VIP Click Chemistry Very Important Paper

International Edition: DOI: 10.1002/anie.201611048
German Edition: DOI: 10.1002/ange.201611048

Multidimensional SuFEx Click Chemistry: Sequential Sulfur(VI) Fluoride Exchange Connections of Diverse Modules Launched From An SOF_4 Hub

*Suhua Li, Peng Wu, John E. Moses, and K. Barry Sharpless**

Abstract: *Sulfur(VI) fluoride exchange (SuFEx) is a new family of click chemistry based transformations that enable the synthesis of covalently linked modules via S^{VI} hubs. Here we report thionyl tetrafluoride (SOF_4) as the first multidimensional SuFEx connector. SOF_4 sits between the commercially mass-produced gases SF_6 and SO_2F_2, and like them, is readily synthesized on scale. Under SuFEx catalysis conditions, SOF_4 reliably seeks out primary amino groups [R-**NH_2**] and becomes permanently anchored via a tetrahedral iminosulfur-(VI) link: R–N=(O=)S(F)$_2$. The pendant, prochiral difluoride groups R–N=(O=)**SF_2**, in turn, offer two further SuFExable handles, which can be sequentially exchanged to create 3-dimensional covalent departure vectors from the tetrahedral sulfur(VI) hub.*

The foundation of click chemistry as a framework for creating functional molecular assemblies, was inspired by examination of the central metabolism of life—a process orchestrated by functional oligomers of a few dozen reactive modules, all stitched together via heteroatom links and reversible condensation processes.[1] Seeking to match the efficiency of Nature's near perfect synthesis machinery, a stringent criterion was defined for a reaction to earn click chemistry status.[1]

The discovery of the Cu^I-catalyzed azide–alkyne cycloaddition reaction (CuAAC) in 2002[2] had a profound influence on the evolution of click chemistry, demonstrating immense versatility and application in fields as diverse as materials science,[3] bioconjugation,[4] and drug discovery.[5,6] In 2014, we reported a new embodiment of ideal click chemistry: SuFEx (sulfur(VI) fluoride exchange)—a technology for creating molecular connections with absolute reliability and unprecedented efficiency through a sulfur(VI) hub.[7] SuFEx reliably allows the flawless substitution of S^{VI}–F with aryl silyl ethers to give S^{VI}–O bonds, and with amines to give S^{VI}–N bonds. While the mechanistic details are yet to be fully elucidated, these transactions are made possible by a special co-action between the hydrogen-bonding environment of fluoride ion, and the kinetic and thermodynamic properties of the bonds to sulfur(VI) and silicon centers. Key to SuFEx activation is the requirement for fluoride to transit from a strong covalent bond to a leaving group—a process mediated by tertiary amine derived catalysts[8] and thought to involve the bifluoride ion and related species.[7,9–13]

Early in the development of SuFEx, we identified sulfuryl fluoride (SO_2F_2)[7,14] as a sulfur(VI) hub for creating diaryl sulfate links between molecules. Under SuFEx conditions, the latent reactivity of the otherwise stable S^{VI}–F bond is roused to react with SuFExable substrates.[7,15]

While SuFEx is still an emerging technology it has already found diverse applications including, for example: the synthesis of tosylates[9] and sulfonyl azides;[10] application in polymer chemistry[11] and post-polymerization modification;[12,13] Suzuki coupling of aryl- and heteroaryl-fluorosulfates with boronic acids.[15] Of particular significance, however, is the potential for SuFEx in biochemical applications: growing evidence supports the notion that proteins provide molecular and dynamic electrostatic field environments that sulfur(VI) fluoride linkages are adept at reading, and reacting to.[16]

In a recent study with the Kelly group, we demonstrated fluorosulfate-based probes as remarkable substrates capable of selectively capturing protein side-chain groups, especially the hydroxy group on tyrosine, in live human cells.[16a]

Seeking to expand the range of useful SuFEx connectors, we considered other sulfur(VI) fluoride gases, including: SF_6 (sulfur hexafluoride) and SOF_4 (thionyl tetrafluoride) (Figure 1 A). While SF_6 is loaded with the most SuFEx potential, it is also famously inert. SOF_4, on the other hand, is a S^{VI} hub with a functional balance between reactivity and available S–F functionality.[17]

As with most of click chemistry, many of the essential features of SOF_4 were discovered long ago: first reported in 1902 by Moissan and Lebeau,[18] SOF_4 is a trigonal bipyramidal colorless gas with a boiling point of −49 °C (Figure 1 A).[19,20] An improved synthesis of SOF_4 (for labs with no access to F_2) was reported in 1960 by Smith and Engelhardt at CRD DuPont. They found that in the presence of a catalytic amount of NO_2, the oxidation of SF_4 by O_2 gave enhanced yields of SOF_4 gas.[21]

Despite being known for more than one hundred years, the reactions of SOF_4 have scarcely been studied, let alone exploited. Cramer and Coffman (also at CRD DuPont) reported the first detailed study of its chemistry in 1961. They

[*] S. Li, J. E. Moses, K. B. Sharpless
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: sharples@scripps.edu
Homepage: http://www.scripps.edu/sharpless
P. Wu
Department of Chemical Physiology, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
J. E. Moses
School of Chemistry, University of Nottingham
Nottingham, NG7 2RD (UK)

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201611048.

