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SuFEx Chemistry of Thionyl Tetrafluoride (SOF_4) with Organolithium Nucleophiles: Synthesis of Sulfonimidoyl Fluorides, Sulfoximines, Sulfonimidamides and Sulfonimidates

Bing Gao,[a] Suhua Li,[a] Peng Wu,[b] John E. Moses,[c] and K. Barry Sharpless[a]*

Abstract: *Thionyl tetrafluoride (SOF_4) is a valuable connective gas for sulfur fluoride exchange (SuFEx) click chemistry, that enables multidimensional linkages to be created via sulfur–oxygen (S–O) and sulfur–nitrogen (S–N) bonds. In this report, we expand the available SuFEx chemistry of SOF_4 to include organolithium nucleophiles, and demonstrate, for the first time, the controlled projection of sulfur–carbon links at the sulfur center of SOF_4-derived iminosulfur oxydifluorides (R^1–N=SOF_2). This protocol enables rapid and modular access to sulfonimidoyl fluorides [R^1–N=$SOFR^2$], another array of versatile SuFEx connectors with readily tunable reactivity of the S–F handle. Divergent connections derived from these valuable sulfonimidoyl fluoride units are also demonstrated, including the synthesis of sulfoximines, sulfonimidamides, and sulfonimidates.*

The sulfur fluoride exchange (SuFEx) family of click reactions enable the modular, reliable and practical formation of sulfur linked connections via connective hubs such as sulfuryl fluoride (SO_2F_2),[1] ethenesulfonyl fluoride (ESF),[2] and thionyl tetrafluoride (SOF_4).[3] Sulfur fluoride derivatives are uniquely suited for click chemistry owing to their inherent thermodynamic and redox stability,[4] yet, given the right conditions have alacrity for certain transformations through a cooperative engagement of catalyst, reagent and solvent.[1] The power of SuFEx click chemistry has been demonstrated in applications, including the development of synthetic methods,[5] the preparation of polymers,[6] and in medicinal chemistry programs.[7] Most intriguingly, there is growing evidence to suggest that S–F handles (e.g. fluorosulfates and sulfonyl fluorides) possess context-dependent protein reactivity that could be selective covalent (or non-covalent) enzyme inhibitors or chemical probes.[1, 7]

We recently demonstrated thionyl tetrafluoride (SOF_4) gas as the first hub for creating multidimensional SuFEx connections.[3a] In a typical process, the treatment of the trigonal bipyramidal SOF_4 with primary amines affords tetrahedral iminosulfur oxydifluorides (Figure 1A, **I**). The later has two further SuFEx-able S–F handles, which readily undergo sequential exchange with amines/anilines or derivatives of phenols. A diverse array of sulfur fluoride compounds and their downstream derivatives obtained from the SOF_4 assembly have dramatically enriched the SuFEx combinatorial library.

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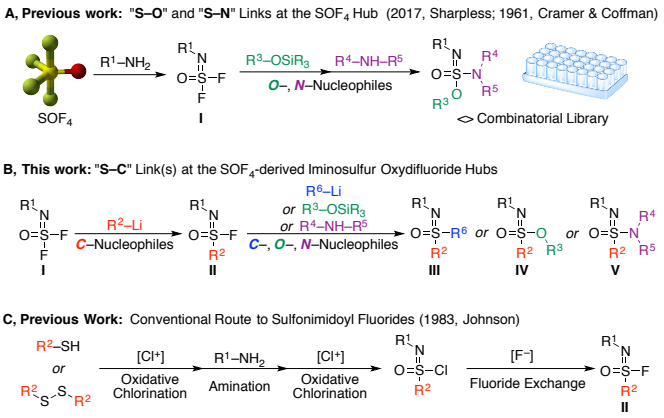


Figure 1. (A) Sulfur–heteroatom links enabled connections at the SOF_4 hub; (B) Sulfur-carbon link(s) enabled connections at the SOF_4 hub; (C) Conventional route to sulfonimidoyl fluorides.

The SuFEx connections created from the SOF_4 hub to date are limited to S–O and S–N links involving naturally abundant nucleophiles (amines and phenols). Connections enabled through the S–C link(s) that would engage carbon nucleophiles, on the contrary, have not been explored. To further expand the scope of SuFEx connectivity and functionality, the S–C bond(s) construction via selective cleavage of S–F bond(s) at the sulfur center of SOF_4 or its derivatives is worthwhile. Because it would enable divergent access to sulfur fluoride derivatives with novel skeletons and reactivity.

