SuFEx-Enabled, Chemoselective Synthesis of Triflates, Triflamides and Triflimidates


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Abstract: Sulfur(VI) Fluoride Exchange (SuFEx) chemistry has emerged as a next-generation click reaction, designed to assemble functional molecules quickly and modularly. Here, we report the ex situ generation of trifluoromethanesulfonyl fluoride (CF$_3$SO$_2$F) gas in a two chamber system, and its use as a new SuFEx handle to efficiently synthesize triflates and triflamides. This broadly tolerated protocol lends itself to peptide modification or to telescoping into coupling reactions. Moreover, redesigning the SVI–F connector with a S=O → S=NR replacement furnished the analogous triflimidoyl fluorides as SuFEx electrophiles, which were engaged in the synthesis of rarely reported triflimidate esters. Notably, experiments showed H$_2$O to be the key towards achieving chemoselective trifluoromethanesulfonation of phenols vs. amine groups, a phenomenon best explained—using ab initio metadynamics simulations—by a hydrogen bonded termolecular transition state for the CF$_3$SO$_2$F triflylation of amines.

Recent interest in high-valent sulfur species has brought about an increasing number of SVI−F bond-containing connective hubs. In the framework of Sulfur(VI)−Fluoride Exchange (SuFEx) chemistry—an umbrella term for substitution events replacing fluoride at the electrophilic sulfur center—these ‘molecular plugins’ allow selective and efficient installation of linkages around the SVI core. Especially in the last seven years, various research groups have demonstrated the potential of SuFEx hubs such as sulfonyl fluorides (R−SO$_2$F), sulfuryl fluoride (SO$_2$F$_2$), thionyl tetrafluoride (SOF$_4$), ethenesulfonyl fluoride (ESF, CH$_2$=CH−SO$_2$F), and others.[5] The chemoselective and straightforward nature of SuFEx chemistry has enabled a range of applications in synthesis and materials.[5]

A particularly intriguing aspect of SuFEx chemistry is its ability to activate oxygen nucleophiles. Various OH-containing materials of different acidities and nucleophilicities have been shown to react cleanly at the sulfur center, and subsequently transform them into useful electrophiles for further derivatization. For example, through SO$_2$F-containing reagents, aliphatic alcohols have been converted into alkyl fluorides,[7] thiocarbonyl tetrafluoride (SOF$_4$),[8] ethenesulfonyl fluoride (ESF, CH$_2$=CH−SO$_2$F),[9, 4] and others.[10] The chemoselective and straightforward nature of SuFEx chemistry has enabled a range of applications in synthesis and materials.[10]

By far, the most commonly employed category of O-based pseudohalides consists of aryl triflates. Apart from being a useful substitute for Cl or Br in transition metal catalysis, the OTf group exhibits some unique properties that allow transformations otherwise not possible for the regular halides.[13, 14, 15, 16, 17, 18] Historically, the preparation of aryl triflates is most commonly performed with triflic anhydride (Tf$_2$O) or trifluryl chloride (TICI), reacting with the corresponding phenol in the presence of an acid scavenger.[19] However, the high moisture sensitivity of these fuming liquids typically demands inert and controlled conditions. Also, their high reactivity is a frequent cause of product mixtures, especially for more complex phenols, which require further
chromatographic separation. A number of nitrogen-based triflyl group (Tf or [SO₂CF₃]) transfer agents have been proposed, such as triflylimidazole (TfIm),[21] phenyl triflimide (PhNTf₂)[22] or Comins’ reagent N-(5-chloro-2-pyridyl)triflimide (Scheme 1B).[23] Although benefiting from higher stability and a milder reactivity pattern, these reagents come at an increased cost, and contain high-molecular-weight leaving groups which need post-reactive separation from the product. A broadly applicable protocol that uses an inexpensive and atom-economic precursor to introduce the trifluoromethanesulfonyl moiety in a chromatography-free and late-stage fashion, is still missing from the toolbox.

