HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2017 November 02.

Published in final edited form as:

Angew Chem Int Ed Engl. 2016 November 2; 55(45): 14155–14158. doi:10.1002/anie.201608807.

A Heck-Matsuda Process for the Synthesis of β-Arylethenesulfonyl Fluorides: Selectively Addressable Bis-electrophiles for SuFEx Click Chemistry

Prof. Hua-Li Qin[+],
Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037 (USA). School of Chemistry, Chemical Engineering and Life Science, Wuhan University of Technology, Wuhan, Hubei Province 430070 (China)

Qinheng Zheng[+],
Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037 (USA)

Dr. Grant A. L. Bare,
Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037 (USA)

Prof. Peng Wu, and
Department of Chemical Physiology, The Scripps Research Institute, La Jolla, CA 92037 (USA)

Prof. K. Barry Sharpless
Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037 (USA)

Peng Wu: pengwu@scripps.edu; K. Barry Sharpless: sharples@scripps.edu

Abstract

A Heck-Matsuda process for the synthesis of the otherwise difficult to access compounds, β-arylethenesulfonyl fluorides, is described. Ethenesulfonyl fluoride (i.e., vinylsulfonyl fluoride, or ESF) undergoes β-arylation with stable and readily prepared arenediazonium tetrafluoroborates in the presence of the catalyst palladium(II) acetate to afford the *E*-isomer sulfonyl analogues of cinnamoyl fluoride in 43–97% yield. The β-arylethenesulfonyl fluorides are found to be selectively addressable bis-electrophiles for sulfur(VI) fluoride exchange (SuFEx) click chemistry, in which either the alkenyl moiety or the sulfonyl fluoride group can be the exclusive site of nucleophilic attack under defined conditions, making these rather simple cores attractive for covalent drug discovery.

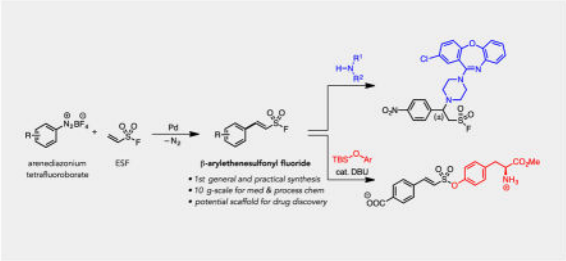
Make it SuFEx-able!

A Heck-Matsuda process for the synthesis of the otherwise difficult to access compounds, β-arylethenesulfonyl fluorides, is described. Ethenesulfonyl fluoride (i.e., vinyl sulfonyl fluoride, or ESF) undergoes β-arylation with stable and readily prepared arenediazonium tetrafluoroborates in the presence of the catalyst palladium(II) acetate to afford the *E*-isomer sulfonyl analogues of cinnamoyl fluoride in 43–97% yield. The β-arylethenesulfonyl fluorides are found to be

Correspondence to: Peng Wu, pengwu@scripps.edu; K. Barry Sharpless, sharples@scripps.edu.

[+]H.L.Q. and Q.Z. contributed equally.

selectively addressable bis-electrophiles for sulfur(VI) fluoride exchange (SuFEx) click chemistry, in which either the vinyl moiety or the sulfonyl fluoride group can be the exclusive site of nucleophilic attack under defined conditions, making these rather simple cores attractive for covalent drug discovery.



Keywords

β-arylethenesulfonyl fluorides; Heck-Matsuda; ethenesulfonyl fluoride (ESF); Michael addition; sulfur(VI) fluoride exchange (SuFEx)

