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International Edition: DOI: 10.1002/anie.201701162
German Edition: DOI: 10.1002/ange.201701162

Palladium-Catalyzed Fluorosulfonylvinylation of Organic Iodides

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Abstract: *A palladium-catalyzed fluorosulfonylvinylation reaction of organic iodides is described. Catalytic $Pd(OAc)_2$ with a stoichiometric amount of silver(I) trifluoroacetate enables the coupling process between either an (hetero)aryl or alkenyl iodide with ethenesulfonyl fluoride (ESF). The method is demonstrated in the successful syntheses of eighty-eight otherwise difficult to access compounds, in up to 99% yields, including the unprecedented 2-heteroarylethenesulfonyl fluorides and 1,3-dienylsulfonyl fluorides.*

Sulfur(VI) fluoride exchange (SuFEx) represents the latest and one of the most powerful reactions in click chemistry. SuFEx features the unusual stability of S^{VI}–F, and the extreme fidelity of its activation in a nucleophilic substitution event under appropriate reaction conditions.[1] By employing three highly connective molecules, sulfuryl fluoride (SO_2F_2),[1] thionyl tetrafluoride ($O{=}SF_4$),[2] and ethenesulfonyl fluoride ($CH_2{=}CH\text{-}SO_2F$; ESF; **1**),[1,3,4] we are able to readily gain SuFEx abilities for compounds from either nature's pool of nucleophiles or from petrochemicals, and achieve functions in service of multiple disciplines[5,6] through catalytic SuFEx protocols (Figure 1a). Searching for new S^{VI}–F functional groups and developing reliable methods for their installations are considered the major challenge for evolving the current SuFEx chemistry.

ESF, among the three irreplaceable scaffolds of SuFEx chemistry, is unique for its versatile reactivity. We have demonstrated ESF as an essential building block to prepare the otherwise difficult to access compounds, 2-arylethenesulfonyl fluorides, through a Heck–Matsuda process (Figure 1b1).[7] 2-Arylethenesulfonyl fluorides represent a rare family of selectively addressable bifunctional electrophiles. Sulfonyl fluorides and vinyl sulfonates (or sulfone) can be readily prepared from 2-arylethenesulfonyl fluorides by Michael addition and SuFEx, respectively, and both are

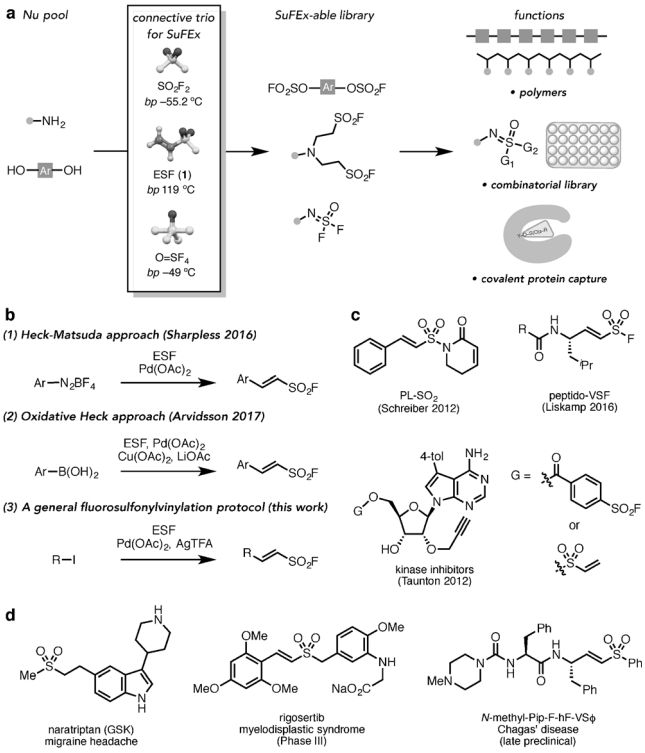

Figure 1. a) Strategic diagram for harnessing the SuFEx click chemistry. b) Evolution of the Heck approach for fluorosulfonylvinylation of organic compounds. c) Bioactive compounds with sulfonyl fluoride or vinylsulfonyl group. d) Drugs (candidates) share the Ar–C–C–SO_2- structural moiety.

