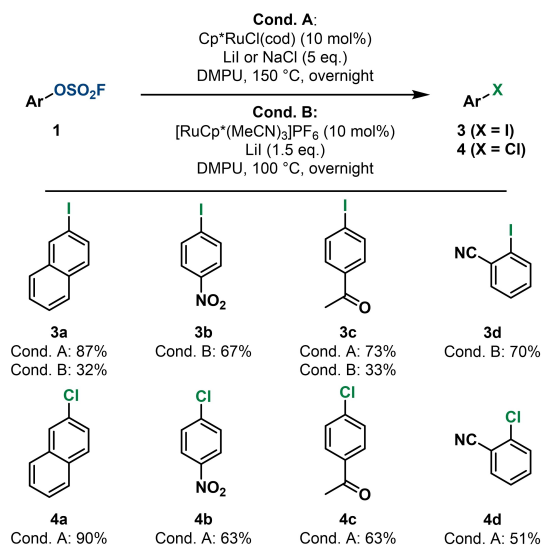
In 2023, our group reported on the ruthenium-catalyzed synthesis of aryl halides from aryl fluorosulfonates.^[46] Aryl halides are key building blocks in organic synthesis that can be used in many subsequent reactions, such as the generation of organometallic reagents^[47,48] or aryl radicals,^[49] which are not commonly accessible from the corresponding sulfonates. As mentioned previously, aryl fluorosulfonates have been involved in a large range of metal-catalyzed processes but no synthesis of aryl halides from aryl fluorosulfonates was reported so far. It is also the first use of ruthenium catalysis with these substrates.

The reaction optimization was conducted for the bromination reaction of aryl fluorosulfonates. Two sets of conditions were developed to maximize the reaction efficiency with both electron-rich and electron-poor aryl fluorosulfonates. The amount of catalyst could be successfully reduced from 20 mol% to 10 mol% with similar efficiency but decreasing it further to 5 mol% led to lower conversion. It should be noted that the ruthenium catalysts used in this work are commercially available to facilitate the broad adoption of this method. Selected examples of the scope are depicted below (Scheme 1). Yields were generally higher starting from electron-poor aryl fluorosulfonates but electron-neutral and even electron-rich ones could also be engaged in this transformation with moderate to good yields using the appropriate set of conditions.

The reaction was extended to the synthesis of aryl iodides and aryl chlorides using lithium iodide (LiI) and sodium chloride (NaCl) as halide sources, respectively (Scheme 2). The



Scheme 1. Selected examples from the substrate scope for the synthesis of aryl bromides. [a] NMR yield determined using bromochloromethane as an internal standard.



Scheme 2. Substrate scope for the synthesis of aryl iodides and chlorides.

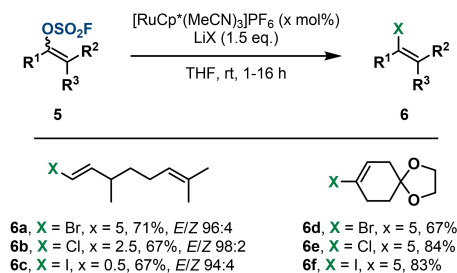
reaction retained a high efficiency for the synthesis of those aryl halides. Here again yields are generally higher with electron-poor substrates but electron-neutral and electron-rich ones are also tolerated leading to moderate to excellent yields. Interestingly, aryl chlorides were not accessible for this same transformation starting from aryl triflates.^[50]

2.2. Synthesis of Alkenyl Halides

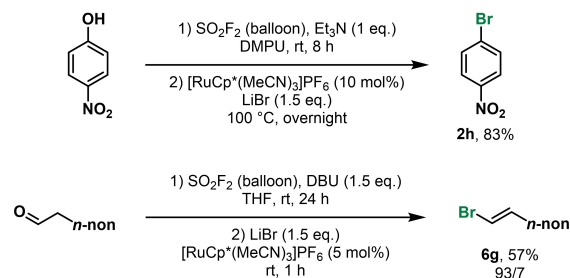
The reaction developed in 2023 by our group for the synthesis of aryl halides from aryl fluorosulfonates was extended to the synthesis of alkenyl halides.^[46] While the formation of aryl fluorosulfonates was already reported in the literature,^[7,13,18,45] the synthesis and use of alkenyl fluorosulfonates have not been widely developed.^[51] The ruthenium-catalyzed halogenation was reoptimized for those specific alkenyl substrates. Starting from the conditions B used for electron-poor aryl fluorosulfonates, the temperature could be decreased to room temperature and the Ru catalyst loading lowered to 5 mol% using tetrahydrofuran (THF) as solvent and LiX as halide sources in all cases (i. e., iodination, bromination, chlorination).

Using these optimized conditions, a set of alkenyl halides were obtained from the corresponding alkenyl fluorosulfonates derived from aldehydes, cyclic ketones and acetophenone (Scheme 3). High *E/Z* selectivity was generally obtained for fluorosulfonates derived from aldehydes, the *E* isomer of the alkenyl halide being the major one even though both the catalyst loading and the reaction time were slightly modified for each case in order to maximize the selectivity.

This transformation is very suitable for one-pot processes, given that the formation of fluorosulfonates only requires a base and sulfonyl fluoride to proceed. Thus, 4-nitrophenol was



Scheme 3. Substrate scope for the synthesis of alkenyl halides.



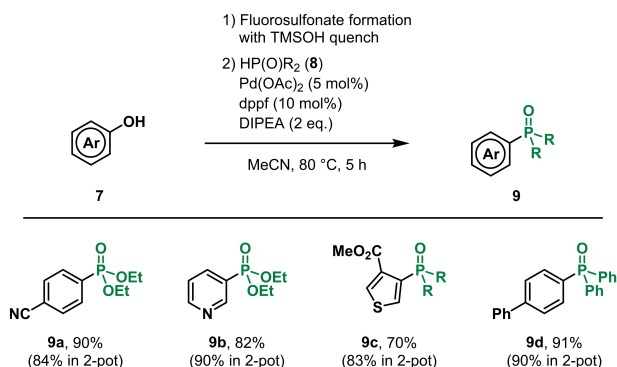
Scheme 4. One-pot fluorosulfonylation-halogenation reactions.

converted into its corresponding aryl bromide **2h** in 83% yield by first forming the fluorosulfonates in *N,N'*-dimethylpropyleneurea (DMPU) and then performing the ruthenium-catalyzed transformation after removing the remaining sulfonyl fluoride. The yield obtained in this one-pot reaction was higher than in two steps, for which the overall yield over the same two steps was 66%. The one-pot reaction was also performed on undecanal, and the desired brominated product was again obtained in a higher yield than when using the two-step protocol (Scheme 4).