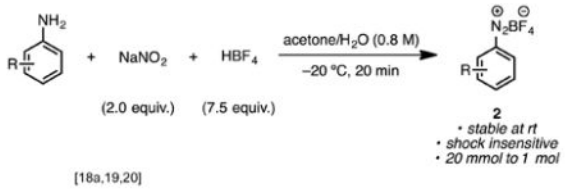
Sulfur(VI) fluoride exchange (SuFEx), a chemistry recently developed in our laboratory, is another valuable addition to the click chemistry reaction toolbox.[1] SuFEx takes advantage of the stringent solvation or activation requirements of the S(VI)–F bond in a nucleophilic substitution event, which results in the special fidelity and efficiency of S(VI)–F compounds for the modular synthesis of S(VI)–X connections (in which X can be OR or NR^1R^2) in either a chemical or biological context.[1a] Within the S(VI)–F family, sulfonyl fluorides ($R–SO_2F$) have found a variety of applications that date back to the mid-twentieth century, for example as surrogate reagents of sulfonyl chlorides for the syntheses of sulfonamides or sulfones,[2] as reactive dyes,[3] and as serine protease inhibitors.[4a,b] In recent years, there has been revived interest in these compounds for the selective modification of proteins,[4c–g] and the fabrication of functionalized materials.[5] Although most alkyl or aryl sulfonyl fluorides can be easily accessed from the corresponding sulfonyl chlorides through chloride-fluoride exchange,[1a,6] the synthesis of β-arylethenesulfonyl fluorides remains a challenge for the synthetic community, which limits its application as a potential scaffold for medicinal chemistry, including for the development of new covalent drugs and enzyme inhibitors.[4d,7]

Prior to this work, there were two existing routes toward the synthesis of β-arylethenesulfonyl fluorides: the sulfonylation of styrene using SO_3 or SO_2Cl_2 (Scheme 1, Eq. 1);[8] and the Horner-Wadsworth-Emmons reaction of benzaldehyde and α-phosphorylmethanesulfonate (Eq. 2).[9] Both approaches suffer from the shortcomings of a very limited substrate scope, multistep operation, and low to moderate overall yield. In our ongoing pursuit of small, highly connective modules for click chemistry, it appeared that ethenesulfonyl fluoride (ESF, **1**) might provide a direct way to access structurally diverse β-arylethenesulfonyl fluorides via a Heck-type β-C–H arylation pathway.[10] Herein, we report the development of the Heck-Matsuda process for the synthesis of β-arylethenesulfonyl fluorides and the discovery of their bis-electrophilic feature.

ESF was reported by Hyatt and Krutak in 1979 to be a uniquely potent and reliable Michael acceptor.[11] Recently, we developed an "on-water" procedure for kilogram-scale preparation of ESF.[1a,12] This new recipe enabled us to examine our proposal to use ESF in the palladium-catalyzed Heck reaction.

Already in 1930, Steinkopf and Jaeger had reported an example of the enormous stability of aryl sulfonyl fluorides to copper catalysts, exemplified in an Ullman coupling of neat 3-iodophenyl sulfonyl fluoride on dry Cu^0 powder at 230 °C.[13] In some recent reports, aryl sulfonyl fluorides were found to tolerate palladium-catalyzed couplings.[4e,14] Even so, the innocence of transition metals for an alkenylsulfonyl fluoride group, in which the sulfonyl fluoride moiety is directly linked to the alkene, appears to have not yet been tested.

This study began with an attempt using the original Heck-Mizoroki conditions, which included phenyl bromide or iodide and ESF in the presence of a catalytic amount of a palladium salt, a phosphine or a pyridine ligand, and a base.[10,15] However, none of the desired product was formed. Also noteworthy is a 2012 report by Prakash and Olah, in which similar conditions were used to carry out a domino hydrolysis/dehydrohalogenation/Heck coupling to produce β-arylethenesulfonate salts in moderate to good yield.[16] We then investigated the Matsuda modification of Heck coupling, i.e., the palladium-catalyzed arylation of an olefin with arenediazonium salts (Scheme 1, Eq. 3),[17,18] the attractive features of this method being the higher reactivity of the arenediazonium species, and hence the absence of need for strong base and heat. Anilines are readily available and their diazonium salts, with tetrafluoroborate counter ions (Eq. 4), are known for the stability.[18a,19,20]



(4)

In a typical experiment of the Heck-Matsuda coupling (synthesis of **3a**), the freshly synthesized benzenediazonium tetrafluoroborate (**2a**, 2.11 g, 11.0 mmol) was treated with ESF (1.10 g, 10.0 mmol) and $Pd(OAc)_2$ (112 mg, 0.500 mmol, 5 mol%) in acetone (40 mL) at room temperature and stirred magnetically. The reaction was monitored by TLC and judged complete after 5 h at room temperature. The ^1H NMR spectrum of the crude material suggested that the arylation process exhibited exclusive *E*-stereoselectivity. The pure product, β-phenylethenesulfonyl fluoride (**3a**, 1.73 g, 9.30 mmol, 93%), was obtained as a white crystalline compound (mp 99–100 °C) using flash column chromatography and subsequent recrystallization. In a further scale-up experiment, we synthesized **3a** at 10 g scale, using the aforementioned procedure.

