

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

Bing-Yu Li,^[a] Lauren Voets,^[a] Ruben Van Lommel,^[a,b] Fien Hoppenbrouwers,^[a] Mercedes Alonso,^[b] Steven H. L. Verhelst,^{[c][d]} Wim M. De Borggraeve*^[a] and Joachim Demaerel*^[a,c]

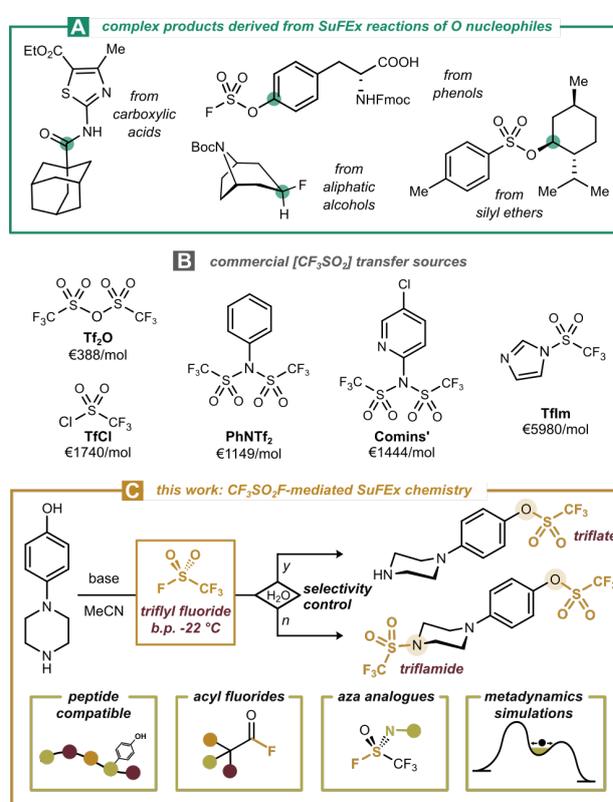
- [a] B.-Y. Li, L. Voets, R. Van Lommel, Dr. J. Demaerel, Prof. Dr. W. M. De Borggraeve, Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, Box 2404, 3001 Leuven, Belgium. E-mail: joachim.demaerel@kuleuven.be, wim.deborggraeve@kuleuven.be
 [b] R. Van Lommel, Prof. Dr. M. Alonso, Eenheid Algemene Chemie (ALGC), Department of Chemistry, Vrije Universiteit Brussel (VUB), Pleinlaan 2, 1050 Brussels, Belgium
 [c] Dr. J. Demaerel, Prof. Dr. S. H. L. Verhelst, Laboratory of Chemical Biology, Department of Cellular and Molecular Medicine, KU Leuven, O&N I bis, Herestraat 49, box 901, 3000 Leuven, Belgium
 [d] Prof. Dr. S. H. L. Verhelst, Leibniz Institute for Analytical Sciences ISAS, e.V., Otto-Hahn-Str. 6b, 44227 Dortmund, Germany

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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 ($\text{CF}_3\text{SO}_2\text{F}$) 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 $\text{S}^{\text{VI}}\text{-F}$ connector with a $\text{S}=\text{O} \rightarrow \text{S}=\text{NR}$ replacement, furnished the analogous triflimidoyl fluorides as SuFEx electrophiles, which were engaged in the synthesis of rarely reported triflimidate esters. Notably, experiments showed H_2O 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 $\text{CF}_3\text{SO}_2\text{F}$ triflylation of amines.

Recent interest in high-valent sulfur species has brought about an increasing number of $\text{S}^{\text{VI}}\text{-F}$ 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 S^{VI} core. Especially in the last seven years, various research groups have demonstrated the potential of SuFEx hubs such as sulfonyl fluorides ($\text{R-SO}_2\text{F}$),^[1] sulfonyl fluoride (SO_2F_2),^[2] thionyl tetrafluoride (SOF_4),^[3] ethenesulfonyl fluoride (ESF , $\text{CH}_2=\text{CH-SO}_2\text{F}$),^[2a, 4] and others.^[5] The chemoselective and straightforward nature of SuFEx chemistry has enabled a range of applications in synthesis and materials.^[6]

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_2F -containing reagents, aliphatic alcohols have been converted into alkyl fluorides^[7] or alkylating agents,^[8] carboxylic acids into acyl fluorides,^[9] and silyl ethers into sulfonate esters^[10] (Scheme 1A). A unique role in this collection is reserved for aromatic alcohols, which in reaction with SO_2F_2 selectively form the valuable aryl fluorosulfates in the presence of various other nucleophiles.^[11, 2a]



Scheme 1. (A) Complex products derived from SuFEx reactions of oxygen nucleophiles; (B) Commercial triflylating agents;^[12] (C) this work: $\text{CF}_3\text{SO}_2\text{F}$ -mediated SuFEx chemistry.