2.3. Metal-Catalyzed Phosphorylation Reaction

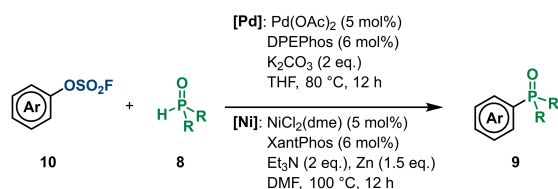
In 2021, three research groups independently reported the metal-catalyzed phosphorylation of aryl fluorosulfonates.^[52–54] Guo, Cai and co-workers reported the Ni-catalyzed coupling of secondary phosphine oxides, dialkyl phosphites and methyl phenylphosphinate with aryl fluorosulfonates using the cheap NiCl₂ catalyst in combination with XantPhos as ligand.^[53] Yields for this transformation were generally good to excellent. However, in this case the telescoped fluorosulfonate formation and coupling reaction was not exemplified.

The same year, Ma, Xu and co-workers reported the palladium-catalyzed phosphorylation of phenols.^[52] First, a two-pot procedure, where the aryl fluorosulfonate was isolated, was tested and gave excellent yields overall (Scheme 5). The authors then tried to apply a one-pot procedure during which the fluorosulfonate would be formed *in situ* and then directly

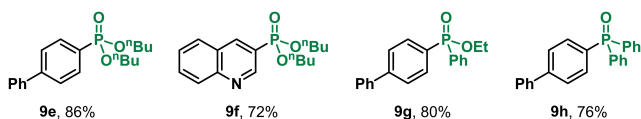
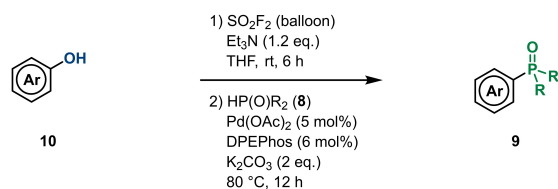


Scheme 5. One-pot Pd-catalyzed phosphorylation reaction of phenols reported by Ma, Xu and co-workers.

Two-pot procedure



One-pot procedure



Scheme 6. Pd- and Ni-catalyzed phosphorylation reaction of phenols reported by Ding and co-workers.

used for the Pd-catalyzed reaction without isolation. However, these conditions gave lower yields which was attributed to the presence of fluoride anion. Trimethylsilanol (TMSOH) was added to the reaction mixture in order to trap the fluoride anion forming the very volatile trimethylfluorosilane (TMSF) which was removed by bubbling argon through the reaction mixture. With this procedure, the one-pot synthesis could deliver the desired phosphorylation products in similar yields to the two-pot protocol, even on gram scale (Scheme 5).

Ding and co-workers independently reported the nickel- and palladium-catalyzed cross-coupling of aryl fluorosulfonates and similar phosphoryl derivatives.^[54] Two sets of conditions were developed, the catalytic systems being either Pd(OAc)₂

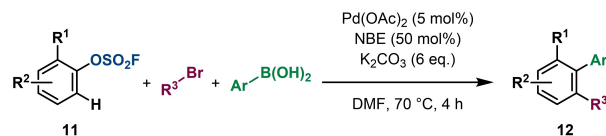
and DPEPhos or NiCl₂(dme) and XantPhos (Scheme 6). Overall, palladium and nickel were similarly efficient in this cross-coupling reaction even if in a few cases nickel showed significantly better yields.

Here again, the reaction could be performed in one pot starting from phenol derivatives with a slight yield loss compared to the phosphorylation step in the two-pot procedure (Scheme 6). Interestingly, it seems that, in this case, the presence of fluoride anions did not affect the cross-coupling reaction efficiency as in Ma and Xu's report.^[52]

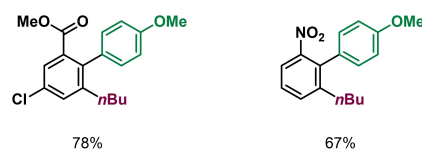
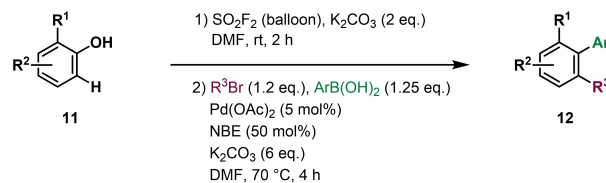
2.4. Catellani Reaction

In 2019, De Borggraeve and co-workers reported the use of aryl fluorosulfonates in Catellani-type reactions with *ortho*-alkylation/*ipso*-arylation.^[55] Using phosphine ligand-free conditions with Pd(OAc)₂ as the catalyst, the authors tested different variations of aryl fluorosulfonates, alkyl halides and aryl boronic acids (Scheme 7). The reaction worked best with aryl fluorosulfonates bearing electron-withdrawing groups. A model aryl fluorosulfonate was compared to the corresponding aryl triflate, mesylate, bromide and iodide. It appeared that the aryl fluorosulfonate and aryl triflate performed equally in this Catellani reaction while the aryl mesylate was recovered unconsumed. On the other hand, the aryl bromide gave a slightly lower yield than the fluorosulfonate while the aryl iodide afforded the desired product in low yield due to the formation of a side product where a second molecule of aryl iodide is coupled in place of the R³ group.

Two-pot procedure



Telescoped Fluorosulfonylation-Catellani reaction



Scheme 7. Catellani reaction starting from aryl fluorosulfonate and one-pot phenol fluorosulfonylation-Catellani reaction.