As shown in Table 1, the substrate scope was explored. Twenty-one new compounds (**3a**–**u**), which were otherwise not directly accessible from simple starting materials prior to this work, were synthesized on at least 10 mmol scale. The Heck-Matsuda process exhibited remarkable fidelity for the β-arylation of ESF, and excellent tolerance for both electron-donating and electron-withdrawing substituents is apparent. The latter contrasts with the earlier known syntheses (vide supra). We determined that *ortho*-, *meta*-, or *para*-monosubstituted and multisubstituted diazonium salts were applicable here as well. For aryl bromides (**2d**, **m**, **s**, and **t**), the C(sp^2)–N bond was selectively cleaved, while the C(sp^2)–Br bond remained untouched in the palladium catalyzed system. This transformation was effective for a carboxylic acid- (**2g**) and a nitro-substituted (**2j**) diazonium salt. We also determined the X-ray structure of **3e** as solid evidence for its *E*-configuration.[21]

Prepared using the Heck-Matsuda process at a decent scale, β-arylethenesulfonyl fluorides inherit both the olefin moiety and the sulfonyl fluoride group from the ESF precursor, for which they can be recognized as bis-electrophiles (i.e., bifunctional electrophiles). We hypothesized that these new compounds might be selectively modified on either electrophilic site under defined conditions. Previously, Pete and co-workers reported that β-arylethenesulfonyl chlorides (ArCH=CH–SO_2Cl) reacted with secondary amines to give sulfonamides (ArCH=CH–SO_2NR_2) in high yield.[22] In sharp contrast, we observed that β-phenylethenesulfonyl fluorides, like their reactive precursor, ESF, possess a strong preference for Michael addition over substitution at the sulfur center (Table 2). They react with cyclic secondary amines, including piperazine (**4a**, **d**, **e**), morpholine (**4b**), and azetidine (**4c**) via this route, resulting in excellent yields of Michael adducts [**(±)-5**]. By employing 1-propargyl piperazine as the nucleophile, we were able to readily install an alkyne-tag onto the sulfonyl fluoride compound (**4d**). This alkyne-tag can further help to identify protein targets captured by [**(±)-5d**] in a Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC)-based pull-down experiment.[23] Importantly, this route provides a straightforward means to modify secondary amine-bearing commercial drugs. For instance, amoxapine, a widely used antidepressant, which inhibits serotonin and norepinephrine reuptake,[24] was easily modified by such a Michael addition [**(±)-5e**].

Compared to ESF, β-arylethenesulfonyl fluorides displayed weaker reactivity toward amine nucleophiles. The desired Michael adducts could only be formed in satisfactory yields when electron-withdrawing groups were present on the aromatic ring [**(±)-5a**–**e**]. However, there are exceptions. Treated with *N*-methylhydrazine, we found that 2-phenylethenesulfonyl fluoride (**3a**) acted as a good Michael acceptor, forming the cyclic sulfonohydrazide **(±)-5f** in near quantitative yield within 10 minutes at room temperature.

In a competition experiment between equimolar amounts of β-(4-nitrophenyl)ethenesulfonyl fluoride (**3j**), a relatively robust compound within the β-arylethenesulfonyl fluoride family, and ESF in the presence of 0.05 equivalents of a secondary amine, 1-phenyl piperazine, we observed 100% conversion and selectivity to the ESF-Michael product (**6**) via ^{1}H NMR, without any detectable formation of **5a** (Scheme 2). This result is qualitatively consistent with Mayr's conclusion in a recent physical organic study that 2-phenylethenesulfonyl fluoride (**3a**) has an electrophilic reactivity 4.5 orders of magnitude lower than that of ESF in the context of Michael additions with sulfonium and pyridinium ylides.[25]