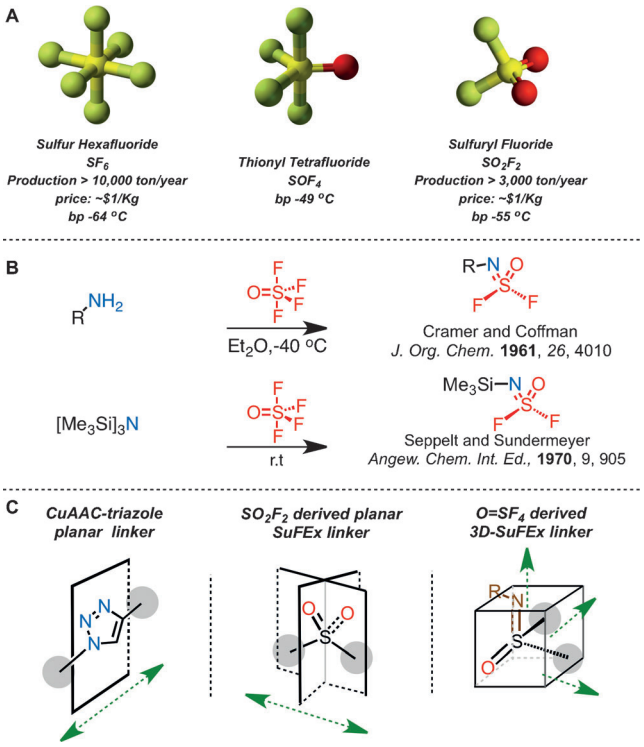


Figure 1. A) Structure and boiling point of SF_6, SOF_4 and SO_2F_2. B) Early examples of fluoride substitution reactions of SOF_4. C) Comparing the trajectories of the click connections derived from: CuAAC-triazole, SO_2F_2 and SOF_4.

found that SOF_4 reacts with primary amines and anilines to form the corresponding tetrahedral iminosulfur oxydifluoride ($R{-}N{=}SOF_2$) products in moderate yields (Figure 1 B).[22] Seppelt and Sundermeyer later reported (1971) an early manifestation of silicon-mediated SuFEx: $[(Me)_3Si]_3N$ upon reaction with SOF_4 gave the TMS-iminosulfur oxydifluoride ($((Me_3Si)_3N + SOF_4 \rightarrow Me_3Si{-}N{=}SOF_2$) in 85 % yield (Figure 1 B).[23] In the 50 years following these seminal reports, we locate no practical applications of SOF_4—perhaps not surprising *before* SuFEx catalysis.

The opportunity for creating connections through the two SuFExable S–F handles of the SOF_4-derived tetrahedral iminosulfur oxydifluoride products did not escape our attention. Until now, the click "linkages" created via CuAAC-derived triazoles and the SuFEx connective gas SO_2F_2, are confined to trajectories in a plane. SOF_4 is different; it is the first polyvalent SuFEx connective gas that opens the door to another dimension and trajectory (Figure 1 C). This is important because from biology to synthetic materials applications, having access to the 3-dimensional world adds value to the existing toolbox of click connections.

Herein, we report our detailed studies on the SuFEx chemistry of SOF_4 and its iminosulfur oxydifluoride products. We discovered that both the rates and yields for SOF_4 transformations are much improved by the presence of tertiary amine bases (e.g. Et_3N and DIPEA). The initial iminosulfur oxydifluoride products have two SuFExable S–F handles, and we demonstrate that these two fluorides can be substituted in a serial manner by secondary alkyl amines and/or phenols (as their aryl silyl ethers under SuFEx catalysis[7]). The final products, for up to three steps, arise in excellent overall yield,[24] thereby allowing controlled projections to be deliberately installed along 3 of the 4 tetrahedral axes departing the S^{VI} central hub.

Given the fidelity and scope of these three serial transformations, we identify thionyl tetrafluoride (SOF_4) as another good connective hub for SuFEx click chemistry.