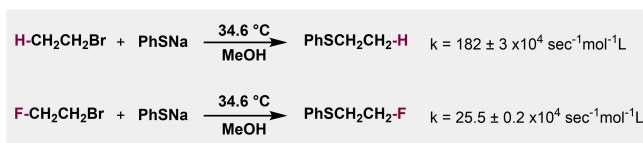
Here also, the fluorosulfonate formation step and the Catellani reaction could be efficiently telescoped (Scheme 7). Thus, it is possible to directly access the product of the Catellani reaction from a phenol derivative in a two-step one-pot procedure.

These examples highlight that the aryl fluorosulfonate formation from phenol and SO_2F_2 followed by a metal-catalyzed reaction in a one-pot process is very efficient and attractive as it usually affords similar yields compared to the two-step process and it is operationally simple.

3. Nucleophilic Substitution on SO_2F_2 -Activated Polyfluoroalkyl Alcohols

SO_2F_2 also reacts with polyfluoroalkyl alcohols of type $\text{R}_f\text{CH}_2\text{OH}$ to form polyfluoroalkyl fluorosulfonates ($\text{R}_f\text{CH}_2\text{OSO}_2\text{F}$) in the presence of an appropriate base. As mentioned above, fluorosulfonates can be seen as rather stable triflate surrogates and therefore be engaged in nucleophilic substitution reactions. In particular, they are of great interest because many polyfluoroalkyl halides are low-boiling compounds, and some of them are classified as ozone-depleting substances (ODS), regulated by the Montreal protocol.^[56] The nucleophilic substitution of polyfluoroalkyl fluorosulfonates was first studied by Shreeve and co-workers in 1984.^[57] However, in her study, amine and alcohol nucleophiles reacted almost exclusively at the sulfur atom of trifluoroethyl fluorosulfonate with S–F bond cleavage. When methanethiol was used as a nucleophile a complex mixture was obtained, with the main components being unreacted fluorosulfonate and methyl 2,2,2-trifluoroethyl sulfide as the product of the nucleophilic substitution in alpha position with regard to the oxygen atom of the fluorosulfonate, i.e., the product of triflate-like reactivity. These first results suggest that when intending to use a polyfluoroalkyl fluorosulfonate as a triflate surrogate, one should beware of the straightforward analogy as reaction at the sulfur atom can also occur. Moreover, regarding polyfluoroalkylation reactions, as reported by Hine and Brader in 1953, the presence of fluorine atoms in alpha position with regard to the electrophilic center significantly decreases the rate of substitution reactions on alkyl halides.^[58] Switching from $\text{CH}_3\text{CH}_2\text{Br}$ to monofluorinated $\text{FCH}_2\text{CH}_2\text{Br}$ the rate constant of the substitution reaction of the alkyl bromide by sodium thiophenolate in MeOH at 34.6°C was already decreased by more than 7-fold (Scheme 8). Therefore *N*-polyfluoroalkylation reactions using polyfluorinated electrophilic species are particularly challenging and thus also of great interest.

Sulfonyl fluoride and fluorinated alcohols are widely available and economically advantageous, whereas the use of triflates usually requires triflic anhydride, which is expensive from an industrial point of view. Alternatively, and as



Scheme 8. Comparison of the reaction rates for the nucleophilic substitution of (fluoro)alkyl bromides by sodium thiophenolate.

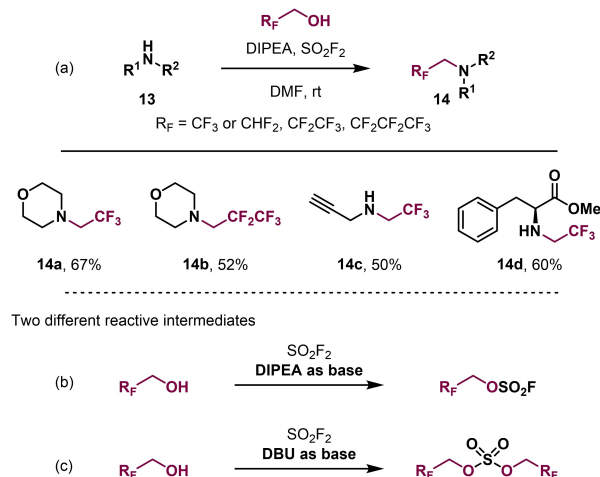
mentioned above, polyfluoroalkyl halides can be used but those are gaseous compounds, of which some are classified as ozone-depleting substances (ODS). It should also be noted that all the processes involving SO_2F_2 described here do not require strictly anhydrous conditions and the exclusion of air is usually not necessary either.

3.1. Amino Group as Nucleophile

3.1.1. *N*-Polyfluoroalkylation of Alkylamines

In 2018, the group of Sammis reported the one-pot *N*-fluoroalkylation of amines using sulfonyl fluoride. This method could be applied to primary, secondary and benzylic amines.^[59] The fluoroalkylated products obtained with this strategy were traditionally made from the corresponding iodides or sulfonates, requiring additional synthetic steps and harsh reaction conditions. The method was applied to polyfluoroalkylation reactions with 2,2,2-trifluoroethanol, 2,2-difluoroethanol, 2,2,3,3,3-pentafluoropropanol and 2,2,3,3-tetrafluoropropanol even though longer reaction times were required when increasing the length of the fluorinated chains (Scheme 9, a).

The reaction between trifluoroethanol and SO_2F_2 or morpholine and SO_2F_2 have similar rate constants as indicated



Scheme 9. *N*-Polyfluoroalkylation of alkylamines.

by React-IR experiments. Therefore, in the standard *N*-polyfluoroalkylation reaction conditions an excess of alcohol (8 eq.) was required to shut down the formation of fluorosulfamide ($-\text{NSO}_2\text{F}$) from the direct reaction of the amino group with SO_2F_2 . Besides trifluoroethyl iodide, trifluoroethyl tosylate or trifluoroethyl mesylate were completely unreactive under their standard reaction conditions, testifying for the interest of using fluorosulfonates. Finally, the authors noted that when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base instead of *N,N*-diisopropylethylamine (DIPEA), no reaction occurred. Indeed, it was shown that bis-(trifluoroethyl)sulfate was exclusively formed and is unreactive toward amine nucleophiles (Scheme 9, b & c). Trifluoroethyl fluorosulfonate was shown to be rather stable in solution and, in particular, could be stored for up to one week as a solution in dichloromethane (DCM). Finally, trifluoroethyl fluorosulfonate appeared to be more stable than trifluoroethyl triflate when exposed to basic aqueous conditions.