The previous examples illustrate that the electron-withdrawing group substituted β-arylethenesulfonyl fluorides are good Michael acceptors for secondary amines. Furthermore, we demonstrate that β-arylethenesulfonyl fluorides can serve as SuFEx coupling partners, undergoing selective substitution at the S(VI)–F bond while leaving the adjacent olefin moiety unaffected (Table 3).[1a,26,27] In the presence of 10 mol % of 1,8-diazabicycloundec-7-ene (DBU), **3a** reacted with the *tert*-butyldimethylsilyl (TBS) ether of estrone (**7a**) in acetonitrile to afford the aryl alkenylsulfonate (**8a**) in 95% isolate yield. Other examples, including silylated derivatives of bisphenol AF (**7b**), coumarin (**7c**), and 3-ethynylphenol (**7d**), were found effective in the SuFEx reaction, giving sulfonate esters (**8b–d**) in excellent yield. In another example, naltrexone, a drug used to manage alcohol or opioid dependence,[28] was readily silylated and modified with a β-arylethenesulfonyl group (**8e**). The carboxylic acid containing compound **3g** reacted with the TBS ether of *O*-methyl tyrosine (**7f**) in the presence of 1.1 equivalents of DBU (in which, 1.0 equivalent of DBU was used to neutralize the acid) to afford the zwitterionic aryl alkenylsulfonate (**8f**) in 91% yield. The excellent chemoselectivity achieved for the SuFEx reaction over the Michael addition pathway of the nucleophilic amine in **7f** is noteworthy. Owing to the ease of their installation onto diverse scaffolds via SuFEx reactions, β-arylethenesulfonyl fluorides are unique and valuable additions to our SuFEx click chemistry tool kit. By contrast, ESF was not a good sulfonyl fluoride partner for the SuFEx-based sulfonate ester synthesis under the same conditions, probably due to the interference of the adjacent “spring-loaded” vinyl group.

In conclusion, we have added ESF as an olefin coupling partner to the repertoire of the Heck-Matsuda reaction. The process described in this communication represents the first direct and practical synthesis of β-arylethenesulfonyl fluorides. We also demonstrate that β-arylethenesulfonyl fluorides are among the rare examples of easily employed and selectively addressable bis-electrophiles. The latter could directly enable quick access to a large unprecedented family of new molecules for medicinal chemistry. Further studies on the utility of these new compounds and their derivatives for covalent drug discovery are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by the National Institutes of Health (R01 GM117145). H.L.Q. is grateful to Wuhan University of Technology for financial support. We thank Dr. Laura Pasternack (TSRI) for assistance in NMR analysis, and Dr. Milan Gembicky and Prof. Arnold L. Rheingold (UCSD) for assistance in X-ray crystal structure analysis.

References

1. a) Dong J, Krasnova L, Finn MG, Sharpless KB. Angew Chem Int Ed. 2014; 53:9430.Angew Chem. 2014; 126:9584.b) Kolb HC, Finn MG, Sharpless KB. Angew Chem Int Ed. 2001; 40:2004.Angew Chem. 2001; 113:2056.