Our experience with SO_2F_2, a sister gas to SOF_4 (Figure 1 A), taught us about the benefits that tertiary amine additives (e.g. TEA, DIPEA, DBU) can have on the speed and yield of the desired reaction.[7] Similarly for SOF_4, the presence of a tertiary amine base significantly improved the outcome of these transformations: exposing a solution of primary amine (**1**) to 2 mol equiv of Et_3N or DIPEA in CH_3CN, to SOF_4 gas, resulted in excellent yields of the tetrahedral iminosulfur oxydifluoride products (**2**) (Figure 2).

The selective decoration of $-NH_2$ moieties in biologically significant building blocks was also readily accomplished, giving the SuFExable steroid-N=SOF_2 cases (**2-21** and **2-22**) and also the nucleotide-N=SOF_2 cases (**2-23** and **2-24**) all in good yields. With the α-amino amide **1-25**, intramolecular displacement of the remaining fluoride, activated by amide hydrogen bonding, gave the cyclic sulfamide **2-25** in moderate yield (Figure 2). Generating the reactive amine in situ from the corresponding azide under Staudinger conditions, did not adversely affect the yield of the iminosulfur oxydifluoride products (**2-9**, **2-22**, **2-23**).

Noteworthy is the observed chemoselective preference of SOF_4 for amines vs. other functional groups, which in the case of catechol (**1-16**→**2-16;** Figure 2) contrasts with the reactivity of the SO_2F_2 sister gas.[7,10] We were curious about the outcomes of reacting aminophenols with both gases (SOF_4 and SO_2F_2) simultaneously. When acetonitrile solutions of the aminophenols **1-26**–**1-28** were exposed to a 1:1 ratio of SOF_4:SO_2F_2 in the presence of Et_3N (3 equiv), the corresponding SuFEx products **2-26**–**2-28** were formed in excellent yields, respectively. This outcome is explained by the preferential reaction pairing of SO_2F_2 with phenol and SOF_4 with amine, together with the decreasing opportunities for cross-over reaction for each gas as the reaction proceeds and, at least in the case of the $F_2OS{=}N\text{-}Ar\text{-}OH$, the enhanced acidity of the phenol group (Figure 3).

Cramer and Coffman surveyed the reactivity of $Ph{-}N{=}SOF_2$ with a selection of amines and found that weakly basic *N*-methylaniline gave no reaction. On the other hand, *tert*-butylamine could substitute both fluorides, while piperidine could substitute only one of them. The difluoride could also react with sodium ethoxide to form the ethyl phenylsulfamate.[22]

With our extensive range of iminosulfur oxydifluorides [$F_2SO(=NR)$], we revisited Cramer and Coffman's early work with a wider selection of amine nucleophiles (Figure 4). The reaction with secondary amines proceeded smoothly: when 2 mol equiv of the given amine were added to a solution of the iminosulfur oxydifluorides (**2**) in acetonitrile at room temperature, the mono-substituted products (**3**) were formed in excellent yields, leaving a single unreacted fluoride in place. These monosubstitution processes were near quantitative and