Herein, we set out to investigate whether SuFEx chemistry can provide this general way of [SO₂CF₃] transfer onto complex organic molecules. Building on our previous work on sulfuryl fluoride, and the resulting gas serves as the electrolytic fluorination of methanesulfonic acid or precursor to all other [CF₃SO₂]-containing bulk chemicals such as TFOH or Tf₂O.[26] Other authors have prepared triflyl fluoride on a precursor to all other [CF₃SO₂]-containing bulk chemicals such as TFOH or Tf₂O.[26] Other authors have prepared triflyl fluoride on a two-chamber reactor technology. We explore the S¹⁻F exchange reaction with phenols, and show that in almost every case, CF₃SO₂F is more functional-group tolerant and effective than existing triflation methods. Other nucleophiles such as carboxylic acids and amines reacted smoothly with the gas under dry conditions, identifying water as a key additive to obtain complete chemoselectivity for aromatic alcohols (Scheme 1C). Conveniently, the generated aryl triflates can engage in cross-coupling chemistry in the same reaction medium, without intermediate handlings. In addition, we report a general synthesis of aryl trifluoromethanesulfinimidate (triflimidate) esters: the trajectory of amines as a model nucleophile, gaining fundamental insight into the key interactions of the SuFEx transition state.

Results and discussion

Triflly fluoride gas was first reported in 1956 by Gramstad for the synthesis of trifluoromethanesulfonic acid derivatives.[24] This smallest perfluorooalkanesulfonyl fluoride is gaseous above –25 °C, and its atmospheric chemistry is relatively innocuous.[25] The most relevant industrial preparation consists of the electrolytic fluorination of methanesulfonic acid or methanesulfonyl fluoride, and the resulting gas serves as the precursor to all other [CF₃SO₂]-containing bulk chemicals such as TFOH or Tf₂O.[26] Other authors have prepared triflyl fluoride on a semibulk scale, by reacting CF₃SO₂O⁻[27, 28] or Tf₉O⁻[28] with a fluoride source.[29] Recently, Pees and coworkers have developed CF₃SO₂⁻[19]F as a carrier gas for nucleophilic [19]F⁻-fluoride, evolving it from PhNTf₂ as a precursor.[30]

We envisaged the generation of CF₃SO₂F in a two-chamber reactor as the most convenient way to employ this gas safely on lab scale.[31] Inspired by the aforementioned results, we set out to develop a CF₃SO₂F gas generation method using PhNTf₂ as a bench-stable and easily handled solid precursor (for optimization, see SI). To our delight, the final reaction conditions allowed conversion of the model substrate 4-fluoro-4’-hydroxybiphenyl into product 1 in 85% yield after 4 hours at room temperature (Scheme 2A). With optimized conditions of method A in hand, a variety of readily accessible phenol derivatives was examined to further explore the scope of this methodology (Scheme 2). First, monosubstituted electron-rich and deficient phenols were successfully transformed into their corresponding triflates (2–8). Sterically hindered triflates 8, 12 and 27 were also formed efficiently. Although ¹⁹F NMR monitoring of catechols showed a high degree of ditriflation at the reaction onset, they nevertheless converged to the monotriflates (14 and 16) after longer reaction times, mostly likely due to subsequent hydrolysis (see SI section 5.1). With a few experimental adaptations and shorter reaction times, however, it was possible to get the less stable ditriflates 15 and 17 in a fair isolated yield. The triflation of two L-tyrosine derivatives not only offered corresponding products in excellent yields (24 and 25), but also without loss of enantiopurity (25). When it comes to naturally occurring phenols, all afforded the corresponding monotriflates in good to excellent yields (4, 9, 10, 19, 20, 26, 27 and 29). In addition, three heteroaryl triflates were obtained in good to excellent yields (21, 22 and 23). It is worth pointing out that in many cases, the two-chamber reactor method afforded the triflates in sufficiently pure form after extractive work-up, without the need for column chromatography.