important classes of electrophiles and potential covalent pharmacophores (Figure 1c).[8–10] The latter provide permanent inhibition of target proteins, which is of special interest for us.[11] Among the 152 approved S^{VI}-containing drugs,[12] 96 (63%) of them are (hetero)aryl sulfonyl molecules [(Het)Ar–SO_2–Q, including aryl sulfones, sulfonamides, sulfonic acids and sulfonate esters]. The vinylogous analogues [(Het)Ar–CH=CH–SO_2–Q] are much less explored, but could be interesting. Rigosertib (Figure 1d), a Phase III drug candidate treating myelodisplastic syndrome, is the first of this kind to show promising bioactivity.[13]

It is reasonable to conclude from the above that general methods for the synthesis of 2-substituted ethenesulfonyl fluorides would open up access to a new and likely valuable scaffold for medicinal chemists. To date, our recent Heck–Matsuda process represents the best route to 2-arylethenesulfonyl fluorides, but the scope is limited. Besides, the use of diazonium salts raises safety issues, especially for potential scale-up purposes. Very recently, Arvidsson and co-workers reported an oxidative Heck coupling of aryl boronic acids and ESF (Figure 1b2).[14] In pursuit of a more general Heck-type

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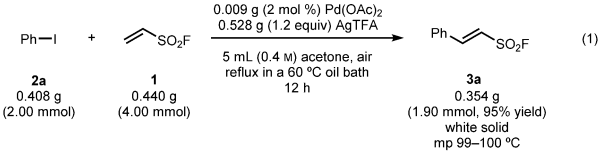
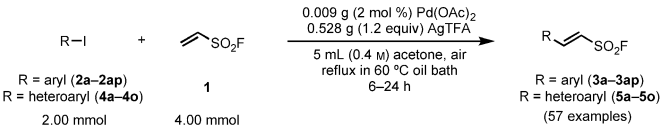
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: http://dx.doi.org/10.1002/anie.201701162.

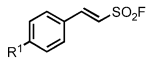
coupling process with ESF,[15,16] we turned to organic iodides. Although the preliminary attempts using either a phosphine ligand or base failed (see the Supporting Information), the combination of an aryl halide/silver(I) salt[17] was found as the fix for this palladium-catalyzed coupling process between iodobenzene (**2a**) and ESF (**1**) [Eq. (1); TFA = trifluoroacetate].[18] With the silver(I) salt boost, we have now extended the fluorosulfonylvinylation reaction to aryl, heteroaryl, and alkenyl iodides (Figure 1b3).



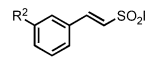
Examination of the examples in Table 1 reveals that our Heck-type reaction has a broad scope for aryl iodides comprising various types of functional groups. Under mild reaction conditions and using simple operations, catalytic amlounts of $Pd(OAc)_2$ and stoichiometric amounts of AgTFA effected the transformations of aryl iodides (**2a**–**ap**) into the corresponding vinyl sulfonyl fluorides **3a**–**3ap** in good to excellent yields. For simple aryl iodides, the corresponding 2-

Table 1: Synthesis of 2-(hetero)arylethenesulfonyl fluorides.[a]