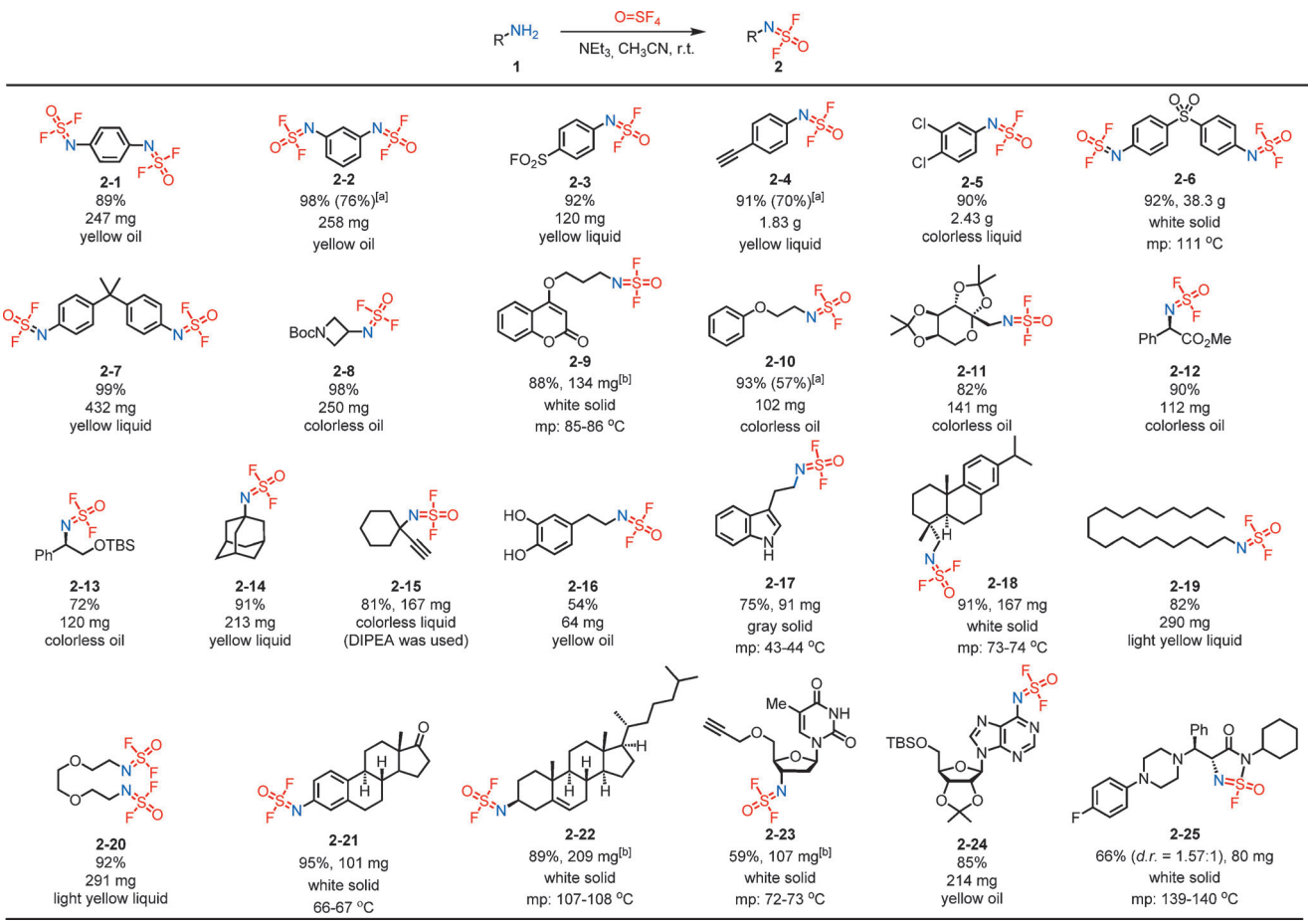


Figure 2. The reactions of primary amines with SOF_4 in the presence of Et_3N. [a] The yield in parenthesis is for the reaction without Et_3N. [b] The amine was generated in situ by reducing the azide under Staudinger conditions with PMe_3 and 1 to 3 equiv of H_2O, see the Supporting Information.

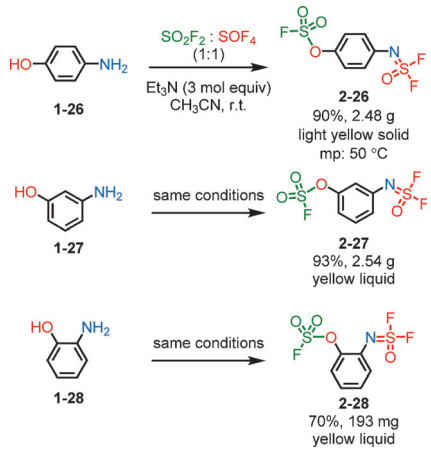


Figure 3. The selectivity of SO_2F_2 and SOF_4 towards aromatic hydroxy and amino groups.

the products did not require purification.[25] Reactions of iminosulfur oxydifluoride (**2-4**) with a selection of amino acids proceeded equally well, albeit with concomitant hydrolytic loss of the second fluoride, giving the unsymmetrical sulfamide products (**4-1**–**4-3**) in excellent yields (Figure 5).

In the spirit of click chemistry (i.e. the goal of creating stable and useful intermolecular linkages), we next investigated the reaction of a selection of iminosulfur oxydifluorides (**2**) with aryl silyl ethers (**5**) under DBU or BEMP activation (Figure 6). With DBU (10 mol%) and 1 mol equiv of aryl silyl ether **5-1**, the SuFEx reaction of iminosulfur oxydifluoride **2-4** reached completion within just 5 minutes, leading to the formation of the sulfurofluoridoimidate product **6-1** in 96% yield. Lowering the catalyst loading of DBU (2 mol%) required longer reaction times (1 h), but still allowed gram scale SuFEx coupling of **2-5** with aryl silyl ether **5-2** in 93% yield (**6-2**). With BEMP (5 mol%) as the catalyst, even the complex reactants: AZT derivative **2-23** and estrone **5-3** were readily connected to give **6-3** in 79% yield.