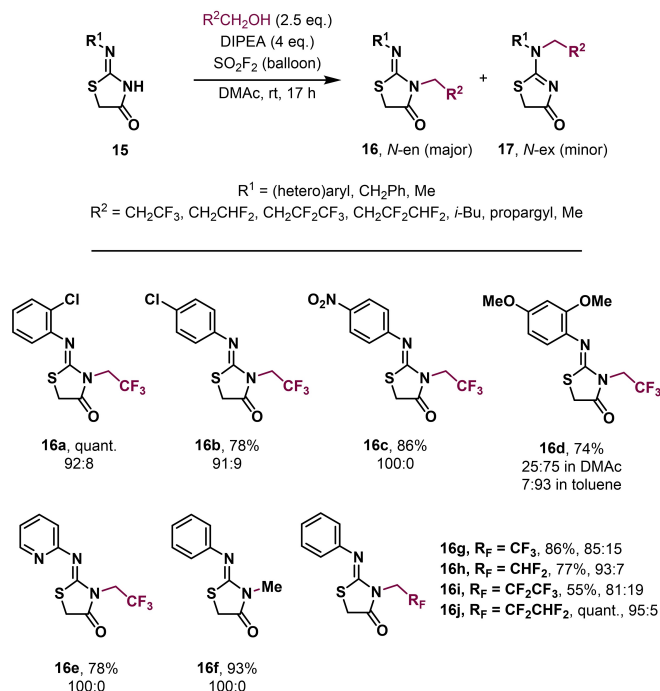
3.1.2. *N*-Polyfluoroalkylation of Imino-Thiazolidinones

The imino-thiazolidinone core is present in diverse biologically active compounds, such as potential anticancer, antimicrobial, anti-inflammatory, anticonvulsant, and hypertensive agents.^[60,61] In 2022, our group reported on the *N*-polyfluoroalkylation of ambident and weakly nucleophilic imino-thiazolidinones via substitution with polyfluoroalkyl fluorosulfonates.^[62]

The main strategy to access imino-thiazolidinones is the use of already *N*-alkylated thiourea synthons which are subsequently reacted with chloroacetyl chloride.^[63,64] However, to introduce diversity on the nitrogen atom in a more efficient manner, a direct *N*-polyfluoroalkylation reaction would be much preferred. We thus focused our attention on the development of a SO_2F_2 -mediated method for the direct *N*-polyfluoroalkylation of imino-thiazolidinones. Because of the poor nucleophilicity of both nitrogen atoms of imino-thiazolidinones, the alkylation was anticipated to be significantly hindered. In addition, the *N*-endocyclic (*N*-en) vs *N*-exocyclic (*N*-ex) polyfluoroalkylation regioselectivity was studied, giving that the substrate exhibits an ambident reactivity.

After optimization of the reaction conditions, the targeted *N*-en regioisomer was predominantly obtained using DIPEA as base in *N,N*-dimethylacetamide (DMAc) at room temperature for 17 hours. Besides, it is important to note that the *N*-en products were always isolated as *Z* diastereomers (Scheme 10).

Interestingly, DBU led to the completion of the reaction in only 2 h with the same *N*-en:*N*-ex ratio. This base had already been investigated to increase the reaction rate of alkyl



Scheme 10. Selected examples for the *N*-polyfluoroalkylation of imino-thiazolidinone derivatives. Isolated yields and *N*-en:*N*-ex ratios are reported. Reproduced from ref. [62] Copyright (2022), with permission from the American Chemical Society (ACS).

fluorosulfonates with diverse nucleophiles as we will show later in this account.^[65] DBU being more expensive and toxic, DIPEA was selected as base for the exploration of the scope. Selected examples are depicted above to highlight the key features and broad applicability of the method (Scheme 10).

First, it is worth mentioning that the regioselectivity of this reaction is mainly controlled by the electronic effects of the substituents on the aromatic ring R^1 attached to the exocyclic nitrogen atom (Scheme 10). It was also brought to light that steric effects have little or no impact on the regioselectivity of the reaction (**16a** vs **16b**). A nitro group in *para* position of the R^1 phenyl ring (Scheme 10, **16c**) afforded exclusively the *N*-en isomer in a good 86% yield, highlighting once more the strong electronic influence of the substituent on the regioselectivity. Contrarily, electron-donating groups such as a methoxy in *ortho* position led to a 36:64 ratio of regioisomers. Adding another methoxy group in *para* position (Scheme 10, **16d**) led to an even greater *N*-ex regioselectivity (25:75). Using this same example, it was shown that switching the solvent from DMAc to toluene led to an increased *N*-ex selectivity with a 7:93 ratio. Electron-poor heterocycles like pyridine as R^1 substituents in **16e** yielded exclusively the *N*-en product in 78% yield. It is also remarkable that *N*-methylation of **15f** was accomplished in excellent yield and with full *N*-endocyclic regioselectivity to afford **16f**. Finally, comparing

examples **16g** to **16h**, we can see that fluorinated chains bearing a CHF₂ group lead to a higher *N*-en selectivity compared to fully fluorinated ones (i. e., CF₃ or CF₂CF₃). This could be due to the ability of the CHF₂ moiety to behave as hydrogen bond donor with the amide thus favoring the alkylation of the endocyclic nitrogen.

This work highlights for the first time that the SO₂F₂-mediated *N*-polyfluoroalkylation of weakly nucleophilic nitrogen-containing compounds could be performed efficiently. Furthermore, the method might be extended to other nucleophiles as we will show in the following parts.