Herein, we report the controlled projection of S–C link(s) from iminosulfur oxydifluorides (**I**) upon reaction with organolithiums (Figure 1B). This protocol allows the synthesis of sulfonimidoyl fluorides in two steps from SOF_4 (Figure 1B, **II**). First reported by Johnson in 1983, sulfonimidoyl fluorides were conventionally prepared by the treatment of sulfonimidoyl chlorides with a fluoride source (Figure 1C).[8] Because of the harsh reaction conditions and a lengthy *de novo* four-step process, however, only a confined number of derivatives were available.[1, 9] Our protocol is complementary, but has significant advantages due to its straightforward, rapid and modular operation.[10] The synthetic convenience for creating diverse connections from sulfonimidoyl fluorides, through either S–C or S–N/O links, is further demonstrated in the preparation of sulfoximines,[11] sulfonimidamides,[12] and sulfonimidates.[13] These compounds are known for their valuable utilities in synthetic transformations and medicinal chemistry.[11–13]

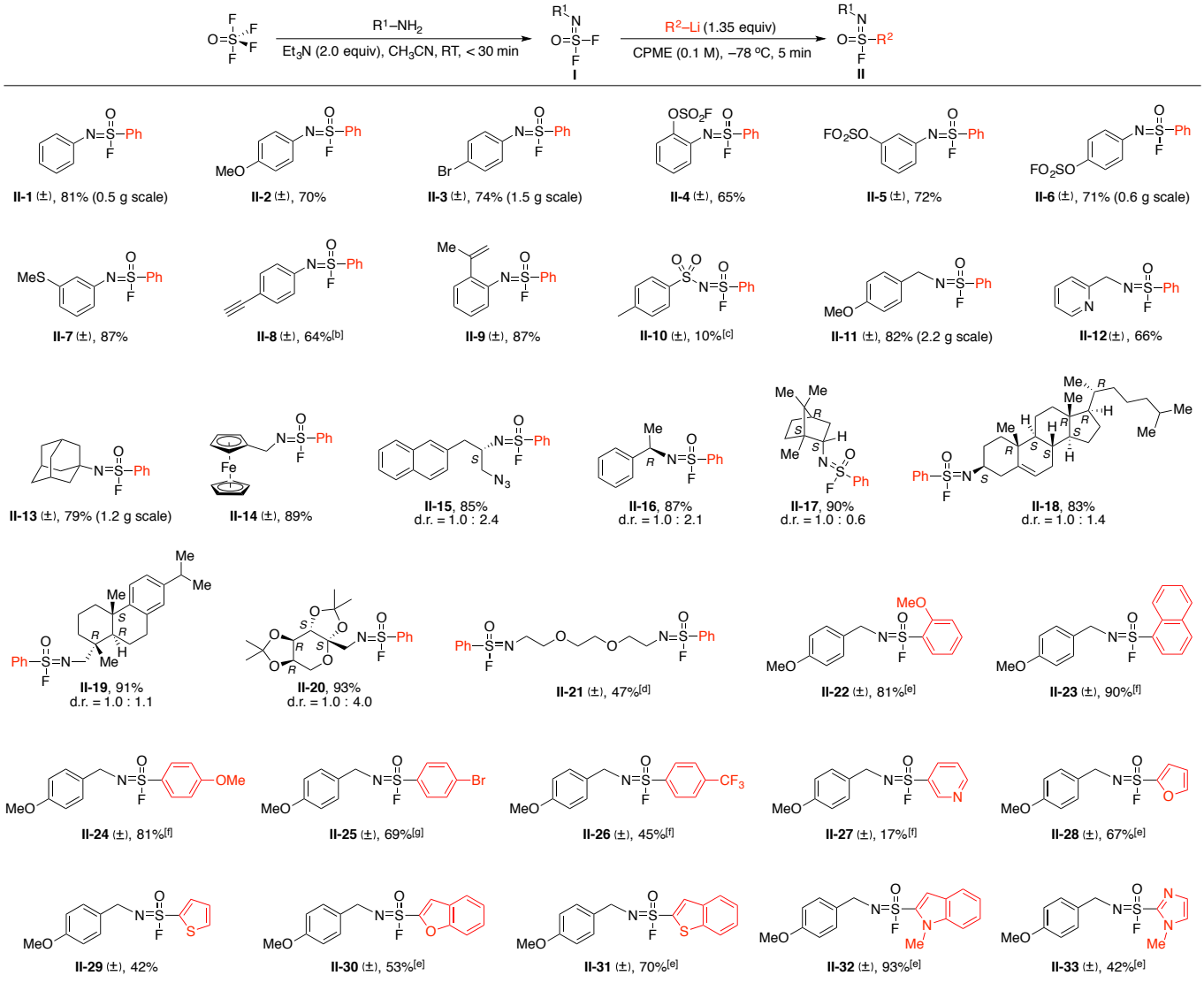
The reaction between phenyliminosulfur difluoride (Ph–N=SF_2, S^{IV}) and phenyllithium was one of the rare examples of sulfur fluorides to react with organometallic reagents, but only affording a mixture of triphenylsulfilimine (Ph–N=$S(Ph)_2$) and diphenyl sulfide (PhSPh).[14] In another case, the reduction of sulfur(VI) to lower-valent adducts was also observed during the nucleophilic substitution of sulfonyl fluoride derivatives (R–SO_2F, S^{VI}) with Grignard reagents.[15] Fortunately, by using aryllithiums at low temperature, we could dramatically diminish the over-substitution