The exchange of just one S–F bond under typical SuFEx conditions revealed that the reactivity of the remaining S–F bond of the sulfurofluoridoimidate is significantly attenuated relative to the S–F bonds of the iminosulfur oxydifluoride. This is a welcome feature, particularly for instances when sequential SuFEx based modification are desirable. To further calibrate the relative reactivity profiles of the various S–F environments, we performed a series of competition experiments on substrates presenting two or more types of S–F functionality (Figure 7). When the *para*-disubstituted ben-

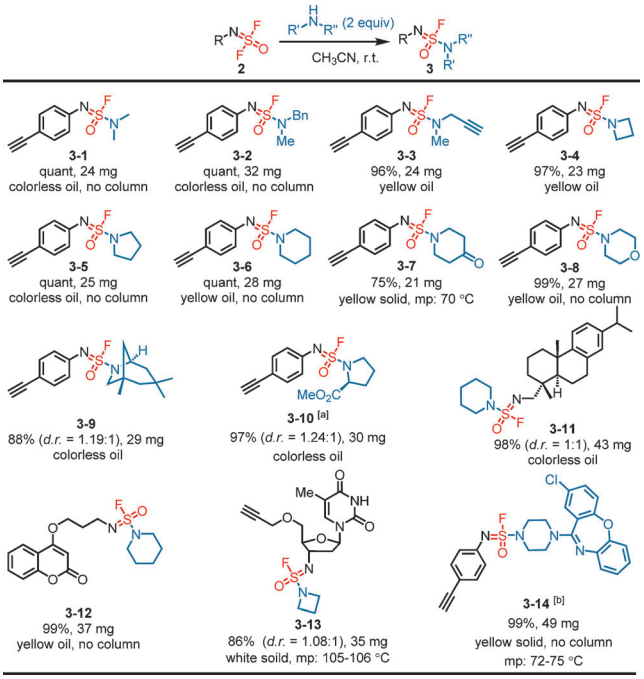


Figure 4. The reaction of iminosulfur oxydifluorides with secondary amines. [a] 1.2 equiv of proline methyl ester and 2 equiv of Et_3N in MeCN. [b] 1 equiv of amoxapine and 2 equiv of Et_3N in DMSO.

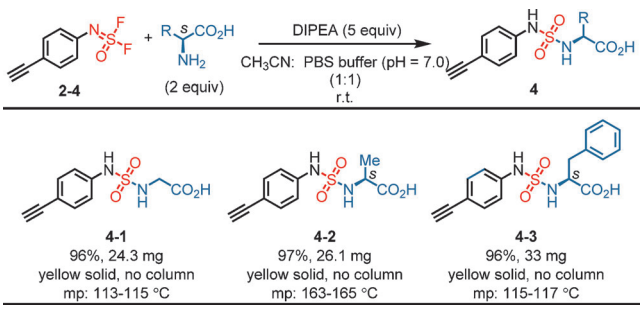


Figure 5. The reaction of iminosulfur oxydifluorides with amino acids.

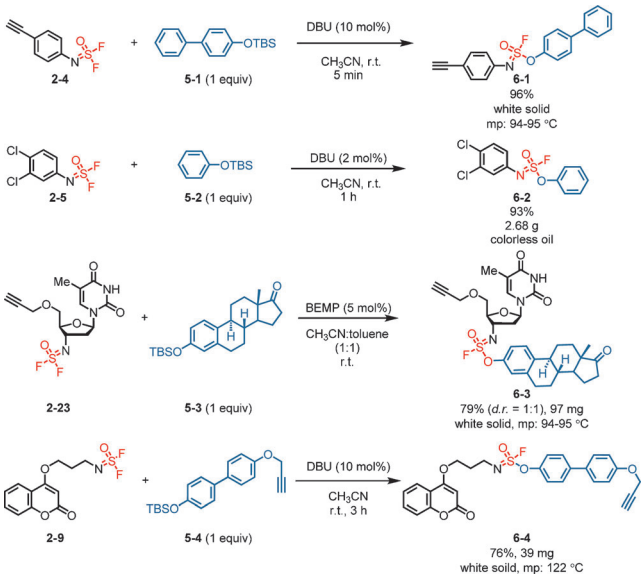


Figure 6. Connecting amines with phenols.

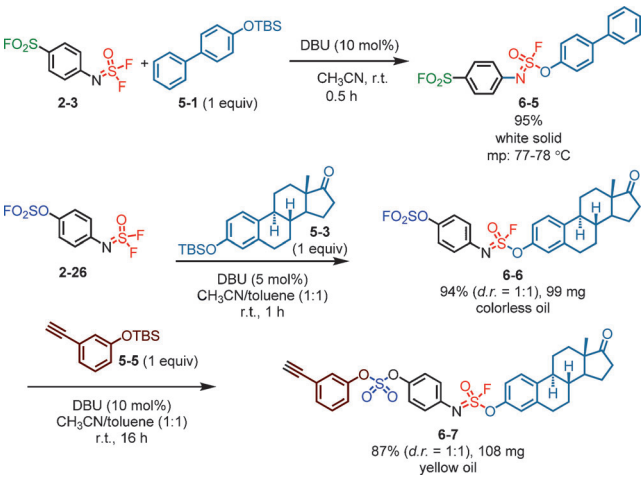


Figure 7. Comparison of the reactivity of iminosulfur oxydifluoride with sulfonyl fluoride and fluorosulfate.