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_2O) or triflyl chloride (TfCl), reacting with the corresponding phenol in the presence of an acid scavenger.^{[19] [20]} 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 (Tflm),^[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,^[2b] we propose trifluoromethanesulfonyl fluoride gas, CF₃SO₂F (b.p. -22 °C), as a new electrophilic SuFEx hub, easily generated *via* two-chamber reactor technology. We explore the S^V-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 trifluoromethanesulfonimidate (triflimidate) esters: the rarely reported aza analogs of the ArOTf scaffold. Ultimately, to shed some light on the origins of the observed chemoselectivity, we use *ab initio* metadynamics simulations to map the reactive trajectory of amines as a model nucleophile, gaining fundamental insight into the key interactions of the SuFEx transition state.

Results and discussion

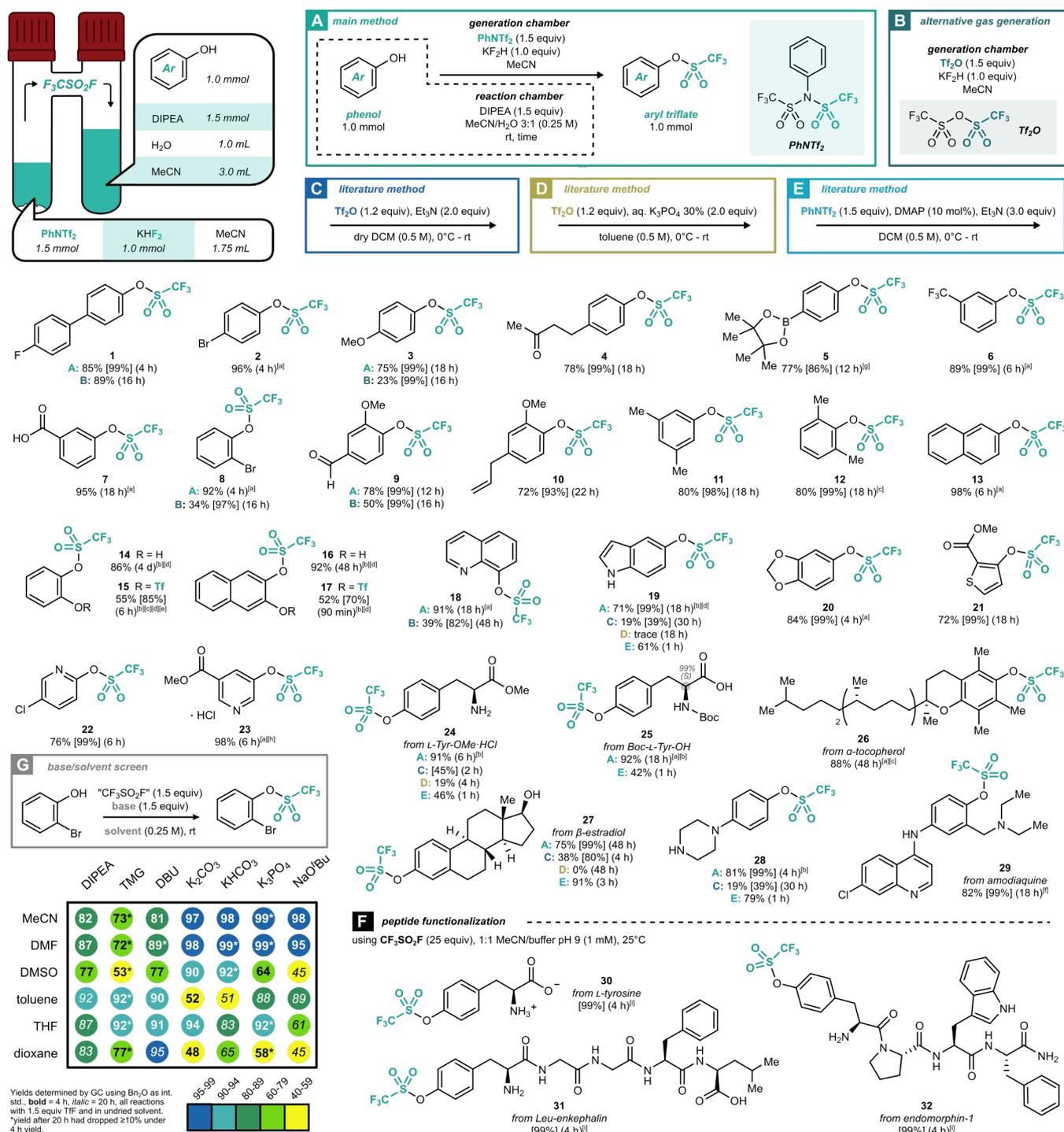
Triflyl fluoride gas was first reported in 1956 by Gramstad for the synthesis of trifluoromethanesulfonic acid derivatives.^[24] This smallest perfluoroalkanesulfonyl fluoride is gaseous above -25 °C, and its atmospheric chemistry is relatively innocuous.^[25] The most relevant industrial preparation 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 CF₃SO₂Cl^[27, 25] or Tf₂O^[28] with a fluoride source.^[29] Recently, Pees and coworkers have developed CF₃SO₂¹⁸F as a carrier gas for nucleophilic [¹⁸F]-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, most 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**);^[32] adding Tf₂O under Frantz' aqueous conditions (method **D**)^[33] 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*-phenyltrifluoromethanesulfonamide (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.