In parallel to this method, a different set of conditions was developed using Tf₂O as the gas precursor,[28] a less expensive and commonly available chemical (method B). Even though good results were obtained for simple phenols (1), the unpleasant nature of this fuming and sensitive liquid, and the reduced yields for more complex phenols (3, 8, 9 and 18) make this method less ideal. Next, in order to further assess the validity of CF₃SO₂F as a triflating agent, our method was benchmarked against other known triflation methods (for details, see SI). Four representative phenols were treated according to three literature triflation protocols: adding Tf₂O to a solution of phenol and organic base (method C),[52] adding Tf₂O under Frantz’ aqueous conditions (method D) and using the PhNTf₂ reagent directly (method E).[34] Even though the gas-free methods required a shorter reaction time, the corresponding triflates were almost universally obtained in lower yield than with CF₃SO₂F. Not only did the literature methods require more careful temperature control or moisture exclusion, also the chemoselectivity was usually inferior when the phenol starting materials contained indoles (19), aliphatic amines (24 and 28), carboxylic acids (25) or aliphatic alcohols (27). Moreover, amine 28 did not show any trace of sulfonamide formation, even with 2.5 equivalents of gas (see SI section 5.1). To sum up, our CF₃SO₂F gas-based two-chamber system allowed triflation to proceed in a stable, productive and chemoselective fashion.

Recognizing that many of these ‘untouched’ functional groups are prevalent in biomolecules, we tried to establish whether method A is also suitable for triflating amino acids and peptides containing aromatic hydroxyl groups. Tailoring the reactive system to more physiologically relevant conditions, the triflation of L-tyrosine was tested on a 4 μmol scale in organic solvent/buffer mixtures. After modifying and optimizing the conditions (see SI), L-tyrosine (30), Leu-enkephalin (31) and endomorphin-1 (32) underwent triflation in good to excellent conversion (average over two runs, Scheme 2F).
Scheme 2. Synthesis of aryl triflates through ex situ generation of CF₃SO₂F gas in a two-chamber reactor. Unless stated otherwise, method A was used. Generation chamber: N-phenyltrifluoromethanesulfonimide (PhNTf₂, 1.5 equiv.), KHF₂ (1.0 equiv.) and MeCN (0.86 M, 1.75 mL) at room temperature. Reaction chamber: (hetero)aryl alcohol (1.0 mmol, 1.0 equiv.), N,N-diisopropylethylamine (DIPEA, 1.5 equiv.) in 3.0 mL of MeCN and 1.0 mL of H₂O. Reaction details see SI. Isolated yield after column chromatography unless stated otherwise. Between brackets is given the ¹⁹F NMR yield using PhCF₃ as internal standard, between parentheses the reaction time. [a] Isolated yield after aqueous work-up. [b] 2.5 equiv. of DIPEA were used in the reaction chamber. [c] 3 mL MeCN was used in the reaction chamber as solvent, and the crude reaction mixture was purified on silica directly without aqueous work-up. [d] 2.5 equiv. of PhNTf₂ and 1.67 equivalents of KHF₂ were used in the generation chamber. [e] The reaction was set under Argon atmosphere. [f] Et₃N (3.5 equiv.) and DMSO (0.25 M, 4.0 mL) were used in the reaction chamber. [g] The corresponding boronic acid was used as the starting material, and protected afterwards with pinacol. [h] Yield corresponds to product isolated as an HCl salt. [i] The assay yield is reported (average over two runs), defined by dividing the [M+132] peak area by the total AUC of the HPLC-MS TIC chromatogram.

During the development of this work, it was observed that the aryl triflate synthesis was relatively insensitive towards the choice of solvent or base. To further showcase the versatility of this SuFEx reaction, a series of solvent-base combinations was explored (Scheme 2G). While maintaining the original gas generation using PhNTf₂, a set of 7 bases (organic and inorganic...
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was screened against a set of 6 commonly used reaction solvents. In almost all cases, the reactions had reached >50% conversion after 20 h, and the majority even >80% under unoptimized conditions. While some of the stronger bases were more prone to cause product degradation, nevertheless this broad compatibility enables a subsequent reaction step without intermediate ArOTf isolation.