zene derivative **2-3**, comprising both aryl sulfonyl fluoride ($Ar–SO_2F$) and aryl iminosulfur oxydifluoride groups ($Ar–N{=}SOF_2$), was treated with one equivalent of the aryl silyl ether **5-1** and DBU 10 mol% in acetonitrile, the SuFEx reaction occurred exclusively at the iminosulfur oxydifluoride center to give the corresponding product **6-5** in 95% yield. The sulfonyl fluoride ($–SO_2F$) group remained untouched (Figure 7). Similarly, when the SuFEx reaction was performed with the analogous fluorosulfate ($–OSO_2F$) substrate **2-26** under modified conditions (5 mol% DBU), the exchange occurred exclusively at the iminosulfur oxydifluoride center to give the corresponding product **6-6** in 94% yield. When the sulfurofluoridoimidate **6-6** itself was exposed to the aryl silyl ether (**5-5**) in the presence of DBU (10 mol%) over 16 h, SuFEx catalysis achieved linkage exchange at the fluorosulfate group, yielding the mixed sulfate–sulfurofluoridoimidate linked product **6-7** (Figure 7). From these few experiments, and related work,[7,15] we tentatively suggest the order of reactivity of SO_2F_2 and SOF_4 derived S–F bonds towards SuFEx reactions with aryl silyl ethers: $–N{=}SOF_2 > –SO_2F > –OSO_2F > –N{=}S(O)(OAr)F$.

From our earlier SuFEx studies with fluorosulfates ($–OSO_2F$), we found that 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) was the superior base for activating challenging substrates for exchange.[7] BEMP was therefore the logical choice for activating the remaining $S^{VI}–F$ bond of the corresponding sulfurofluoridoimidates (**6**). Indeed, the treatment of **6-2** with the aryl silyl ether **5-1** in the presence of 10 mol% BEMP (CH_3CN, r.t., 1 h), gave the corresponding sulfurimidate **7-1** in almost quantitative yield. BEMP proved equally efficient at lower concentrations (5 mol%), and even two phenol linkages could be installed in one pot without compromising yield (**7-2**). Interestingly, secondary amines alone react

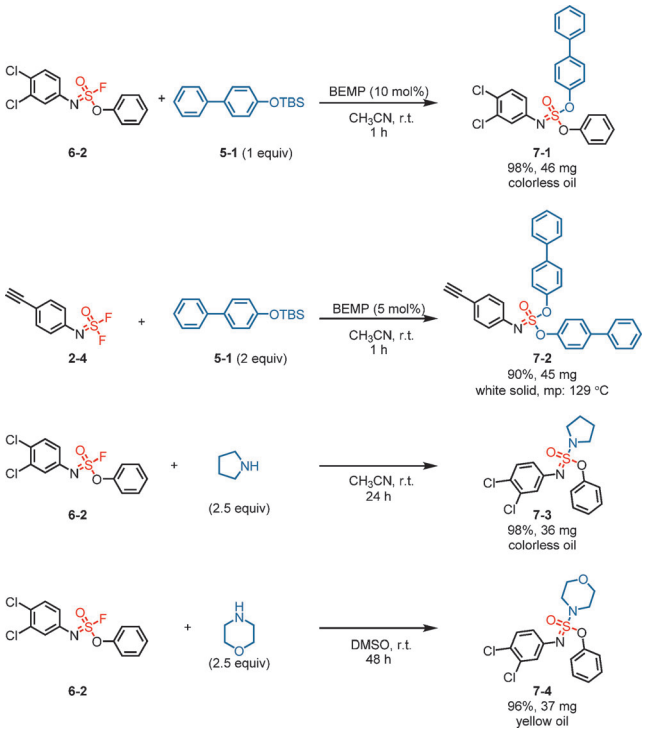


Figure 8. The connections of primary amines with two phenols or one phenol and one secondary amine.

directly with **6-2**, producing **7-3**, **7-4** in excellent yields (Figure 8).