3.1.3. *N*-Polyfluoroalkylation of Sulfonamides

The sulfonamide functional group is commonly encountered in the structure of active ingredients. In a report from 2008, it was found that more than 110 commercialized drugs contain at least one sulfonamide group, such as triafamone and amprenavir, used as herbicide and HIV treatment respectively (Scheme 11, a).^[66] Moreover, the metabolic stability of amino groups attached to electron-withdrawing groups (EWG) is greatly improved compared to their amine or aniline parent compounds.^[67–69] Reported methods for the *N*-polyfluoroalkylation of sulfonamides generally relied on polyfluoroalkyl halides or polyfluoroalkyl sulfonates which typically require an additional step for their synthesis. Therefore, in 2023, our group reported a general method for the SO₂F₂-mediated *N*-

fluoroalkylation of sulfonamides from readily available fluorinated alcohols.^[70]

Our study started by using the poorly nucleophilic saccharin moiety (*N*=10.78 according to Mayr's scale)^[71] as a model substrate for the optimization of the reaction conditions. This optimization mainly focused on the choice of the base, which shows significant effect on the reaction outcome for most SO₂F₂-alkylation processes reported to date.^[59,62,65,72] Whereas DBU was very efficient for the *N*-alkylation of imino-thiazolidinone moieties,^[62] we were surprised to see that the same conditions gave only traces of the desired alkylated saccharin. Replacing DBU by DIPEA and increasing the temperature to 50 °C resulted in a great yield improvement up to 95% with a mixture of *N*- and *O*-polyfluoroalkylation products in a 61:39 ratio. Ultimately inorganic economic bases were tested and K₂CO₃ was selected in this method as it showed higher selectivity for the *N*-alkylation which translates into higher yields in the *N*-polyfluoroalkylation of sulfonamides (Scheme 11, b).

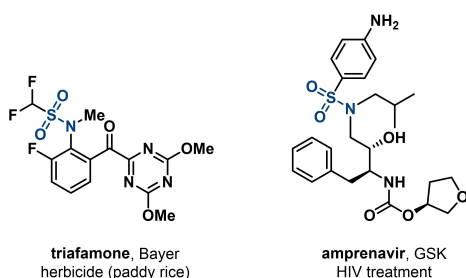
The optimal conditions were then applied to a large scope of sulfonamides (Scheme 12). Modifications on the sulfonyl part were well tolerated with both EDG (electron-donating group)- and EWG-substituted benzenesulfonyl derivatives as well as the mesyl group. On the amino part, the study was mainly focused on aniline derivatives. Here again, a large variety of substituents were tolerated, including EDG, EWG and sterically hindered groups with *ortho* substitution. The scope was extended to various electron-rich heterocyclic amines with good to excellent yields. However, electron-poor heterocyclic amines or sulfonamides derived from alkylamines afforded the expected products in poor yields.

3.1.4. Accessing *N*-Polyfluoroalkyl Anilines from *N*-Polyfluoroalkylated Sulfonamides

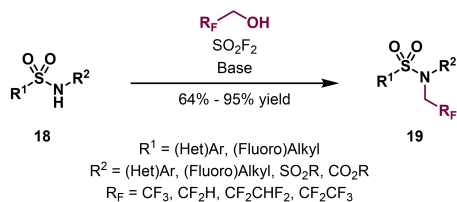
We were then interested to see if the sulfonyl group of sulfonamides could be cleaved to access the corresponding *N*-polyfluoroalkyl anilines starting from *N*-polyfluoroalkylated sulfonamides derived from anilines.^[70] There are already several methods reported to access the latter compounds but, these methods suffer from several limitations such as for example the use of air-sensitive metal catalysts^[73–81] or starting materials that are expensive or even not commercially available.^[82] It would thus be of high interest to access *N*-polyfluoroalkyl anilines from easily synthesized *N*-polyfluoroalkylated sulfonamides.

For this purpose, 4-nitrobenzenesulfonamide substrates were selected as the 4-nitrobenzenesulfonyl (nosyl) group is easily cleaved via S_NAr reaction, under mild reaction conditions. Using thioglycolic acid as a nucleophile and potassium carbonate as base in DMF, *N*-polyfluoroalkyl anilines were efficiently obtained from *N*-polyfluoroalkylated

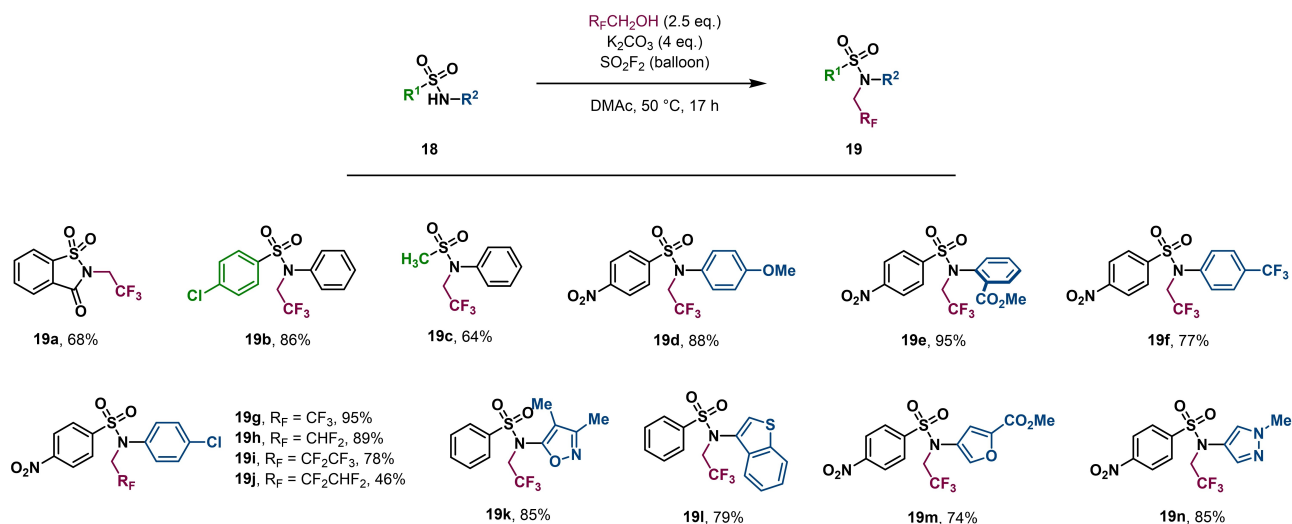
(a) Sulfonamide groups in bioactive compounds



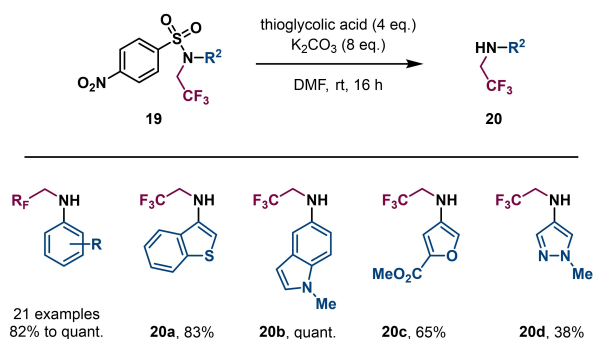
(b) SO₂F₂-mediated polyfluoroalkylation of sulfonamides



Scheme 11. Sulfonamide groups in bioactive compounds (a) and SO₂F₂-mediated *N*-polyfluoroalkylation of sulfonamides (b).