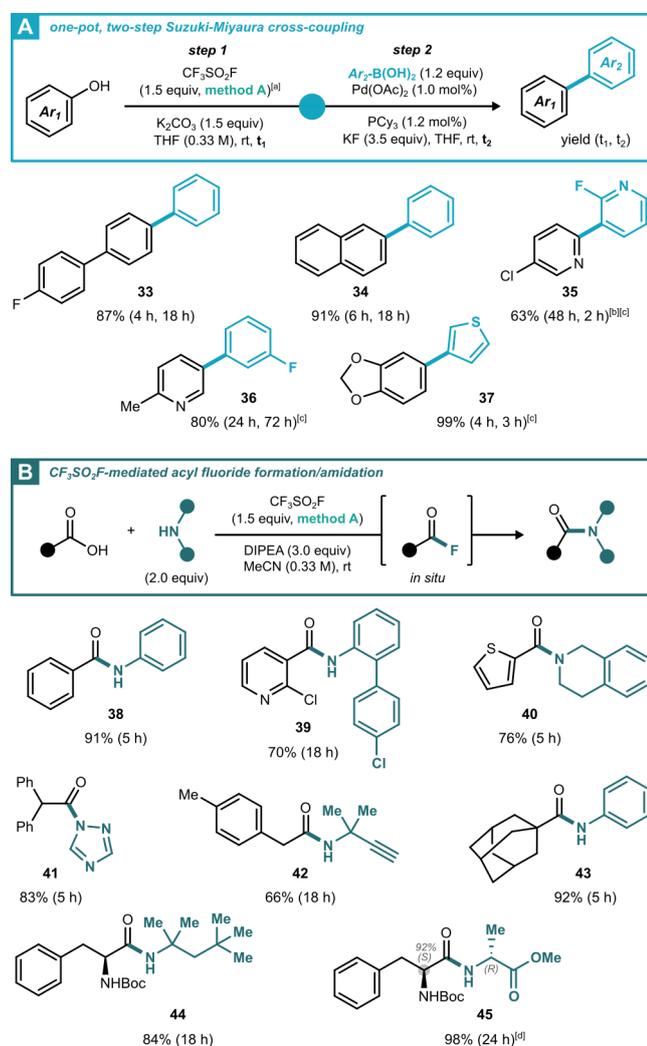
Given the variety of allowed solvent/base combinations, we wondered whether the triflation method can reach further synthetic utility in a one-pot Suzuki-Miyaura cross-coupling reaction. Based on a literature protocol,^[14b] we found that the (hetero)aryl triflates underwent efficient cross-coupling 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.^[35] In addition, this Suzuki cross-coupling afforded 2-methyl-5-(3-fluoro phenyl) pyridine **36**, the pharmacophore of vorapaxar^[36] in 80% yield without purifying the intermediate triflate.