Another manifestation of the 3rd dimension of SuFEx plugin reactions from SOF_4-derived hubs is the direct reaction of phenyliminosulfur oxydifluorides (**2–4**) with TMS-protected catechols (Figure 9). The entrained inter- and intramolecular SuFEx reactions proceeded smoothly with DBU (5 mol%) to form the four (**9-1**–**9-4**) iminooxy cyclic catechol

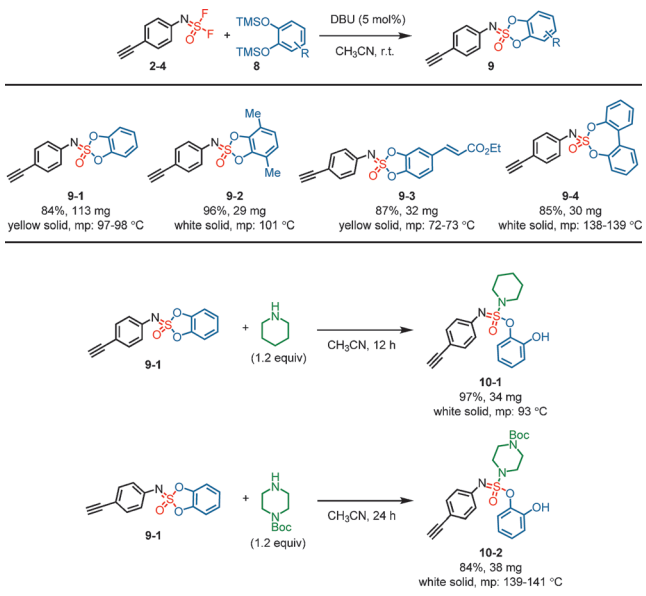


Figure 9. The reaction of iminosulfur oxydifluorides with catechols and the activity of the product towards amines.

sulfuryl derivatives in excellent yields (Figure 9). Of particular significance: the imino cyclic catecholate **9-1** is readily ring-opened by piperidine and Boc- piperazine to give the corresponding amino sulfonimidate products **10-1** and **10-2** in excellent yields.

In summary, SOF_4 gas is the first multidimensional connector that reacts efficiently with primary amines to form reactive iminosulfur oxydifluoride derivatives. Tuning the SuFEx catalyst conditions allows the sequential activation and exchange of these SuFExable S–F bonds, which project outward along roughly tetrahedral vectors from the central S^{VI} hub. This study complements our earlier work with SO_2F_2, by expanding the SuFEx universe of available connectors. The additional SuFExable S^{VI}–F bonds enrich the scope of this valuable click chemistry linker by allowing the extra departure links into the 3-dimensional tetrahedral world.

Acknowledgements

We thank the NIH (P50 GM103368, R01 GM117145) for financial support for this project. S.L. was partially supported by the Skaggs Institute for Chemical Biology.

Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · click chemistry · phenols · SuFEx reaction · thionyl tetrafluoride

[1] a) K. B. Sharpless, H. C. Kolb, *Book of Abstracts, 217th ACS National Meeting, Anaheim, CA, March 21–25* **1999**, ORGA-105, Accession Number 1999:145538; b) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004; *Angew. Chem.* **2001**, *113*, 2056.

[2] a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596; *Angew. Chem.* **2002**, *114*, 2708; b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.

[3] a) For examples see: W. Xi, T. F. Scott, C. J. Kloxin, C. N. Bowman, *Adv. Funct. Mater.* **2014**, *24*, 2572; b) Y. Liu, D. D. Díaz, A. A. Accurso, K. B. Sharpless, V. V. Fokin, M. G. Finn, *J. Polym. Sci. Part A* **2007**, *45*, 5182; c) D. D. Díaz, S. Punna, P. Holzer, A. K. McPherson, K. B. Sharpless, V. V. Fokin, M. G. Finn, *J. Polym. Sci. Part A* **2004**, *42*, 4392; d) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2004**, *43*, 3928; *Angew. Chem.* **2004**, *116*, 4018.

[4] a) S. H. Rouhanifard, L. U. Nordstrøm, T. Zheng, P. Wu, *Chem. Soc. Rev.* **2013**, *42*, 4284; b) C. S. McKay, M. G. Finn, *Chem. Biol.* **2014**, *21*, 1075.

[5] a) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128; b) P. Thirumurugan, D. Matosiuk, K. Jozwiak, *Chem. Rev.* **2013**, *113*, 4905.

[6] J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249.

[7] J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430; *Angew. Chem.* **2014**, *126*, 9584.