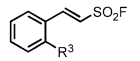




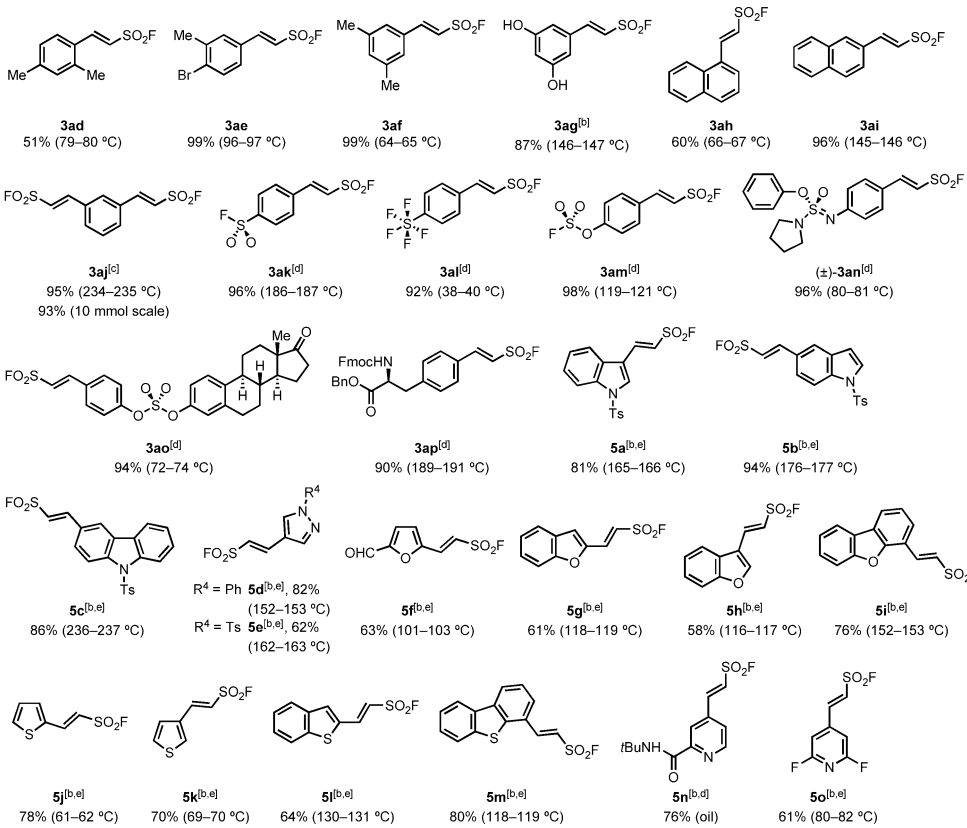
R^1	product	R^1	product
H	**3a**, 95% (99–100 °C)	OCF_3	**3i**, 78% (118–119 °C)
Et	**3b**, 99% (94–95 °C)	CF_3	**3j**, 67% (133–134 °C)
OPh	**3c**, 98% (109–110 °C)	C(O)Me	**3k**, 87% (123–124 °C)
OMe	**3d**, 91% (70–71 °C)	NO_2	**3l**, 79% (159–160 °C)
Ph	**3e**, 88% (145–146 °C)	CN	**3m**, 91% (129–130 °C)
F	**3f**, 88% (87–88 °C)	CO_2Et	**3n**, 97% (122–123 °C)
Cl	**3g**, 92% (129–130 °C)	CHO	**3o**, 81% (135–136 °C)
Br	**3h**, 86% (144–145 °C)	OH	**3p**, 98% (114–115 °C)



R^2	product
OMe	**3q**, 94% (71–72 °C)
Me	**3r**, 97% (29–30 °C)
F	**3s**, 88% (69–70 °C)
Br	**3t**, 89% (81–82 °C)
CF_3	**3u**, 91% (67–68 °C)
C(O)Me	**3v**, 92% (114–115 °C)
NO_2	**3w**, 61% (118–119 °C)
OH	**3x**[b], 98% (127–128 °C)



R^3	product
OMe	**3y**, 59% (oil)
Me	**3z**, 60% (27–28 °C)
C(O)Me	**3aa**, 90% (80–81 °C)
CHO	**3ab**, 56% (73–74 °C)
OH	**3ac**[b], 94% (73–75 °C)



[a] Yields of isolated products and melting points (within parentheses) are reported. [b] 5 mol% $Pd(OAc)_2$ was used. [c] 17 mol% $Pd(OAc)_2$, and 3.0 equiv AgTFA were used. [d] 0.2 mmol scale. [e] A second portion of 2.5 mol% $Pd(OAc)_2$, and 0.6 equiv AgTFA was added after the general procedure, and refluxed for another 12 h. Fmoc = fluorenylmethoxycarbonyl, Ts = 4-toluenesulfonyl.

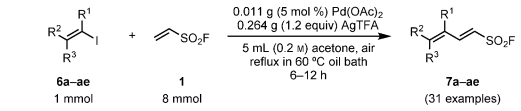
arylethenesulfonyl fluorides were obtained in either similar or better yields than those obtained by a previously described Heck–Matsuda protocol.[7] It is notable that a phenolic hydroxy group (**3p**, **3x**, **3ac**, and **3ag**) is well tolerated in this process, and was incompatible in the Heck–Matsuda process. Not surprisingly, the catalytic system distinguished between iodide and other potential reactive halides (Br: **3h**, **3t** and Cl: **3g**). Moreover, this new protocol succeeded with the multivalent substrate, 1,3-diiodobenzene (**2aj**), for the first time. 1,3-Phenylene bis(ethenesulfonyl fluoride) (**3aj**) was obtained in excellent yield, and was readily scaled up to 10 mmol with the same outcome. The resulting divalent compound was found applicable in a SuFEx poly(aryl vinylsulfonate) synthesis.[18] Three S^{VI}–F functional groups resident in the aryl iodides were tested and found to be untouched in the fluorosulfonylvinylation conditions, including sulfonyl fluoride (SO_2F; **3ak**), sulfur pentafluoride (SF_5; **3al**), and oxysulfonyl fluoride [aryl fluorosulfate (OSO_2F; **3am**)]. Furthermore, to show the superiority of sulfur(VI) as a connective scaffold, the compounds **3an** and **3ao** were synthesized, thus taking advantage of $O{=}SF_4$ and SO_2F_2, respectively, as the S^{VI} hub displaying variable ligands in tetrahedral arrays eminating from the sulfur center.