Another class of oxygen nucleophiles that was subjected to CF₃SO₂F-enabled post-transformations, consists of carboxylic acids. In line with Moses^[9a] and Qin's^[9b] 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 alkylamines 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.^[37]

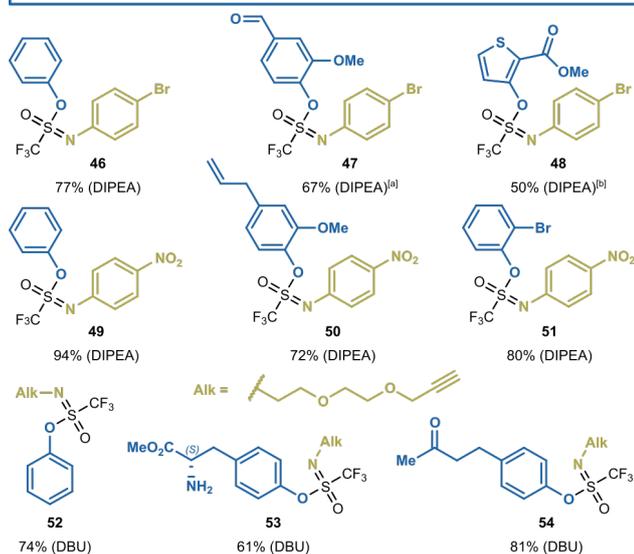
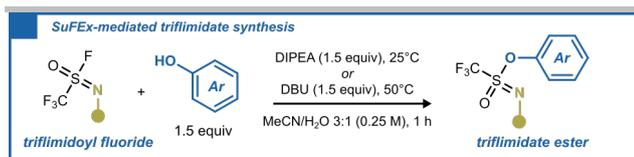
After investigating the chemistry of CF₃SO₂F with oxygen nucleophiles, we were curious to see whether S=N analogs uphold the same substitution reactions. By replacing a single oxo-group with a substituted nitrogen in the S^{VI}-F hub, trifluoromethanesulfonimidoyl (triflimidoyl) fluorides are obtained. 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,^[38] the recent report by Oehrich and co-workers is the only example of triflimidoyl fluorides reacting with phenols to form trifluoromethanesulfonimidate (triflimidate) esters.^[39] Given that only two examples were made under strongly basic conditions, we surmised that an improved synthesis under mild SuFEx conditions should be possible.^[3b, 40] 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,^[41, 3b] required DBU as a stronger base and an elevated reaction temperature of 50 °C. Naturally occurring phenols such as vanillin (**47**), eugenol (**50**), L-tyrosine methyl ester (**53**), raspberry ketone (**54**), as well as sterically hindered 2-bromophenol (**51**) and thiophen-2-ol (**48**) 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 triflylating reaction to form the trifluoromethanesulfonamides (triflamides) (Scheme 5). Based on a literature SuFEx reaction between SO₂F₂ and secondary amines,^[2a] 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.



Scheme 3. One-pot reactions enabled by CF₃SO₂F gas generation. A: One-pot, two-step method of aryl triflate generation followed by Suzuki-Miyaura cross-coupling. B: Amide synthesis with *in situ* generated acyl fluorides. The yield corresponds in all cases to the isolated yield after column chromatography without isolation of the intermediates. [a] DMF was used in the generation chamber instead of MeCN for volatility reasons. [b] NaHCO₃ was used as the only base (1.5 + 2.2 equiv. in step 1 and 2, resp.), with 1,4-dioxane/H₂O 5:1 as the solvent, step 2 was heated to 80 °C. [c] Pd(OAc)₂ (2.0 mol%) and PCy₃ (2.4 mol%) were used. [d] The product was isolated as a 92:8 mixture of diastereoisomers, which was detected by ¹H NMR.