Given the variety of allowed solvent/base combinations, we wondered whether the triflation method can reach further synthetic utility in a one-pot Suzuki-Miyaura cross-coupling reaction. Based on a literature protocol, we found that the (hetero)aryl triflates underwent efficient cross-coupling by transferring the reaction mixture to a vial with the (hetero)aryl boronic acid, palladium(II) acetate and tricyclohexylphosphine (Scheme 3A). With this protocol, biaryls 33–37 were synthesized under mild conditions with good to near-quantitative isolated yield over two steps. The more challenging bipyridine 35 was prepared in a 1,4-dioxane/H2O mixture in 63% yield, which was higher than the 42% yield reported in literature. In addition, this Suzuki cross-coupling afforded 2-methyl-5-(3-fluoro phenyl) pyridine 36, the pharmacophore of vorapaxar in 80% yield without purifying the intermediate triflate.

Another class of oxygen nucleophiles that was subjected to CF3SO2F-enforced post-transformations, consists of carboxylic acids. In line with Moses and Qin work on SuFEx-mediated carboxylic acid activation, we aimed to develop a new method based on generating acyl fluoride intermediates via CF3SO2F gas (Scheme 3B). Without isolating the acyl fluorides, they were reacted immediately to build amides with various degrees of steric congestion. Where the biphasic conditions developed in Scheme 2A left carboxylic acids untouched (products 7 and 25), simply shifting to a pure organic solvent led to smooth deoxofluorination. To explore the substrate scope and functional group tolerance of the amidation process, a variety of aromatic and aliphatic carboxylic acids were examined for coupling with different kinds of amines, including anilines, primary and secondary alkanamines and azoles. All coupling reactions proceeded in fair to excellent yields (Scheme 3, 38–44). This work could be extended to peptide formation, and dipeptide 45 was obtained in 98% isolated yield, while retaining 84% of its enantiopurity. Especially noteworthy is the procedure’s tolerance of bulky coupling partners, a known feature of acyl fluorides.

After investigating the chemistry of CF3SO2F with oxygen nucleophiles, we were curious to see whether S=N analogs uphold the same substitution reactions. By replacing a single oxo-group with a substituted nitrogen in the SF3L hub, trifluoromethanesulfonimidoyl (triflimidoyl) fluorides are obtained. These chiral molecules are characterized by a milder electrophilicity compared to CF3SO2F, due to the increased electron density around the sulfur atom. Since the first description of triflimidoyl fluorides in 2002, the recent report by Oehrich and co-workers is the only example of triflimidoyl fluorides reacting with phenols to form trifluoromethanesulfonimidate (triflimidate) esters. Given that only two examples were made under strongly basic conditions, we surmised that an improved synthesis under mild SuFEx conditions should be possible. We synthesized three different triflimidoyl fluoride compounds containing N-aryl or N-alkyl substituents (for preparation, see SI). These electrophiles were engaged in SuFEx reactions with various phenols to generate a small library of triflimidate esters. The N-aryl substituted triflimidoyl fluorides reacted efficiently under mild conditions to afford the corresponding products in moderate to excellent yields (Scheme 4, 46–51). The N-alkyl counterparts, which are less electrophilic, required DBU as a stronger base and an elevated reaction temperature of 50 °C. Naturally occurring phenols such as vanillin, eugenol, L-tyrosine methyl ester, raspberry ketone, as well as sterically hindered 2-bromophenol and thiophen-2-ol were all well tolerated (Scheme 4).

After the transformation of various oxygen nucleophiles into reactive handles with CF3SO2F, we also wanted to investigate nitrogen nucleophiles. To this end, a range of aliphatic amines, anilines and azoles was engaged in a triflylation reaction to form the trifluoromethanesulfonamides (triflamides) (Scheme 5). Based on a literature SuFEx reaction between SO2F2 and secondary amines, we selected DMAP as a stoichiometric base, although we found later that Et3N furnishes the same products in equal reaction times and yields. Dry MeCN served as the solvent.
Under these conditions, secondary amines (55−60, 62) reacted efficiently to form the tertiary sulfonamides. Also, primary amines (61, 63−65) were suitable reaction partners to form N-monosubstituted triflamides, an interesting contrast with monosubstituted sulfamoyl fluorides, which cannot be formed under basic conditions.[2a] Finally, except for a few unsuccessful substrates (see SI section 7.7), various N-triflyl heterocycles were prepared in the same manner in fair to good yields (66−70). It is worth noting that the N,O-bis(trifluoromethanesulfonyl) compound 60 was formed in high yield using 2.5 equivalents of the generated gas. This stands in contrast to the reaction leading to 28, where no trace of N-triflyl product was observed. The same discrepancy was observed for 70 vs. 19. It was also verified that N-triflyl compounds 60 and 70 were not hydrolyzed by water (see SI section 5.3, 5.4). Since the only difference between these reaction conditions is the presence or absence of water, it seems that water influences the mechanism in such a way that it plays a decisive role in the reaction outcome.