10.1002/anie.201712145

and sulfur-reduction side paths in the reaction with iminosulfur oxydifluorides (**I**). The optimized conditions, 1.35 equivalents of phenyllithium in anhydrous cyclopentyl methyl ether (CPME) at –78 °C for 5 mins, allows mono-substitution of difluorides **I** into the corresponding sulfonimidoyl fluorides **II** in excellent yields (Table 1, see supporting information for condition optimization).[16]

In general, aniline-derived difluorides **I** exhibited good selectivity for mono-substitution (**II-1**–**II-9**), while strong electron-withdrawing substituents (R^1), such as *p*-toluenesulfonyl group (**II-10**), tended to induce over-substitution. It is noteworthy that iminosulfur oxydifluorides (–N=SOF_2) are more electrophilic than fluorosulfates (–OSO_2F) in **II-4**–**II-6** that could be selectively functionalized by phenyllithium.[3a] Such a differentiation implies it is possible for divergent functionalization of compounds containing multiple S–F handles.[17] On the other hand, aliphatic primary amine-derived difluorides are relatively less electrophilic compared to the aniline derivatives, therefore exhibit even enhanced selectivity for mono-substitution (**II-11**–**II-20**).[18] Functional groups that might be liable to the oxidative chlorination conditions in Johnson's route, such as methylthio motif (**II-7**), alkyl motif (**II-8**), olefin (**II-9**, **II-18**) and ferrocenyl group (**II-14**), are well tolerated under our conditions. Bromide and azide motifs are also compatible, thereby allowing for further functionalization (**II-3, II-15**). Finally, the synthesis of bis(sulfonimidoyl fluoride) **II-21** is showcased with moderate yield.

Table 1, Synthesis of Sulfonimidoyl Fluorides from SOF_4.[a]



[a] See supporting information (SI) for the preparation of **I**; For the substitution reaction: **I** (0.2 mmol), ArLi (0.27 mmol), cyclopentyl methyl ether (CPME, 2.0 mL), –78 °C, 5 mins; then quenched with CH_3CO_2H (1.0 M in MeOH) at –78 °C. Isolated yields from **I** to **II** were reported. [b] 2.4 equiv of PhLi used. [c] Di-substituted product **III-1** was isolated in 54% yield. [d] 2.7 equiv of PhLi used. [e] ArLi was prepared from direct C–H lithiation, see SI. [f] ArLi were prepared from aryl bromides (ArBr) via halogen-lithium exchange and THF were used as solvent in most cases, see SI. [g] ArLi was prepared from aryl iodide (ArI) via halogen-lithium exchange, see SI.