Scheme 12. Selected examples from the scope of *N*-polyfluoroalkylated sulfonamides.



Scheme 13. Selected examples from the scope of *N*-polyfluoroalkylanilines.

sulfonamides. Anilines bearing either electron-donating or electron-withdrawing groups are equally tolerated as well as heterocyclic amines as depicted in Scheme 13.

3.1.5. *N*-Polyfluoroalkylation of *N*-Sulfonyl Carbamates – Access to *N,N*-bis(polyfluoroalkyl)amines

The scope of the *N*-polyfluoroalkylation reaction of sulfonamides was also extended to *N*-sulfonyl carbamates with high yields as depicted below (Scheme 14).^[70]

These compounds were then engaged in a second *N*-polyfluoroalkylation reaction after Boc removal with TFA. This second polyfluoroalkylation was also very efficient and after nosyl cleavage, *N,N*-bis(polyfluoroalkyl)amines could be obtained as hydrochloride salts in high yields (Scheme 14).

3.1.6. *N*-Polyfluoroalkylation of Phthalimide – Accessing Primary Polyfluoroalkylamines

The *N*-polyfluoroalkylation reaction of phthalimide was also disclosed in the same article.^[70] In this case, using DBU as base at room temperature for 30 min was optimal to reach full conversion and high yields (Scheme 15, a).

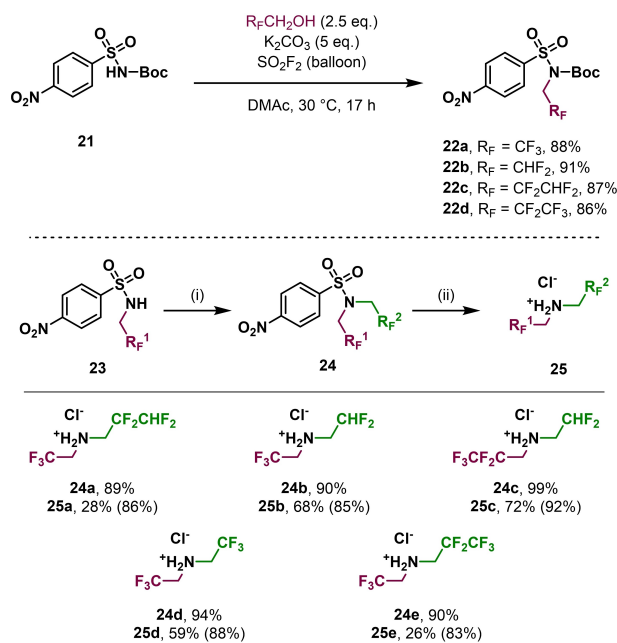
Four different fluorinated alcohols were tested and afforded the products in good to quantitative yields. Phthalimide alkylation mediated by SO_2F_2 was also reported by Sammis and co-workers but using only non-fluorinated alcohols.^[65] However, in their case, the phthalimide was used in excess whereas we used the alcohol in slight excess and phthalimide as limiting reagent. The reaction tolerates various primary and benzylic alcohols but secondary alcohols led to poor results.

Then the phthalimide cleavage was performed with hydrazine hydrate to afford primary polyfluoroalkylamines as hydrochloride salts in excellent to quantitative yields (Scheme 15, b).^[65]

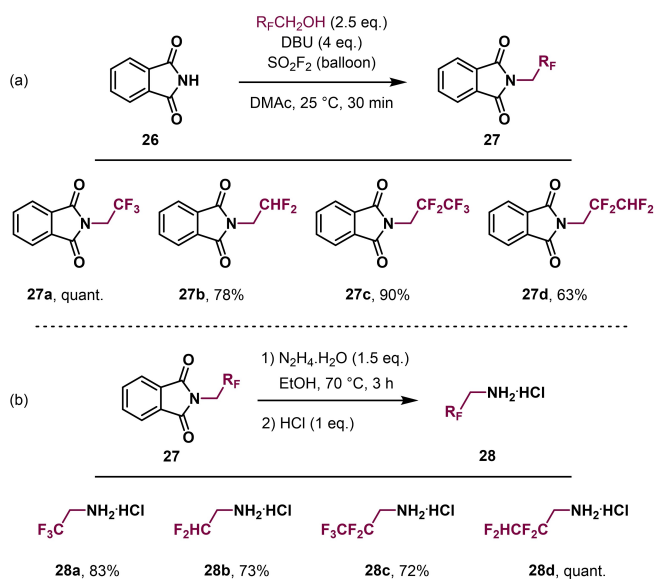
3.2. Thiols & Thiophenols as Nucleophiles

Early reports from Shreeve and co-workers on the polyfluoroalkylation of thiols using trifluoroethyl fluorosulfonates showed that this transformation was not very efficient. Indeed, low conversions were observed, while the thiol nucleophile also reacted on the sulfur atom of the fluorosulfonate, regenerating detectable amounts of the fluoroalkyl alcohol presumably via the S–O bond scission on the trifluoroethyl fluorosulfonate.^[57]

Therefore, in 2019, Sammis and co-workers got interested in this reaction and reported a new SO_2F_2 -mediated polyfluoroalkylation of thiols from simple polyfluorinated alcohols (Scheme 16, a).^[72]