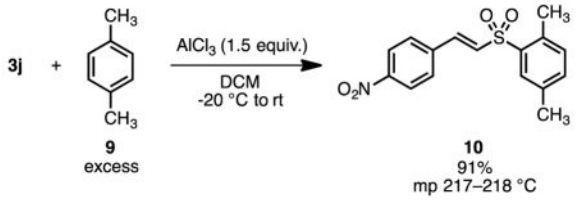
2. a) Köbrich G. Chem Ber. 1959; 92:2981.b) Hyatt JA, White AW. Synthesis. 1984:214.c) Lalonde MP, McGowan MA, Rajapaksa NS, Jacobsen EN. J Am Chem Soc. 2013; 135:1891. [PubMed: 23321009]
3. Krazer B, Zollinger H. Helv Chim Acta. 1960; 43:1513. b) Cassella Farbwerke Mainkur Aktiengesellschaft, FR1193706, 1959
4. a) Gold AM. Methods Enzymol. 1967; 11:706.b) Fahrney D, Gold AM. J Am Chem Soc. 1963; 85:997.c) Zhou Y, Guo T, Tang G, Wu H, Wong NK, Pan Z. Bioconjugate Chem. 2014; 25:1911.d) Narayanan A, Jones LH. Chem Sci. 2015; 6:2650.e) Hett EC, Xu H, Geoghegan KF, Gopalsamy A, Kyne RE Jr, Menard CA, Narayanan A, Parikh MD, Liu S, Roberts L, Robinson RP, Tones MA, Jones LH. ACS Chem Biol. 2015; 10:1094. [PubMed: 25571984] f) Hoppmann C, Wang L. Chem Commun. 2016; 52:5140.g) Chen W, Dong J, Plate L, Mortenson DE, Brighty GJ, Li S, Liu Y, Galmozzi A, Lee PS, Hulce JJ, Cravatt BF, Saez E, Powers ET, Wilson IA, Sharpless KB, Kelly JW. J Am Chem Soc. 2016; 138:7353. [PubMed: 27191344]
5. a) Dong J, Sharpless KB, Kwisnek L, Oakdale JS, Fokin VV. Angew Chem Int Ed. 2014; 53:9466.Angew Chem. 2014; 126:9620.b) Yatvin J, Brooks K, Locklin J. Angew Chem Int Ed. 2015; 54:13370.Angew Chem. 2015; 127:13568.c) Oakdale JS, Kwisnek L, Fokin VV. Macromolecules. 2016; 49:4473.
6. a) Davies W, Dick JH. J Chem Soc. 1931:2104.b) Bianchi TA, Cate LA. J Org Chem. 1977; 42:2031.c) Kim DW, Jeong HJ, Lim ST, Sohn MH, Katzenellenbogen JA, Chi DY. J Org Chem. 2008; 73:957. [PubMed: 18166063]
7. a) Baillie TA. Angew Chem Int Ed. 2016; 55doi: 10.1002/anie.20160191b) Shannon DA, Weerapana E. Curr Opin Chem Bio. 2015; 24:18. [PubMed: 25461720] c) Singh J, Petter RC, Baillie TA, Whitty A. Nat Rev Drug Discovery. 2011; 10:307. [PubMed: 21455239] d) Brienne MJ, Varech D, Leclercq M, Jacques J, Radembino N, Dessalles MC, Mahuzier G, Gueyouche C, Bories C, Loiseau P, Gayral P. J Med Chem. 1987; 30:2232. [PubMed: 3681893] e) Adams DJ, Dai M, Pellegrino G, Wagner BK, Stern AM, Shamji AF, Schreiber SL. Proc Natl Acad Soc USA. 2012; 109:15115.f) Granato M, Lacconi V, Peddis M, Lotti LV, Renzo LD, Gonnella R, Santarelli R, Trivedi P, Frati L, D'Orazi G, Faggioni A, Cirone M. Cell Death Dis. 2013; 4:730.
8. a) Bordwell FG, Suter CM, Holbert JM, Rondestvedt CS. J Am Chem Soc. 1946; 68:139.b) Truce WE, Gunberg PF. J Am Chem Soc. 1950; 72:2401.Rondestvedt CS, Bordwell FG. Org Synth. 1954; 34:85.d) Truce WE, Hoerger FD. J Am Chem Soc. 1954; 76:3230.e) Culbertson BM, Dietz S. J Chem Soc C. 1968:992.
9. Wipf P, Aslan DC, Southwick EC, Lazo JS. Bioorg Med Chem Lett. 2011; 11:313.
10. Heck RF. J Am Chem Soc. 1968; 90:5518.
11. Krutak JJ, Burpitt RD, Moore WH, Hyatt JA. J Org Chem. 1979; 44:3847.
12. Zheng Q, Dong J, Sharpless KB. submitted.
13. Steinkopf W, Jaeger P. J Prakt Chem. 1930; 128:63.
14. Chinthakindi PK, Kruger HG, Govender T, Naicker T, Arvidsson PI. J Org Chem. 2016; 81:2618. [PubMed: 26900892]
15. Mizoroki T, Mori K, Ozaki A. Bull Chem Soc Jpn. 1971; 44:581.
16. Prakash GKS, Jog PV, Krishnan HS, Olah GA. J Am Chem Soc. 2011; 133:2140. [PubMed: 21268583]
17. Kikukawa K, Matsuda T. Chem Lett. 1977; 6:159.
18. a) Oger N, d'Halluin M, Le Grognec E, Felpin F-X. Org Process Res Dev. 2014; 18:1786.b) Mo F, Dong G, Zhang Y, Wang J. Org Biomol Chem. 2013; 11:1582. [PubMed: 23358692] c) Taylor JG, Moro AV, Correia CRD. Eur J Org Chem. 2011:1403.d) Roglans A, Pla-Quintana A, Moreno-Manas M. Chem Rev. 2006; 106:4622. [PubMed: 17091930] e) Felpin FX, Miqueu K, Sotiropoulos JM, Fouquet E, Ibarguren O, Laudien J. Chem Eur J. 2010; 16:5191. [PubMed: 20373307]
19. Mass G, Tanaka M, Sakakura T. Benzenediazonium Tetrafluoroborate. e-EROS Encyclopedia of Reagents for Organic Synthesis. 2001
20. A recent full paper by Schmidt describes the syntheses of β-arylethenesulfonate esters and β-arylethenesulfonamides via a Heck-Matsuda reaction from the corresponding vinylsulfonate esters or vinylsulfonamides, see: Schmidt B, Wolf F, Brunner H. Eur J Org Chem. 2016:2972.