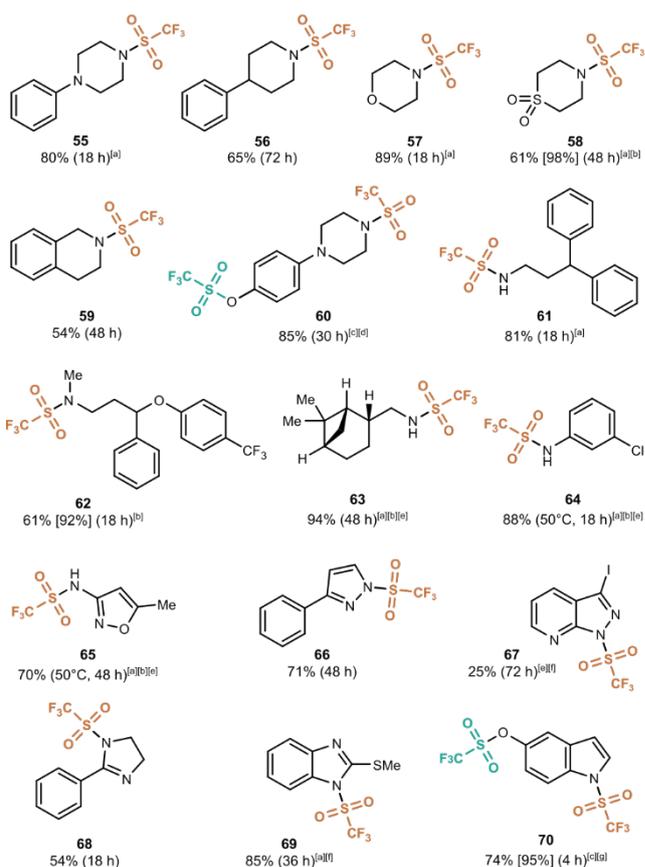
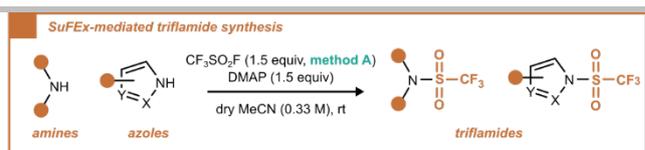
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Scheme 4. SuFEX-enabled synthesis of aryl triflimidate esters from triflimidoyl fluorides. Reactions were carried out at a 0.2 mmol scale. [a] 1.1 equiv. of ArOH was used. [b] 1.2 equiv. of ArOH used, reaction time was 3 h.

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*



Scheme 5. Synthesis of triflamides by reaction of CF₃SO₂F with amines and azoles. Reaction was carried out on 1.0 mmol scale and reported yields are after column chromatography unless noted otherwise. Between brackets is given the ¹⁹F NMR yield using PhCF₃ as internal standard, between parentheses the reaction time. [a] Isolated yield of pure material after aqueous work-up. [b] 3.0 equiv. of base was used. [c] 2.5 equiv. of CF₃SO₂F gas was used. [d] 3.5 equiv. of base was used. [e] 2.0 equiv. of CF₃SO₂F was generated. [f] K₂CO₃ was used as the base. [g] 2.5 equiv. of base was used.

metadynamics (AIMtD) to retrieve the mechanism as well as quantify the associated activation barriers.^[43] In contrast to static DFT computations, AIMtD 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 AIMtD to elucidate reaction mechanisms, quantify reaction barriers and unveil solvation effects.^[44]