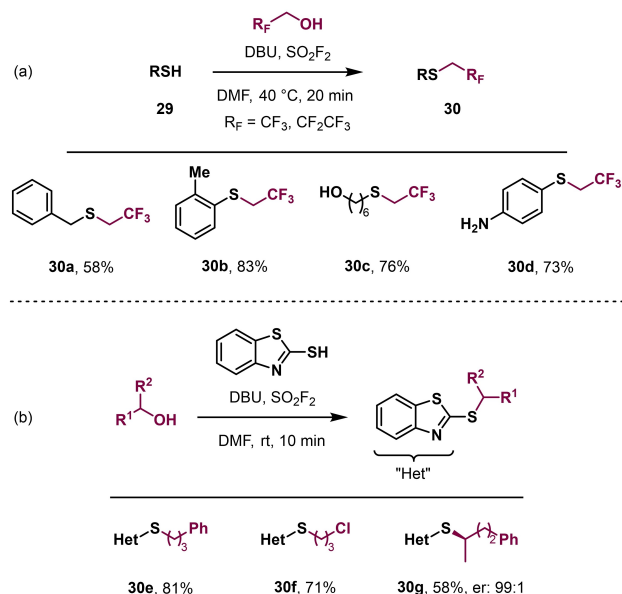


Scheme 14. *N*-Polyfluoroalkylation of *N*-sulfonyl carbamates for the synthesis of *N,N*-bis(polyfluoroalkyl)amines. ¹⁹F NMR yields are given in parentheses. (i) Polyfluoroalkyl alcohol (2.5 eq.), K₂CO₃ (4 eq.), SO₂F₂ (balloon), DMAc, 50 °C, 3 h. (ii) Thioglycolic acid (4 eq.), K₂CO₃ (8 eq.), DMF, rt., 16 h. The HCl salts were obtained after a liquid-liquid extraction followed by treatment of the ethereal phase with a HCl solution in diethyl ether.



Scheme 15. Scope for the phthalimide *N*-polyfluoroalkylation and cleavage yielding primary *N*-polyfluoroalkylamines.

They discovered that when using DBU as a base during the alcohol activation with SO₂F₂, a bis(polyfluoroalkyl) sulfate reagent was formed instead of the polyfluoroalkyl fluorosulfo-

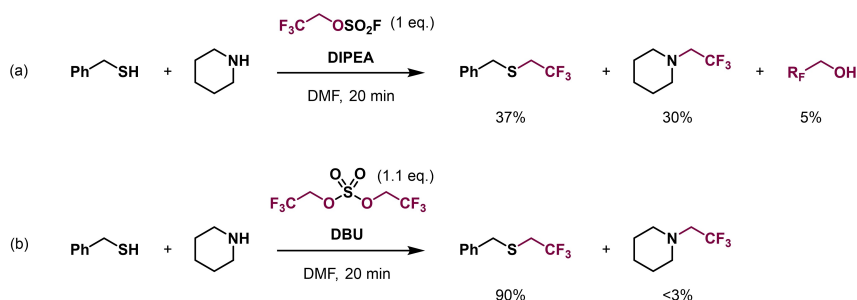


Scheme 16. Selected examples of the *S*-(polyfluoro)alkylation of thiols, thiophenols and benzothiazole thiols.

nate reported in all other SO₂F₂-mediated polyfluoroalkylation reactions published at the time (see Scheme 9, c). This reagent exhibits singular reactivity compared to the fluorosulfonate. The bis(polyfluoroalkyl) sulfate was shown to react very selectively with thiols in the presence of other nucleophilic functional groups such as alcohol, carboxylic acid, pyridine, aniline and alkylamine. Moreover, yields are greatly improved for the alkylation of thiols compared to previous reports using a fluorosulfonate.^[57] Last, the reaction is not sensitive to steric hindrance nor electronic effects in the case of thiophenol derivatives and works well in a large variety of solvents.

Competition experiments illustrate this strong selectivity of this new reagent toward sulfur alkylation, while polyfluoroalkyl fluorosulfonate is not selective (Scheme 17).

In 2020, Sammis and co-workers also reported the SO₂F₂-mediated alkylation of benzothiazole thiol (Scheme 16, b).^[65] This work differs from the one described above by the fact that here, the alcohol is used as limiting reagent and only non-fluorinated alcohols were tested. In this case, even secondary alcohols were tolerated and enantiopure alcohols could be inverted to sulfides with almost no erosion of the enantiomeric ratio. Alkylation using non-fluorinated alcohols could also be applied to thiophenols or 1-phenyltetrazole-5-thiol as nucleophiles. These were the first examples of a polyfluoroalkylation process based on a bis(polyfluoroalkyl) sulfate as alkylating agent. Here again, the one-pot SO₂F₂-mediated polyfluoroalkylation process shows outstanding practicability, efficiency and robustness.



Scheme 17. Competing experiments between a thiol and an amine as nucleophiles using trifluoroethyl fluorosulfonate (a) and bis(trifluoroethyl) sulfate (b) as electrophilic species.

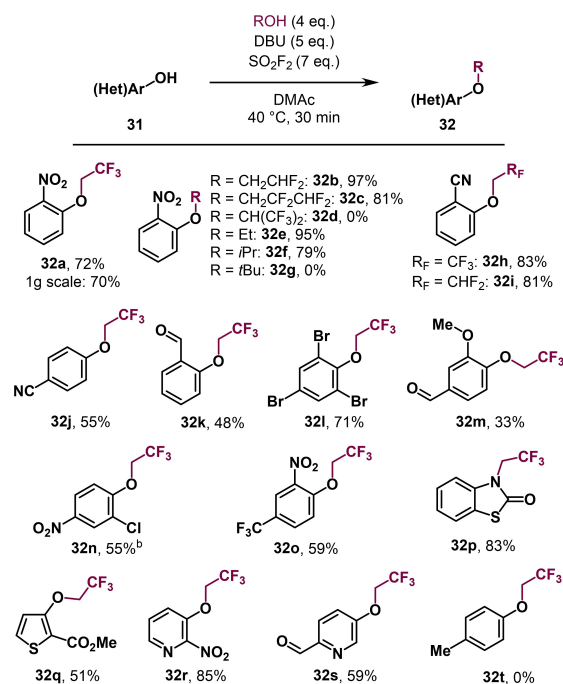
3.3. Phenols as Nucleophiles

Very recently, our group reported on the SO_2F_2 -mediated synthesis of polyfluoroalkyl aryl ethers from fluorinated alcohols.^[83] While most previously reported, processes for the polyfluoroalkylation of phenols require harsh conditions (high temperature, strong base, metal catalyst), the present method involves mild conditions and a short reaction time (30 min). There was only one example of SO_2F_2 -mediated alkylation of a phenol reported by Sammis and co-workers, using a non-fluorinated alcohol.^[65] Applying these conditions to the model substrate *o*-nitrophenol with trifluoroethanol as alkylating agent led to a low conversion. The reaction conditions were optimized by tuning the number of equivalents of each reagent and increasing the temperature to 40 °C. Moreover, the fluorinated alcohol and the base (DBU) were added slowly via a syringe pump while SO_2F_2 was regularly added over the reaction time (Scheme 18).