21. X-ray information for compound **3e** can be obtained free of charge from The Cambridge Crystallographic Data center with the deposition number CCDC 1479893.

22. Pete B, Simig G, Poszávácz L, Töke L. Heterocycles. 2003; 60:2441.

23. a) Baker BR. Annu Rev Pharmacol. 1970; 10:35. [PubMed: 4986559] b) Tornøe CW, Christensen C, Meldal M. J Org Chem. 2002; 67:3057. [PubMed: 11975567] c) Rostovtev VV, Green LG, Fokin VV, Sharpless KB. Angew Chem Int Ed. 2002; 41:2596.Angew Chem. 2002; 114:2708.

24. Kinney JL, Evans RL Jr. Clin Pharm. 1982; 1:417. [PubMed: 6764165]

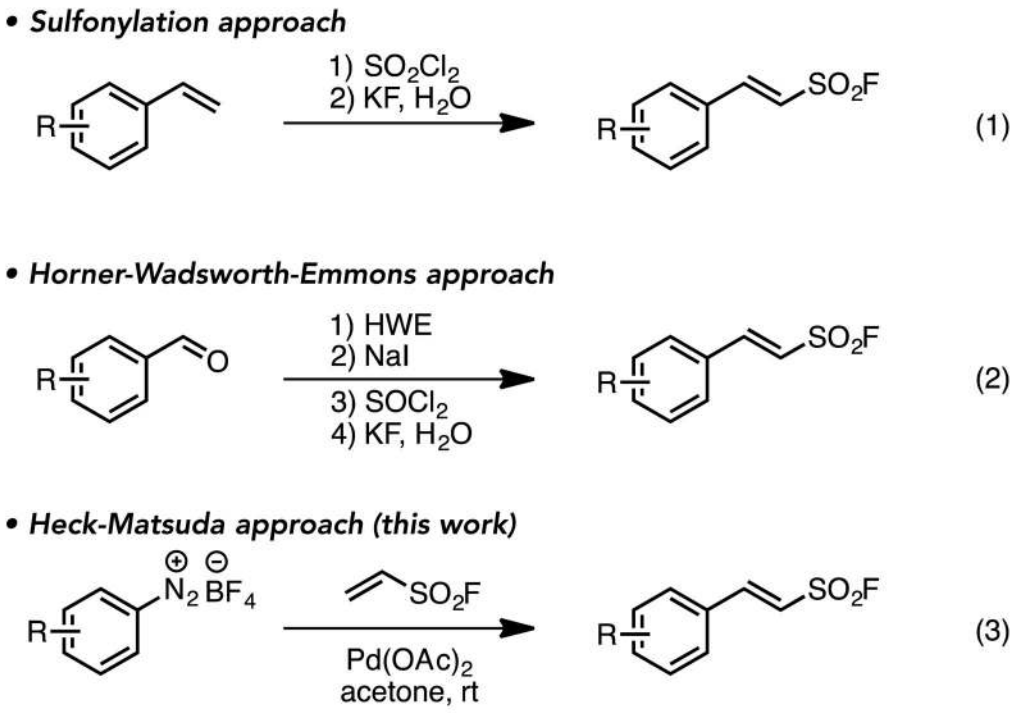


25. Chen Q, Mayer P, Mayr H. Angew Chem Int Ed. 2016; 55doi: 10.1002/anie.201601875

