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

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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!

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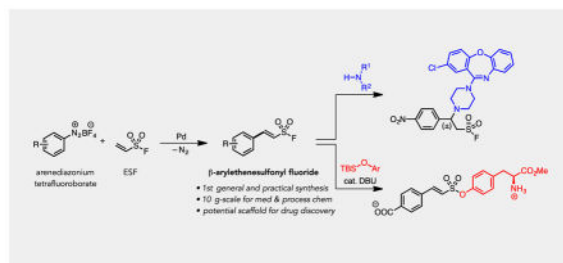
Keywords

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]
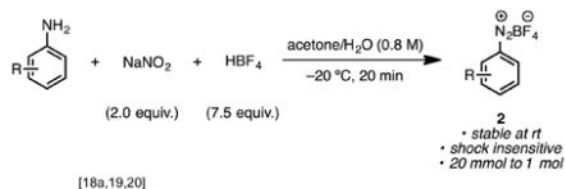
(4)

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 ^{1}H 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$_2$Cl) reacted with secondary amines to give sulfonamides (ArCH=CH–SO$_2$NR$_2$) 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

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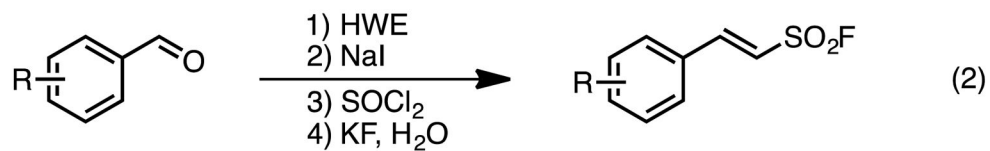24. Kinney JL, Evans RL Jr. Clin Pharm. 1982; 1:417. [PubMed: 6764165]
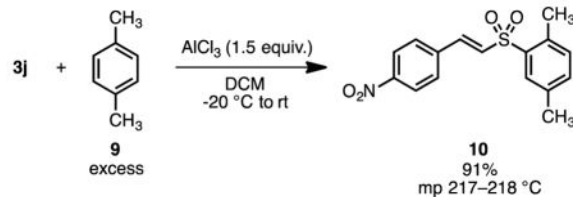
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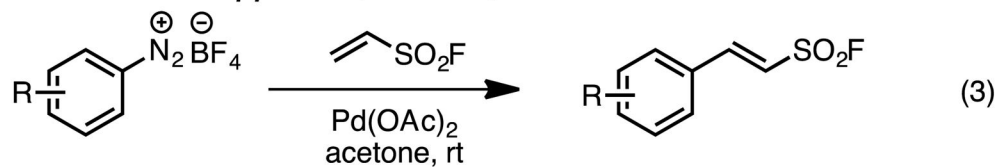
- *Sulfonylation approach*

$$R \overset{\text{1) } SO_2Cl_2}{\underset{\text{2) KF, H}_2O}{\longrightarrow}} R \diagdown SO_2F \qquad (1)$$
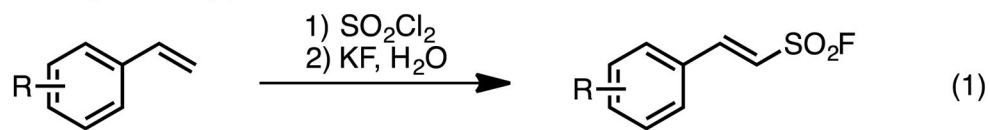
- *Horner-Wadsworth-Emmons approach*

$$R \overset{\text{1) HWE}}{\underset{\text{3) SOCl}_2 \\ \text{4) KF, H}_2O}{\longrightarrow}} R \diagdown SO_2F \qquad (2)$$