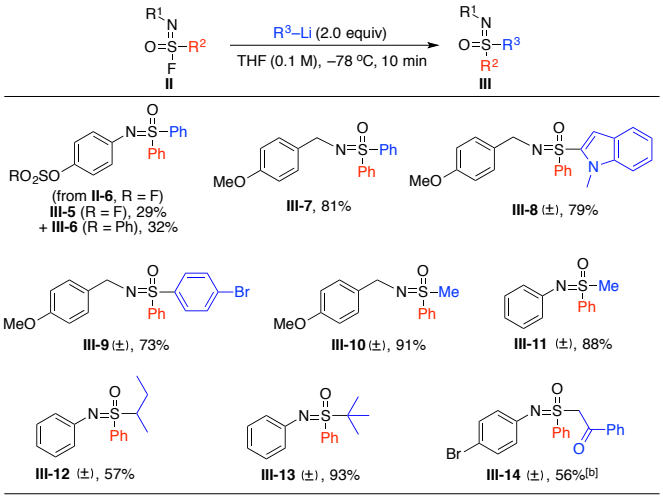
A variety of aryllithiums, prepared from halogen-lithium exchange or direct deprotonation,[19] were investigated in the reaction with difluoride **I-11**.[20] Especially, various heteroaryllithiums afforded the mono-substituted products in good to excellent yield (Table 1, **II-21**–**II-33**). Vinylic and alkynylic lithiums were examined, but no substitution was observed, probably due to their poor nucleophilicity. These results are also in good accordance with examples **II-8** and **II-9**, where terminal alkyl and olefin motifs would not interfere with the substitution reactions with phenyllithium. Alkyllithium reagents were also investigated in the

10.1002/anie.201712145

reaction with **I-2**. Primary and secondary alkyllithium, such as *n*-butyllithium and *s*-butyllithium, mainly afford di-substituted products (sulfoximines **III-2**, **III-3**) rather than mono-substituted ones (**II-34**, **II-35**). In contrast, tertiary alkyllithiums *t*-butyllithium led exclusively to mono-substituted product **II-36**, with only trace amount of di-substituted sulfoximine **III-4**. This is probably due to a combined effect of steric hindrance and basicity of the nucleophiles and the products.[21]

With a reliable process to sulfonimidoyl fluorides **II**, we next studied the formation of a second S–C link with the remaining S–F handle for the preparation of sulfoximines. THF was used as solvent to enhance the reactivity of organolithium nucleophiles for the more demanding second substitution.[19] As illustrated in Table 2, the treatment of **II** with 2.0 equivalents of aryllithiums or alkyllithiums afforded the corresponding sulfoximines **III** in excellent yields. Importantly, we also identified an interesting trend that sulfonimidoyl fluoride motif in **II-6** is slightly more electrophilic than fluorosulfate motif to react with phenyllithium (determined based on the ratio of **III-5** and **III-6**). Finally, a Lewis acid induced S–F bond cleavage and subsequent S–C bond formation also gave sulfoximine **III-14** from sulfonimidoyl fluoride **II-3**.[8]

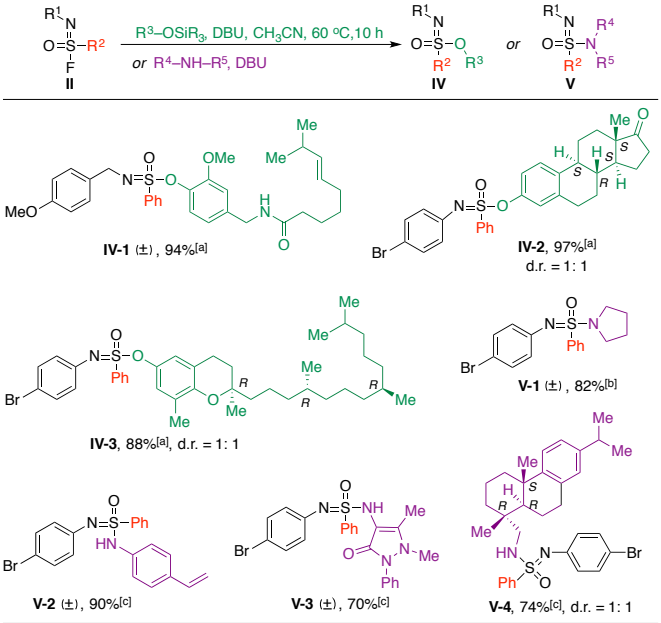
Table 2, Sulfoximines from Sulfonimidoyl Fluorides.[a]



[a] **II** (0.2 mmol), R^2–Li (0.4 mmol), THF (2.0 mL), –78 °C, 10 mins. [b] **II** (0.2 mmol), Ph(TMSO)=CH_2 (0.26 mmol), $TiCl_4$ (0.2 mmol), DCM (2.0 mL), –78 °C, 30 mins.