Having established a robust procedure for installing a triflyl group through our CF₃SO₂F SuFEx hub, we turned towards the mechanism of this reaction. More specifically, we investigated the base-mediated triflylation of secondary amines, aiming to elucidate the reaction pathway and the specific role of the base. As a result, we hope to shed light on the observed chemoselectivity, by comparing our simulations for secondary amines with the better-studied mechanism of phenol SuFEx reactions.[40, 42] To achieve this goal, we use ab initio metadynamics (AIMD) to retrieve the mechanism as well as quantify the associated activation barriers.[43] In contrast to static DFT computations, AIMD usually includes all molecules in the simulation box, meaning explicit interactions between reactants and additives or solvents are accurately modeled, with the tradeoff of a significant increase in computational workload (for theoretical background, see SI section 8.1). We, among others, have previously shown the ability of AIMD to elucidate reaction mechanisms, quantify reaction barriers and unveil solvation effects.[44]
Here, piperidine served as a case study for the computationally modeled CF$_3$SO$_2$F triflylation reaction (Figure 1A). In parallel, a series of experimental studies was performed, to complement the in silico findings (Figure 1B). Initially, three different systems were considered. A single CF$_3$SO$_2$F and one piperidine molecule were placed in the simulation box together with explicit acetonitrile (I), or with DMAP (II) or Et$_3$N (III) included as a base (Figure 1A). All simulations in this study followed the Born-Oppenheimer molecular dynamics scheme at the DFT level of theory, with the GGA PBE functional and DZVP-MOLOPT-GTH plane wave basis set. Additionally, the description of long-range dispersion interactions was improved by Grimme’s D3 dispersion correction. The CP2K code (version 6.1) was used together with the Quickstep implementation (for full computational details see SI section 8.1).

From analyzing the trajectory obtained for the non-activated CF$_3$SO$_2$F triflylation of piperidine (I), a concerted bimolecular reaction mechanism was observed, akin to an S$_2$2-type pathway...
(see Supplementary Movie). Indeed, bond length analysis shows a simultaneous S–F bond breaking and S–N\textsubscript{NP} bond formation (see SI section 8.1) and the free energy surface displays a reactant and product phase, without an additional intermediate basin (Figure 1A, I). Notably, without a base, the piperidine nucleophile attacks the sulfur-center from the frontside, which for most S\textsubscript{NP}2 reactions would be less favorable compared to the corresponding backside pathway.[49] Herein, frontside attack allows F\textsuperscript{−} to directly scavenge the amine hydrogen of piperidine.

While this mechanism coincides with the findings of Luy and Tonner, the AIMD simulations result in a Helmholtz free energy of activation (\(\Delta F^\ddagger\)) of 29 ± 4 kcal mol\(^{-1}\), which exceeds a barrier that can readily be crossed at ambient conditions.[42] As the non-activated triflylation of 55 yielded 49% of product at room temperature after 18 hours (Figure 1B, entry 1), the obtained high activation barrier raises questions on the validity of this mechanism. When adding a base such as DMAP (A, II) or Et\textsubscript{3}N (A, III) to the simulation box, a significantly reduced \(\Delta F^\ddagger\) is observed (13 ± 1 kcal mol\(^{-1}\) and 22.1 ± 0.05 kcal mol\(^{-1}\), respectively, Figure 1A). These activation barriers are reasonable, given the high experimental yields obtained for the base-mediated triflylation of 55 (entries 2–3). Mechanistically, the reaction occurs concerted when DMAP or Et\textsubscript{3}N are used, similar to the non-activated CF\textsubscript{3}SO\textsubscript{2}F-triflylation of piperidine. (see SI section 8.1, and Supplementary Movie). Moreover, the trajectory indicates that the base forms a Lewis adduct with piperidine through a hydrogen bond, enhancing the nucleophilicity of N\textsubscript{NP}. Collectively, these observations indicate that the transition state has a termolecular nature, meaning the reaction follows an S\textsubscript{NP}3-type pathway. While initially these findings might seem surprising, such S\textsubscript{NP}3 pathways have previously been proposed as mechanisms for substitution reactions on sulfonyl substrates.[50] Moreover, when the reaction is activated by DMAP or Et\textsubscript{3}N, backside attack of the nucleophile is preferred.