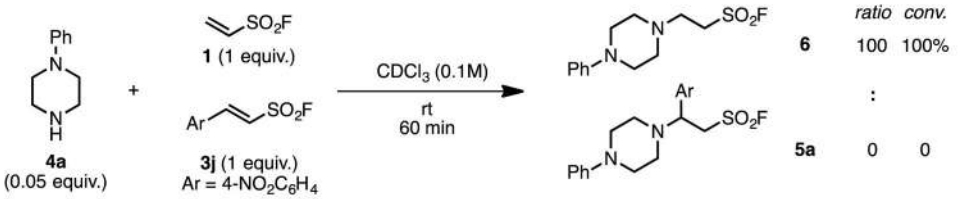
26. Gembus V, Marsais F, Levacher V. Synlett. 2008:1463.

27. Other than SuFEx-based sulfonate synthesis, **3j** undergoes a Friedel-Crafts reaction with *p*-xylene affording **10**.[2b]

28. Pettinati HM, O'Brien CP, Rabinowitz AR, Wortman SP, Oslin DW, Kampman KM, Dackis CA. J Clin Psychopharmacol. 2006; 26:610. [PubMed: 17110818]



Scheme 1.
An overview of the synthesis of β-arylethenesulfonyl fluorides.

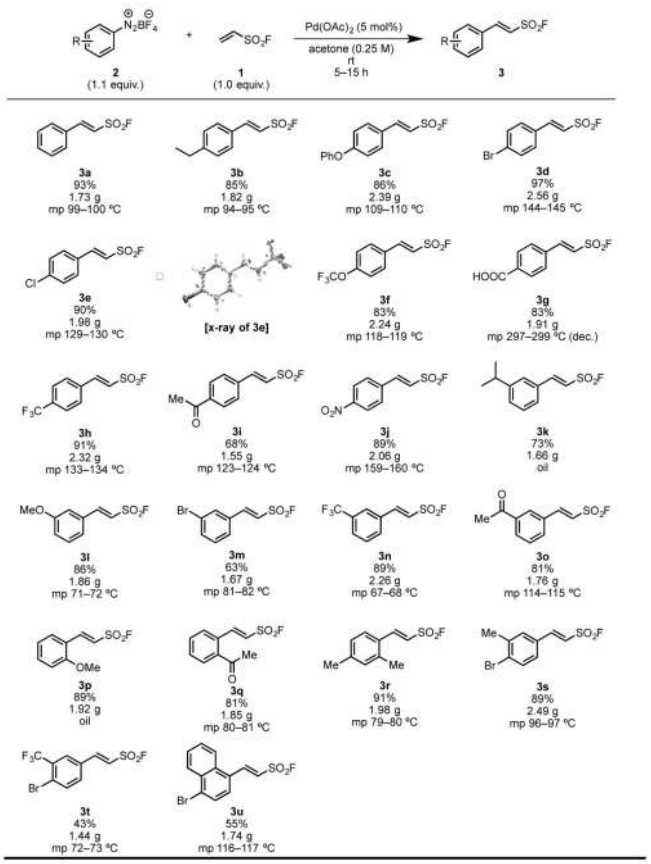


Scheme 2.

The competition reaction between **3j** and ESF as a Michael acceptor.

Table 1

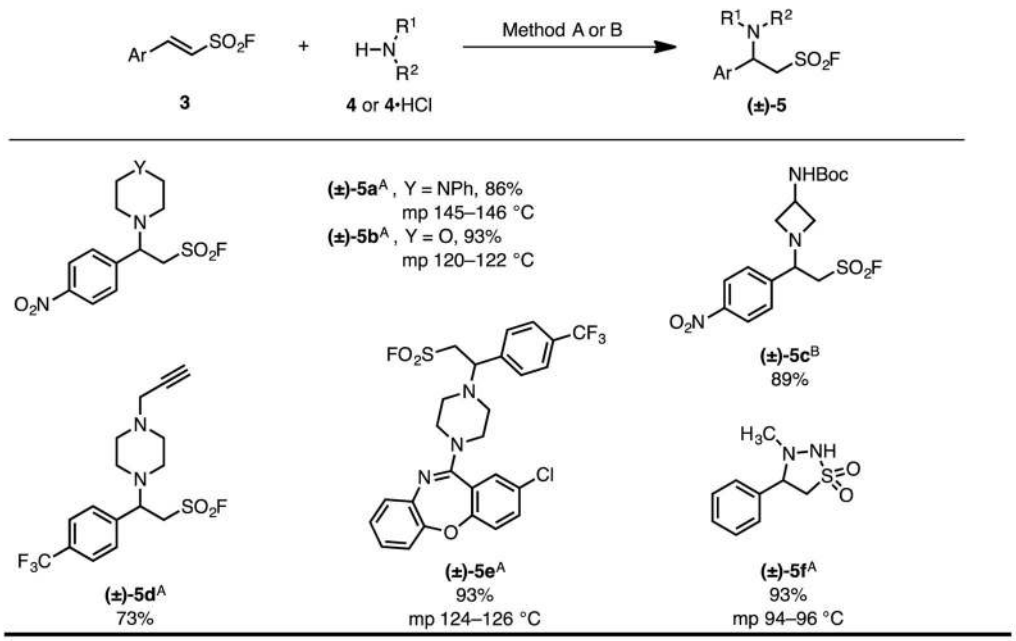
Synthesis of β-arylethenesulfonyl fluorides by a palladium-catalyzed Heck-Matsuda reaction.[a]