Different fluorinated alcohols could be used as well as a variety of EWG-substituted phenol substrates. Phenols that are too electronically enriched react preferentially with sulfonyl fluoride leading mainly to the formation of the aryl fluorosulfonate. Non-fluorinated alcohols were also well tolerated with a 95% yield using EtOH and most impressively 79% yield from a secondary alcohol, namely isopropanol. As one could expect, no product was formed from *tert*-butanol. Finally, the reaction could also be scaled up to 1 g without significant yield drop.

3.4. Carbon Nucleophiles

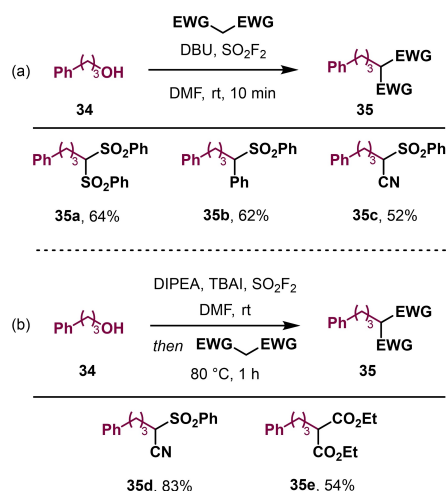
The use of *C*-nucleophiles in SO_2F_2 -mediated alkylation reactions is much less established than for the other nucleophiles presented above, and only a few examples are known to date. As previously mentioned, in 2020, Sammis and co-workers published the SO_2F_2 -mediated substitution of aliphatic alcohols with various nucleophiles.^[65] Among them, a few carbon nucleophiles were found to be compatible



Scheme 18. Selected examples of the *O*-polyfluoroalkylation of phenols.

substrates. Using the same conditions that were applied to phthalimide and benzothiazole thiol in this same report, three activated-methylene compounds were alkylated in moderate yields (Scheme 19, a).

In 2021, Sammis and co-workers reported an improved scope, including those *C*-nucleophiles, for the one-pot SO_2F_2 -mediated activation and substitution of alcohols (Scheme 19, b).^[84] For this purpose, the formed fluorosulfonate was converted *in situ* to a corresponding alkyl halide with TBAX, and consecutively reacted with the appropriate nucleophile. The conversion of the fluorosulfonate was fast (within 12 min) and allowed to overcome the limitations associated with the limited stability of non-fluorinated alkyl fluorosulfonates.



Scheme 19. SO_2F_2 -mediated C-alkylation of activated methylene-type nucleophiles.

Under these conditions, improved yields could be obtained with C-nucleophilic substrates that were already alkylated with alkyl fluorosulfonates in the standard procedure. Diethyl malonate which was unsuccessful with the previous method could be alkylated in 54% yield whereas compound **35d** was obtained in a good 83% compared to the 52% yield with the previous method.

However, at the present time, the scope of C-nucleophiles in alkylations by fluorosulfonates remains extremely limited.

4. Summary and Outlook

In this account we have discussed recently developed methods using activation by sulfonyl fluoride. Even if sulfonyl fluoride is a toxic gas, it has the strong advantage to be non-flammable and non-corrosive. In our research work in collaboration with Bayer we seek robust, safe, scalable and economical methodologies. The activation of widely available alcohols or phenols by means of SO_2F_2 fulfills these criteria while these reactions can generally be achieved in one pot with yields comparable to those of the two-pot processes. In view of the wide availability of phenols, the use of aryl fluorosulfonates in metal-catalyzed reactions is highly advantageous. Regarding polyfluoroalkylation reactions described above, fluorosulfonates are an attractive alternative to triflates, that are too expensive in an industrial setting, but also to polyfluoroalkyl halides, several of which are classified as ozone-depleting substances (ODS). Moreover, except for the metal-catalyzed transformations, most of the methodologies described in this account do not require the use of strictly anhydrous solvents nor the exclusion of air from the system. As shown in this account, the use of aryl fluorosulfonates in various chemical transformations, as well as N-, O- and S- (polyfluoro)alkylation reactions have

been growing very fast in the last few years. Furthermore, fluorosulfonates are versatile reagents that can be involved in a large variety of reactions. However, the reaction of SO_2F_2 -activated (polyfluoro)alkyl alcohols with most C-nucleophiles remains a challenge that should be addressed in the future. Metal-catalyzed transformations of alkenyl fluorosulfonates are also underdeveloped and could open access to numerous highly valuable products. Finally, for transformations of both aryl and alkenyl fluorosulfonates, catalysts based on non-precious metals are highly desirable while most reported methods to date involve the use of palladium catalysts.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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PERSONAL ACCOUNT



One-pot reaction with
two nucleophiles

Atom economic &
Low waste generation

Economical & Industrially
relevant transformations

A long-standing industrial collaboration in our research group drove our work on the sulfonyl fluoride-mediated transformations. Recent work on metal-catalyzed

transformations of aryl fluorosulfonates and nucleophilic substitution reactions on (polyfluoro)alkyl alcohols are discussed in this personal account.

*F. Audet, Dr. M. Donnard, Dr. A. Panossian, Dr. D. Bernier, Dr. S. Pazenok, Dr. F. R. Leroux**

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**New Chemical Transformations
Involving SO₂F₂-Mediated Alcohol
Activation**