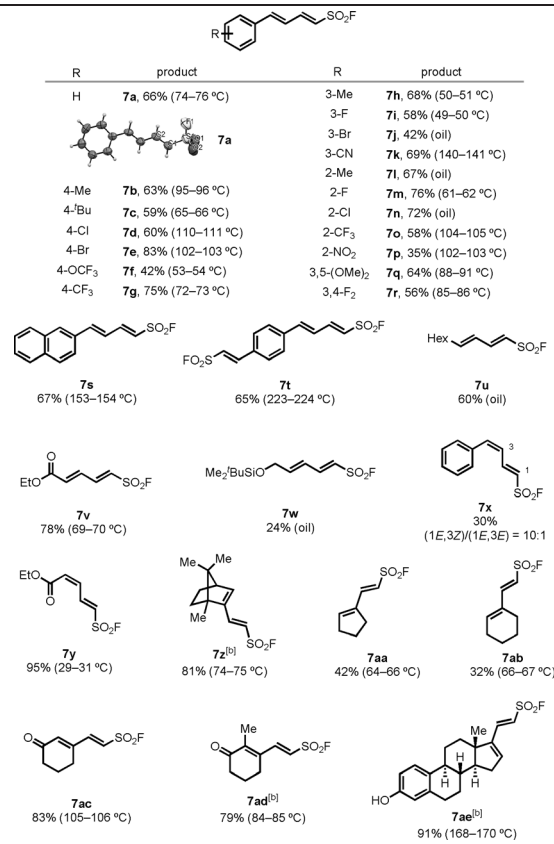
We then examined heteroaryl iodides in this process. Iodine-substituted heterocycles, including indoles (**5a**, **5b**), carbazole (**5c**), pyrazoles (**5d**, **5e**), (benzo)furans (**5f–i**), (benzo)thiophenes (**5j–m**), and pyridines (**5n**, **5o**), underwent fluorosulfonylvinylation reactions efficiently to give the corresponding and unprecedented heteroarylethenesulfonyl fluorides. However, under the current reaction conditions we were not able to utilize aza-heterocycles, wherein the ring nitrogen atom is exposed. Either steric hindrance (**5n**) or electron-withdrawing substituents (**5a–e**, **5n**, **5o**) are essential for the reactions.

Encouraged by these facile syntheses of 2-(hetero)arylethenesulfonyl fluorides, we next turned to alkenyl iodide substrates. For the first time, the 1,3-dienylsulfonyl fluorides (**7a–ae**) were obtained (Table 2). (*E*)-styryl iodides containing a variety of functional groups were found applicable in this process, thus yielding (1*E*,3*E*)-dienylsulfonyl fluorides (**7a–r**) in moderate to good yields with exclusive *E*-selectivity of the Δ^1-olefin and full retention of configuration of the Δ^3-olefin. X-ray crystallography studies proved the structure of **7a**, including the *E* configuration of the two double bonds.[19]

Further evaluation of the substrate scope showed that a wide range of alkenyl iodides could be transformed into the corresponding dienyl sulfonyl fluorides. It was found possible to manipulate an aryl iodide and a styryl iodide in the same substrate molecule, thus realizing a twofold fluorosulfonylvinylation (**7t**). Nonstyryl-type alkenyl iodides also yielded the desired products(**7u–w**). When the (*Z*)-alkenyl iodides (**6x**, **6y**) were examined, the *E* configuration of the Δ^1-double bond in the resulting vinyl sulfonyl fluoride is unambiguous. However, in the case of (*Z*)-styryl iodide (**7x**), the Δ^3-double bond ended up with a 10:1 (*Z*/*E*) ratio. We suggest that the hydridopalladium(II) species from β-elimination might reinsert into the Δ^3-olefin to isomerize it into the thermodynamically more stable *E* configuration.