[a]The isolated yields and total mass of the isolated product is reported for a representative 10 mmol scale reaction.

Table 2

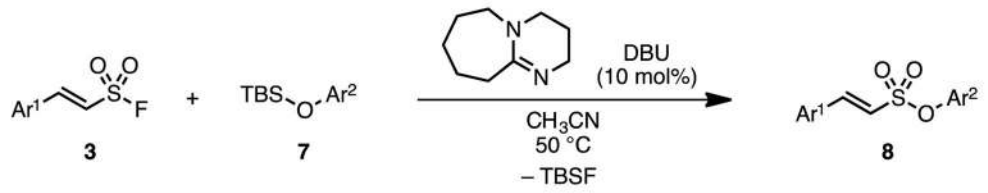
Michael addition of amines to β-arylethenesulfonyl fluorides.[a]

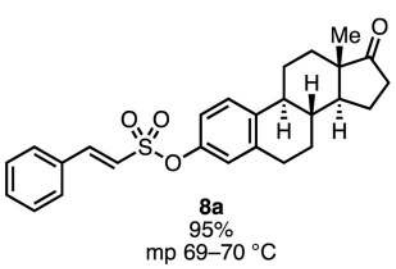


[a]Method A: **3** (1.0 equiv.), **4** (1.2–1.5 equiv.), THF (1 M) or DCM/H_2O (5/1 v/v, 0.2 M), rt or 50 °C. Method B: **3** (1.0 equiv.), **4**•HCl (1.1 equiv.), NEt_3 (1.1 equiv.), MeOH (0.1 M), 50 °C.

Table 3

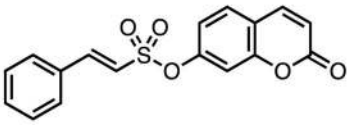
Synthesis of aryl alkenylsulfonates via SuFEx.[a]



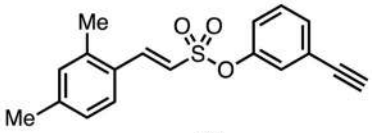


8a
95%
mp 69–70 °C

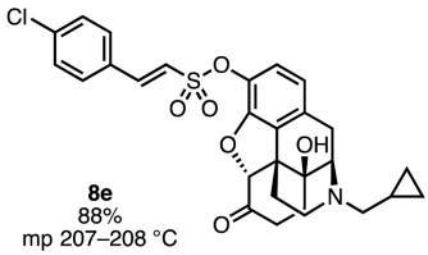
8b
99%
mp 63–65 °C



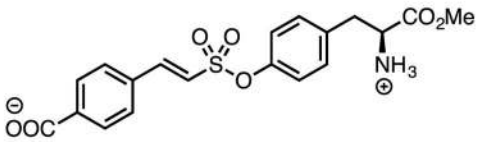
8c
90%
mp 110–111 °C



8d
93%
mp 114–115 °C



8e
88%
mp 207–208 °C



8f
91% (1.1 equiv. DBU)
179–182 °C (dec.)

[a]Conditions: **3** (1.0 equiv.), **7** (1.0 equiv.), DBU (10 mol %), CH_3CN (0.5 M), 50 °C.