Another intriguing observation was the difference between \(\Delta F^\ddagger\) of the DMAP and Et\textsubscript{3}N activated triflylation. One would expect that a stronger base would activate the nucleophile more efficiently and thus further decrease the activation barrier. Nevertheless, our AIMD simulations resulted in a value for \(\Delta F^\ddagger\) of 13 ± 1 kcal mol\(^{-1}\) and 21.9 ± 0.5 kcal mol\(^{-1}\) for DMAP and Et\textsubscript{3}N, respectively. In other words, the activating role of Et\textsubscript{3}N is significantly less effective compared to DMAP, notwithstanding Et\textsubscript{3}N is the stronger base. To further study the differences between the DMAP-mediated and Et\textsubscript{3}N-mediated triflylation of piperidine, NCI analyses were performed on their transition states (for theoretical background, see SI section 8.2).[91] Remarkably, the 3D NCI isosurface of the DMAP-mediated transition state and bond length analysis reveals an attractive non-classical CH\textsuperscript{\cdots}\text{O} hydrogen bond connecting DMAP with CF\textsubscript{3}SO\textsubscript{2}F (Figure 1, C, purple arrow and SI section 8.1). The synergy between this CH\textsuperscript{\cdots}\text{O} hydrogen bond and Lewis adduct formation between DMAP and piperidine favorably align both reactants in the transition state. Furthermore, the isosurface of the Et\textsubscript{3}N-mediated transition state is characterized by larger repulsive (red) surfaces compared to the DMAP-mediated transition state, especially between Et\textsubscript{3}N and CF\textsubscript{3}SO\textsubscript{2}F. From the number of peaks present in the plot of \(s\) against \(\rho\text{sign}(\lambda)\), it can also be inferred that the Et\textsubscript{3}N-mediated transition state contains considerably more noncovalent interactions (Figure 1C). Based on these results, we believe that the activating role of the base in the CF\textsubscript{3}SO\textsubscript{2}F-triflylation of piperidine transcends beyond deprotonation of the amine. Clearly, intricate non-covalent interactions such as hydrogen bonding or steric repulsion due to the bulkiness of all reactants involved play an important role in the stability of the termolecular transition state.

After establishing plausible reaction pathways for the activated triflylation of piperidine, we reconsidered the mechanism for the non-activated reaction (A, I). We reasoned that, besides acting as the nucleophile, a second equivalent of piperidine could activate the reaction, similar to an added base. Such a mechanistic picture would also coincide with the non-activating triflylation of 55 yielding 49% of product (Figure 1B entry 1). Indeed, a maximum of 50% would be expected when the substrate acts as its own base. To our delight, we obtained an energetically more reasonable mechanism for the non-activated triflylation of piperidine when a second piperidine molecule was added to the simulation box, resulting in a \(\Delta F^\ddagger\) of 18 ± 4 kcal mol\(^{-1}\) (A, IV). In this mechanism, a second equivalent of piperidine forms a Lewis adduct with the piperidine nucleophile and a termolecular transition state is observed. A notable difference with the activated pathways (A, II and III), is that herein substitution preferably proceeds through frontside attack of the nucleophile. To further strengthen our hypothesis, the relative amount of phenylpiperazine with respect to CF\textsubscript{3}SO\textsubscript{2}F was increased (2:1 ratio). As expected, the experimental yield of the reaction increased to 79% (entry 4), suggesting that indeed a second equivalent of piperidine plays an active part in the reaction. Intriguingly, when the water content is gradually increased, as little as 1.5 equivalent shuts down the reaction completely (entries 5–7).