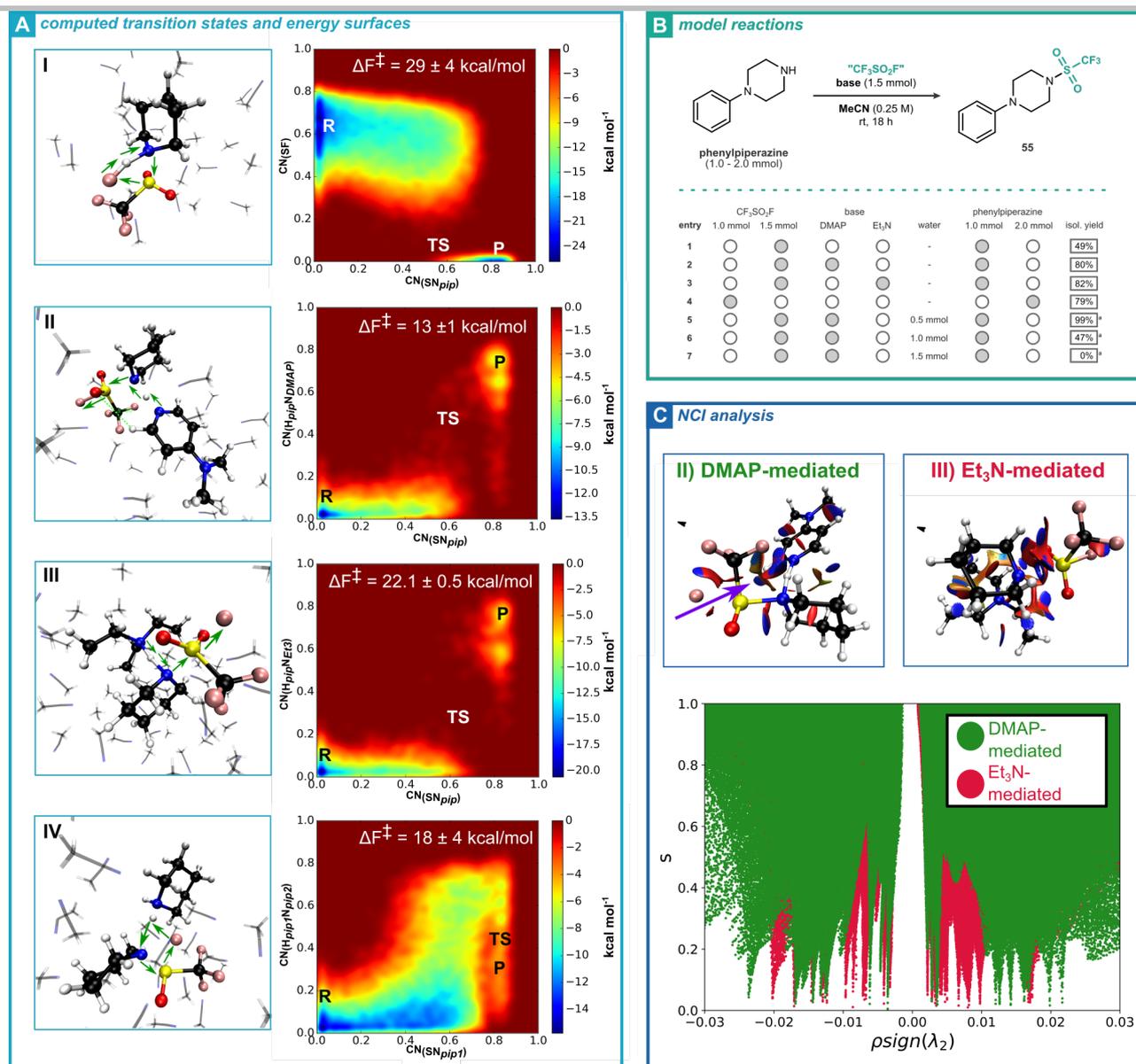


Figure 1. (A) Transition states obtained through metadynamics simulations for: I) the non-activated CF₃SO₂F-triflylation of piperidine in acetonitrile, II) the DMAP-activated CF₃SO₂F-triflylation of piperidine in acetonitrile, III) the Et₃N-activated CF₃SO₂F-triflylation of piperidine in acetonitrile and IV) the non-activated CF₃SO₂F-triflylation of piperidine in acetonitrile including two molecules of piperidine. In all cases, electron displacement is schematically illustrated using green arrows. During the simulations, Gaussian shaped potentials were placed along two coordination numbers, resulting in a free energy surface and Helmholtz free energy of activation (ΔF^\ddagger). Simulations were performed in triplicate. (B) Triflylation of phenylpiperazine as model reaction varying the base, solvent and relative amounts of substrate and CF₃SO₂F. Isolated yields are provided unless stated otherwise. [^a] ¹⁹F NMR yield relative to int. std. after 72 h reaction time. (C) NCI analyses were performed on the transition states of the DMAP-mediated CF₃SO₂F triflylation (II, green) and Et₃N-mediated CF₃SO₂F triflylation (III, red). Analyses were performed in absence of the solvent to focus on the noncovalent interactions present in and between the reactive species. Top; 3D NCI isosurfaces ($s=0.5$) visualized for both reactive systems. An RGB-scale is used to differentiate between repulsive (red) and attractive (green) interactions, set from -0.005 a.u. to 0.005 a.u. For the DMAP-mediated triflylation, a non-classical CH...O hydrogen bond is observed as an attractive blue surface, which connects DMAP with CF₃SO₂F (purple arrow). Bottom; an overlay plot of s against $\rho\text{sign}(\lambda_2)$ is presented for both NCI analyses.