Table 2: Synthesis of dienylsulfonyl fluorides.[a]





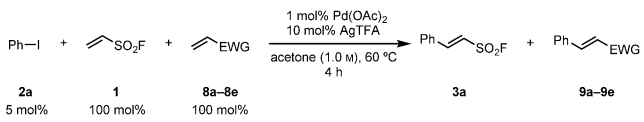
[a] Yields of isolated products and melting points (within parentheses) are reported. [b] 0.2 mmol scale, 0.4 mmol (2 equiv) ESF was used.

Other than the simple alkenyl iodides, olefins with more substituents are also applicable. Readily derived from ketones by employing Barton's hydrazone iodination protocol,[20] these alkenyl iodides were coupled with ESF to give unique new conjugated dienes (**7z–ae**), which have either a trisubstituted or fully substituted olefinic moiety adjacent to the vinyl sulfonyl fluoride group. The 1,3-dienylsulfonyl fluoride derivatives of (*R*)-camphor, cyclic ketones, 1,3-diketones, and estrone were synthesized in moderate to excellent yields.

To evaluate ESF's reactivity as a Heck coupling partner, the relative rates of other Heck ene reactants (**8**) versus ESF were determined by competition experiments (Table 3). It was found that all the carbonyl-substituted olefins are more reactive than ESF in the Heck-type coupling reaction. When ESF was allowed to compete *N*,*N*-dimethylacrylamide (**8d**), no **3a** was observed by ^{1}H NMR spectroscopy, and the sole product was **9d**. Phenyl vinyl sulfone (**8e**), another commonly used vinyl sulfone, showed lower reactivity than ESF.

In summary, we have developed a general method for the preparation of 2-(hetero)arylethenesulfonyl fluorides and 1,3-dienylsulfonyl fluorides. Eighty-eight structurally diverse vinyl sulfonyl fluorides, including seventy-one unprecedented

Table 3: Competition experiments.[a]



Entry	Olefin **8** (EWG)	Products	Relative rates[b]
1	ESF (SO_2F)	**3a**	1.0
2	**8a** (CO_2Me)	**9a**, **3a**	27.1
3	**8b** (CN)	**9b**, **3a**	3.5
4	**8c** [C(O)Et]	**9c**, **3a**	90.4
5	**8d** [C(O)NMe_2]	**9d**	>100
6	**8e** (SO_2Ph)	**9e**, **3a**	0.38

[a] Each of the competition experiments was carried at 1 mmol scale to about 2.5% conversion of "total olefin" (i.e., based upon the number of moles of double bonds) by limiting the amount of iodobenzene added. [b] The ratios refer to relative rates of olefin (**8**) versus ESF, and were determined by ^{1}H NMR spectroscopy and based on the integrations of the α-olefinic hydrogen atom of the products. EWG = electron-withdrawing group.

cases, were synthesized on decent scale with full characterization. Studies on the potential bioactivities of these compounds are currently underway and will be reported in due course.

Acknowledgments

Financial support was provided by the Fundamental Research Funds for the Central Universities (2016-YB-012 to H.L.Q), the National Institutes of Health (R01GM117145 to K.B.S.), and Wuhan University of Technology. We thank Prof. John E. Moses (University of Nottingham) for helpful suggestions on the manuscript preparation.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkenes · click chemistry · drug discovery · fluorine · palladium

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Manuscript received: February 2, 2017
Revised: March 7, 2017
Final Article published: ■■ ■■, ■■■■

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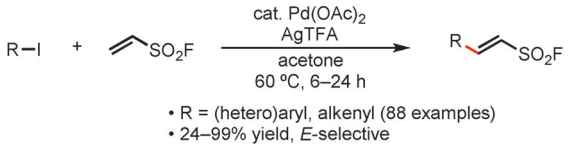
Palladium-Catalyzed Fluorosulfonylvinylation of Organic Iodides



Adding a fluorosulfonylvinyl group: Catalytic $Pd(OAc)_2$ with a stoichiometric amount of silver(I) trifluoroacetate enables the coupling process between either an (hetero)aryl or alkenyl iodide with ethenesulfonyl fluoride. The method is demonstrated in the successful syntheses of eighty-eight otherwise difficult to access compounds, in up to 99% yields. The method does not require base, phosphine ligand, anhydrous solvent, or an inert atmosphere.