[8] The catalysis is exceedingly facile.
[9] V. Gembus, F. Marsais, V. Levacher, *Synlett* **2008**, 1463.
[10] A. S. Barrow, J. E. Moses, *Synlett* **2016**, 1840.
[11] J. Dong, K. B. Sharpless, L. Kwisnek, J. S. Oakdale, V. V. Fokin, *Angew. Chem. Int. Ed.* **2014**, *53*, 9466; *Angew. Chem.* **2014**, *126*, 9620.
[12] J. Yatvin, K. Brooks, J. Locklin, *Angew. Chem. Int. Ed.* **2015**, *54*, 13370; *Angew. Chem.* **2015**, *127*, 13568.
[13] J. S. Oakdale, L. Kwisnek, V. V. Fokin, *Macromolecules* **2016**, *49*, 4473.
[14] a) As a fumigant, sulfuryl fluoride (SO_2F_2) has been produced annually at more than 3 million kilograms per year since 2000, with a price as low as $1/kg. see M. P. Sulbaek Andersen, D. R. Blake, F. S. Rowland, M. D. Hurley, T. J. Wallington, *Environ. Sci. Technol.* **2009**, *43*, 1067.
[15] a) Q. Liang, P. Xing, Z. Huang, J. Dong, K. B. Sharpless, X. Li, B. Jiang, *Org. Lett.* **2015**, *17*, 1942; b) E. Zhang, J. Tang, S. Li, P. Wu, J. E. Moses, K. B. Sharpless, *Chem. Eur. J.* **2016**, *22*, 5692.
[16] a) Notable for its highly selective in vivo SuFEx result, the lipid binding protein CRAPB2, in human MC7 breast cancer cells was adducted at Tyr134 via a specifically catalyzed SuFEx reaction with a small biarylfluorosulfate molecule. Moreover, this capture event on Tyr134, was also shown to suppress the transcription of the expected, rar-linked, downstream proteins, see: W. Chen, J. Dong, L. Plate, D. E. Mortenson, G. J. Brighty, S. Li, Y. Liu, A. Galmozzi, P. S. Lee, J. J. Hulce, B. F. Cravatt, E. Saez, E. T. Powers, I. A. Wilson, K. B. Sharpless, J. W. Kelly, *J. Am. Chem. Soc.* **2016**, *138*, 7353; b) A. Narayanan, L. H. Jones, *Chem. Sci.* **2015**, *6*, 2650; c) A. Warshel, R. P. Bora, *J. Chem. Phys.* **2016**, *144*, 180901.
[17] a) H. C. Cowen, F. Riding, E. Warhurst, *J. Chem. Soc.* **1953**, 4168; b) B. Siegel, P. Breisacher, *J. Inorg. Nucl. Chem.* **1970**, *32*, 1469; c) L. Brewer, C.-A. Chang, B. King, *Inorg. Chem.* **1970**, *9*, 814; d) https://en.wikipedia.org/wiki/Sulfur_hexafluoride#cite_note-6.
[18] a) H. Moissan, P. Lebeau, *C. R. Hebd. Seances Acad. Sci.* **1901**, *132*, 374; b) H. Moissan, P. Lebeau, *Ann. Chim. Phys.* **1902**, *26*, 145.
[19] H. Jonas, *Z. Anorg. Allg. Chem.* **1951**, *265*, 273.
[20] F. B. Dudley, G. H. Cady, D. F. Eggers, Jr., *J. Am. Chem. Soc.* **1956**, *78*, 1553.
[21] W. C. Smith, V. A. Engelhardt, *J. Am. Chem. Soc.* **1960**, *82*, 3838.
[22] a) R. Cramer, D. D. Coffman, *J. Org. Chem.* **1961**, *26*, 4010; b) R. D. Cramer, U.S. Patent US3410669 A, **1968**.
[23] a) K. Seppelt, W. Sundermeyer, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 905; *Angew. Chem.* **1970**, *82*, 931; b) W. Sundermeyer, A. Roland, K. Seppelt, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 419; *Angew. Chem.* **1971**, *83*, 443.
[24] Including the initial anchoring step, introducing the imido ligand and leaving two fluorides.
[25] Although they are all stable to silica gel chromatography and TLC analysis.

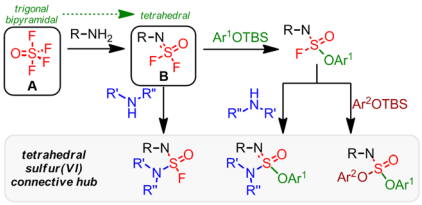
Manuscript received: November 11, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Click Chemistry

S. Li, P. Wu, J. E. Moses,
K. B. Sharpless* ——— ■■■■–■■■■

Multidimensional SuFEx Click Chemistry: Sequential Sulfur(VI) Fluoride Exchange Connections of Diverse Modules Launched From An SOF_4 Hub



Multidimensional clicking: SOF_4 gas is reported as the first multidimensional sulfur(VI) hub for SuFEx click chemistry. Reliably seeking out primary amino groups, the trigonal bipyramidal SOF_4 (**A**) becomes permanently anchored via a tetrahedral iminosulfur(VI) (**B**) link (see scheme). The difluoride groups in R–N=(O=)SF_2, in turn, offer two further SuFExable and prochiral S–F bonds, which can be sequentially exchanged to project 3-dimensional covalent vectors.