![Scheme 6: triflylation of phenols and amines](image)

Based on these mechanistic insights, we propose an explanation for the observed chemoselectivity when comparing the triflylation of amines and phenols. When performing the reaction in MeCN:H\textsubscript{2}O (3:1), phenols are selectively triflylated, while amines remain unaffected (compounds 19 and 28). On the other hand, in dry MeCN (0.33 M), both phenols and amines are converted (compounds 60 and 70). We believe that the influence of H\textsubscript{2}O on chemoselectivity can be explained through the difference in mechanism. A trialkylamine (pK\textsubscript{a} ≈ 11) will partially deprotonate the phenol (pK\textsubscript{a} ≈ 10) towards the phenolate, which is likely to undergo triflylation via a bimolecular S\textsubscript{NP}2 type mechanism, as shown by Zuilhof and co-workers.[46] In contrast, our simulations showed that under the same conditions, amines would undergo an S\textsubscript{NP}3 type mechanism, in which a hydrogen bond driven Lewis adduct between the nucleophile and the base is formed (Scheme 6). We assume H\textsubscript{2}O to disrupt these essential hydrogen bonds, explaining why the reaction in MeCN:H\textsubscript{2}O is
selective towards phenols, while in dry MeCN both phenols and amines showcase a high reactivity towards triflylation.

To summarize, we designed a two-chamber procedure for the safe and efficient ex-situ handling of triflyl fluoride gas (CF₃SO₂F) as a new type of SuFEx connector. Herewith, a diverse library of triflates and triflamides was built straightforwardly, often without the need for further purification. Comparing with literature triflation methods, CF₃SO₂F consistently furnished higher yields and selectivities. A particularly interesting finding was the lack of reactivity of carboxylic acids and amines in the presence of water, allowing a completely chemoselective triflation of phenolic nucleophilic.

In a more in-depth study of this phenomenon, ab initio metadynamics (AIMtD) simulations offered insight into the reactivity of the CF₃SO₂F triflation with secondary amine nucleophiles. In contrast to phenolates reacting in a bimolecular fashion, the simulations for amines suggested a formal S₃N mechanism with a termolecular transition state that relies on hydrogen bond formation between base and nucleophile. Due to the absence of such H-bonds in aqueous media, we believe this mechanism explains the observed difference in reaction outcome.

The formation of aryl triflates proved amenable to peptide functionalization and reaction telescoping into one-pot Suzuki-Miyaura cross-coupling. In addition, the sulfonylation chemistry developed for trifyl fluoride CF₃SO₂F was found to be fully translatable to triflimidoyl fluorides CF₃SO(NR)F. These aza-SuFEx hubs provided an efficient route to aryl triflimidates. Also, process chemistry may benefit from the clean chemoselective, lab-scale synthesis of valuable aryl triflates and triflamides. Furthermore, computational resources and services that were used in this work were provided by the VSC, funded by the FWO and the Flemish Government—department EWI.

**Keywords:** SuFEx chemistry • sulfonyl fluorides • chemoselectivity • click chemistry • ab initio calculations

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**References**


The cost comparison in Scheme 1, B was calculated on 5 g scale (or the prices and exchange rates of 16/04/2021).

References that report selective cross-electrophile coupling involving aryl halides (Scheme 1, C) include:


[45] N-phenylpiperazine was chosen a higher-MW substrate for the mechanistic experiments because N-triflyl piperidine (the product in the simulations) is volatile and less suited for isolated yield determination.


Here we report a general method to employ trifluoromethanesulfonfonyl fluoride (CF$_3$SO$_2$F) gas as a new SuFEx activator. This SVI–F reagent and its aza analogues react efficiently with a variety of nucleophiles, yet the presence of water grants complete chemoselectivity to phenols, even in Tyr-containing peptides. 

*Ab initio* metadynamics simulations reveal a crucial H-bond in the triflylation of amines, which we propose as a mechanistic explanation.

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