Here, piperidine served as a case study for the computationally modeled CF₃SO₂F triflylation reaction (Figure 1A). In parallel, a series of experimental studies was performed, to complement the *in silico* findings (Figure 1B).^[45] Initially, three different systems were considered. A single CF₃SO₂F and one piperidine molecule were placed in the simulation box together with explicit acetonitrile (I), or with DMAP (II) or Et₃N (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.^[46] Additionally, the description of long-range dispersion interactions was improved by Grimme's D3 dispersion correction.^[47] The CP2K code (version 6.1) was used together with the Quickstep implementation (for full computational details see SI section 8.1).^[48]

From analyzing the trajectory obtained for the non-activated CF₃SO₂F-triflylation of piperidine (I), a concerted bimolecular reaction mechanism was observed, akin to an S_N2-type pathway

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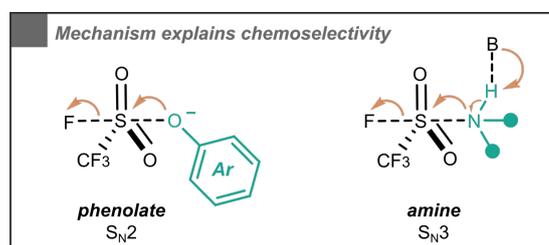
(see Supplementary Movie). Indeed, bond length analysis shows a simultaneous S–F bond breaking and S–N_{pip} bond formation (see SI section 8.1) and the free energy surface displays a reactant and product phase, without an additional intermediate basin (Figure 1A, I). Notably, without a base, the piperidine nucleophile attacks the sulfur-center from the frontside, which for most S_N2 reactions would be less favorable compared to the corresponding backside pathway.^[49] Herein, frontside attack allows F⁻ to directly scavenge the amine hydrogen of piperidine.

While this mechanism coincides with the findings of Luy and Tonner, the AIMtD simulations result in a Helmholtz free energy of activation (ΔF^\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 Et₃N (**A, III**) to the simulation box, a significantly reduced ΔF^\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 concertedly when DMAP or Et₃N are used, similar to the non-activated CF₃SO₂F-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_{pip}. Collectively, these observations indicate that the transition state has a termolecular nature, meaning the reaction follows an S_N3-type pathway. While initially these findings might seem surprising, such S_N3 pathways have previously been proposed as mechanisms for substitution reactions on sulfonyl substrates.^[50] Moreover, when the reaction is activated by DMAP or Et₃N, backside attack of the nucleophile is preferred.

Another intriguing observation was the difference between ΔF^\ddagger of the DMAP and Et₃N activated triflylation. One would expect that a stronger base would activate the nucleophile more efficiently and thus further decrease the activation barrier. Nevertheless, our AIMtD simulations resulted in a value for ΔF^\ddagger of 13 ± 1 kcal mol⁻¹ and 21.9 ± 0.5 kcal mol⁻¹ for DMAP and Et₃N, respectively. In other words, the activating role of Et₃N is significantly less effective compared to DMAP, notwithstanding Et₃N is the stronger base. To further study the differences between the DMAP-mediated and Et₃N-mediated triflylation of piperidine, NCI analyses were performed on their transition states (for theoretical background, see SI section 8.2).^[51] Remarkably, the 3D NCI isosurface of the DMAP-mediated transition state and bond length analysis reveals an attractive non-classical CH^{•••}O hydrogen bond connecting DMAP with CF₃SO₂F (Figure 1, C, purple arrow and SI section 8.1). The synergy between this CH^{•••}O hydrogen bond and Lewis adduct formation between DMAP and piperidine favorably align both reactants in the transition state. Furthermore, the isosurface of the Et₃N-mediated transition state is characterized by larger repulsive (red) surfaces compared to the DMAP-mediated transition state, especially between Et₃N and CF₃SO₂F. From the number of peaks present in the plot of *s* against $\rho_{\text{sign}}(\lambda_2)$, it can also be inferred that the Et₃N-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 CF₃SO₂F-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 ΔF^\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 CF₃SO₂F 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: The CF₃SO₂F triflylation of phenols (phenolate as reactive species) and amines occurs through different pathways.