Aside from creating sequential S–C linkages, the SuFEx reaction with heteroatom linkages has proved a robust approach for diverse functionalization through S–F handles. Sulfonimidates and sulfonimidamides hitherto have mainly been prepared from sulfonimidoyl chlorides, which are liable to hydrolysis and redox side reactions.[22,23] In Table 3, we demonstrate the modification of the natural products Capsaicin, Estrone and (+)-δ-Tocopherol, through DBU-promoted formation of S–O links with sulfonimidoyl fluorides, giving the corresponding sulfonimidates in excellent yields and with good functional group tolerance. As highlighted earlier in this manuscript, an *N*-alkyl substituent (**IV-1**) generally makes the S-center less electrophilic in comparison with an *N*-aryl substituent (**IV-2**, **IV-3**), and therefore requires excess DBU to get full conversion from the corresponding sulfonimidoyl fluorides. Again, DBU also serves as a promising base in the reaction with secondary amines (showcased in example **V-1**). For the reaction with primary amine and anilines, we found that deprotonation of the amino group with *n*-butyllithium prior to the nucleophilic substitution is necessary (**V-2**–**V-4**). These conditions are representative and generally applicable to a wide range of substrates.

Table 3, Sulfonimidates and Sulfonimidamides from Sulfonimidoyl Fluorides.



[a] **II** (0.2 mmol), R^3OTBS (0.2 mmol), DBU (20 mol% to 2.0 equiv), CH_3CN (2.0 mL), 60 °C, 10 h. [b] **II** (0.2 mmol), Pyrrolidine (0.4 mmol), DBU (0.4 mmol), CH_3CN (2.0 mL), 60 °C, 24 h. [c] R^3NH_2 (0.4 mmol), *n*-BuLi (0.4 mmol), THF (2.0 mL), –70 °C, 15 mins, then **II** (0.2 mmol), 0 °C to RT.

To summarize, we have developed a new protocol for the controlled installation of S–C link(s) at the sulfur center of iminosulfur oxydifluorides (R^1–N=SOF_2), by sequential exchange of S–F bonds. As part of the fast modular assembly idea for the construction of multidimensional connections from the SOF_4 hub, this transformation might not be perfect, but is highly worthwhile. It enables a practical route for the rapid synthesis of sulfonimidoyl fluorides. Sulfonimidoyl fluorides themselves serve as versatile tetrahedral connectors with tunable reactivity of the S–F handles. Through the subsequent reaction with diverse nucleophiles, they readily afford sulfoximines, sulfonimidates and sulfonimidamides that are conventionally prepared through tedious routes. The current process is complementary to the established SuFEx chemistry featuring S–O/N links, yet offers enriched diversity to the family of sulfur fluorides and their derivatives that are valuable scaffolds for synthetic transformations and medicinal utilities.

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Conflict of Interest

A patent application covering this work has been filed by The Scripps Research Institute (TSRI, PCT Patent Application No. PCT/US2017/063746).

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Click Chemistry

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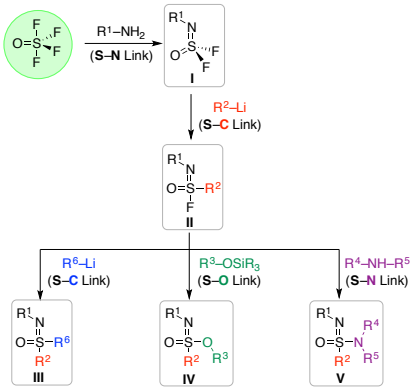

***SuFEx with Sulfur–Carbon Link**: Thionyl tetrafluoride (SOF_4) is a connective gas that enables multidimensional linkages to be created through sulfur fluoride exchange (SuFEx). The installation of sulfur–carbon bond(s) at the sulfur center of SOF_4-derived iminosulfur oxydifluorides is realized in the reaction with organolithium nucleophiles, affording sulfonimidoyl fluorides as versatile SuFEx-able connectors. The synthetic convenience of sulfonimidoyl fluorides is further demonstrated in the preparation of sulfoximines, sulfonimidamides and sulfonimidates.*