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:H₂O (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 H₂O on chemoselectivity can be explained through the difference in mechanism. A trialkylamine (pK_{aH} ~11) will partially deprotonate the phenol (pK_{aH} ~10) towards the phenolate, which is likely to undergo triflylation via a bimolecular S_N2 type mechanism, as shown by Zuilhof and co-workers.^[40] In contrast, our simulations showed that under the same conditions, amines would undergo an S_N3 type mechanism, in which a hydrogen bond driven Lewis adduct between the nucleophile and the base is formed (Scheme 6). We assume H₂O to disrupt these essential hydrogen bonds, explaining why the reaction in MeCN:H₂O is

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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 nucleophiles. In a more in-depth study of this phenomenon, *ab initio* metadynamics (AIMD) simulations offered insight into the reactivity of the CF₃SO₂F triflylation with secondary amine nucleophiles. In contrast to phenolates reacting in a bimolecular fashion, the simulations for amines suggested a formal S_N3 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 triflyl fluoride CF₃SO₂F was found to be fully translatable to triflimidoyl fluorides CF₃SO(NR)F. These aza-analogous SuFEx hubs provided an efficient route to aryl triflimidate esters, a barely reported class of compounds with three-dimensional, potentially chiral character and unknown biological properties. Overall, we believe that the *ex situ* gas generation method will lead to increased use of CF₃SO₂F in chemoselective, lab-scale synthesis of valuable aryl triflates and triflamides. Also, process chemistry may benefit from the clean reaction profiles demonstrated here, when using gaseous CF₃SO₂F directly as a low-MW progenitor to current standard Tf₂O. Ultimately, we believe the insights derived from high-quality *ab initio* calculations form the next step in understanding the fundamental interactions during S^{VI}-F chemistry, and provide a better-informed basis for future applications.

Acknowledgements

We are grateful to Bart Van Huffel and Luc Baudemprez for the assistance with NMR measurements and to Bart Van Huffel for the elemental analysis. We kindly acknowledge Marcus Frings for HPLC analyses. B-Y.L thanks the CSC (Chinese Scholarship Council) for her fellowship received. J.D., L.V, R.V.L, M.A and W.M.D.B. thank FWO Vlaanderen (Research Foundation - Flanders) for fellowships and grants received (12ZL820N, 1SA1121N, 1185221N, 12F4416N, G0D6221N). M.A. thanks Vrije Universiteit Brussel (VUB) for financial support. W.M.D.B. thanks KU Leuven for financial support via Project DOA/2020/013. S.H.L.V. acknowledges financial support from the Ministerium für Kultur und Wissenschaft des Landes Nordrhein-Westfalen, the Regierende Bürgermeister von Berlin-inkl. Wissenschaft und Forschung, and the Bundesministerium für Bildung und Forschung. Mass spectrometry was made possible by the support of the Hercules Foundation of the Flemish Government (grant 20100225-7). Tier2 computational resources and services were provided by the Shared ICT Services Centre funded by the VUB,

the Flemish Supercomputer Center (VSC) and FWO. Tier1 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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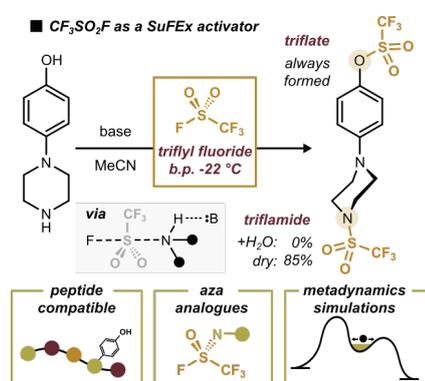
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Here we report a general method to employ trifluoromethanesulfonyl fluoride ($\text{CF}_3\text{SO}_2\text{F}$) gas as a new SuFEx activator. This $\text{S}^{\text{VI}}\text{-F}$ reagent and its aza analogues react efficiently with a variety of nucleophiles, 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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