- *Heck-Matsuda approach (this work)*

$$R-N_2^{\oplus} BF_4^{\ominus} + \diagup SO_2F \overset{\diagup SO_2F}{\underset{\text{Pd(OAc)}_2 \\ \text{acetone, rt}}{\longrightarrow}} R \diagdown SO_2F \qquad (3)$$
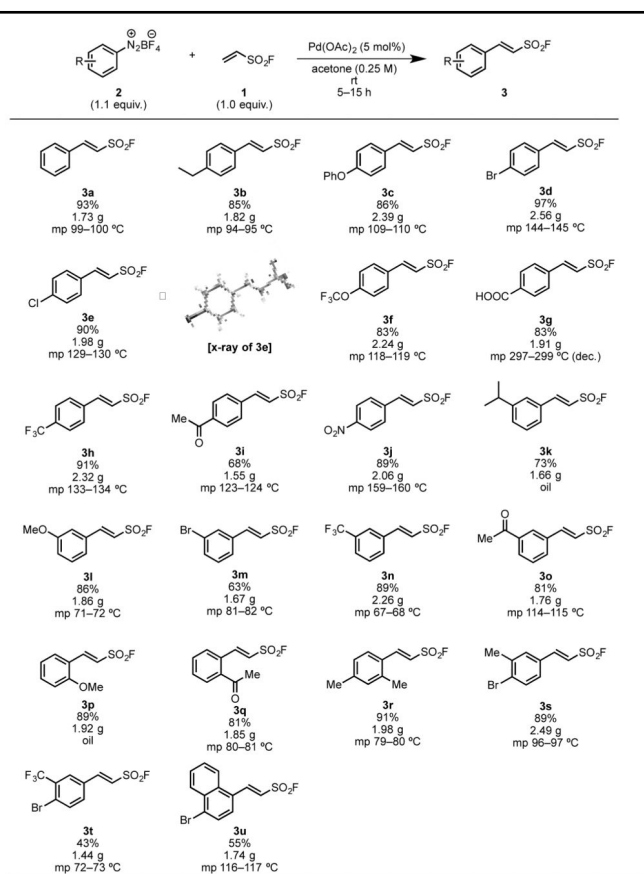
Scheme 1.
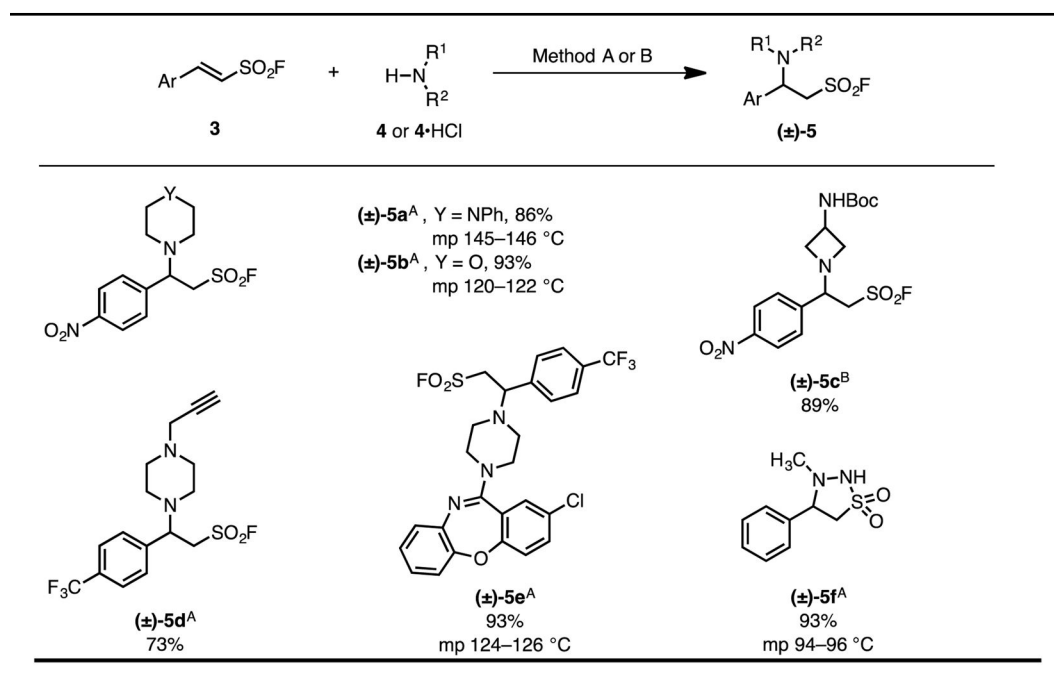An overview of the synthesis of β-arylethenesulfonyl fluorides.
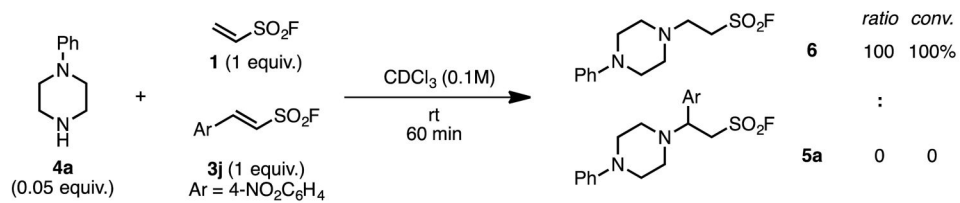
Scheme 2.
The competition reaction between **3j** and ESF as a Michael acceptor.

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]

$(\pm)$-5a[A] , Y = NPh, 86%
mp 145–146 °C

$(\pm)$-5b[A] , Y = O, 93%
mp 120–122 °C

$(\pm)$-5c[B]
89%

$(\pm)$-5d[A]
73%

$(\pm)$-5e[A]
93%
mp 124–126 °C

$(\pm)$-5f[A]
93%
mp 94–96 °C

[a]Method A: **3** (1.0 equiv.), **4** (1.2–1.5 equiv.), THF (1 M) or DCM/H2O (5/1 v/v, 0.2 M), rt or 50 °C. Method B: **3** (1.0 equiv.), **4•HCl** (1.1 equiv.), NEt3 (1.1 equiv.), MeOH (0.1 M), 50 °C.

Table 3

Synthesis of aryl alkenylsulfonates via SuFEx.[a]
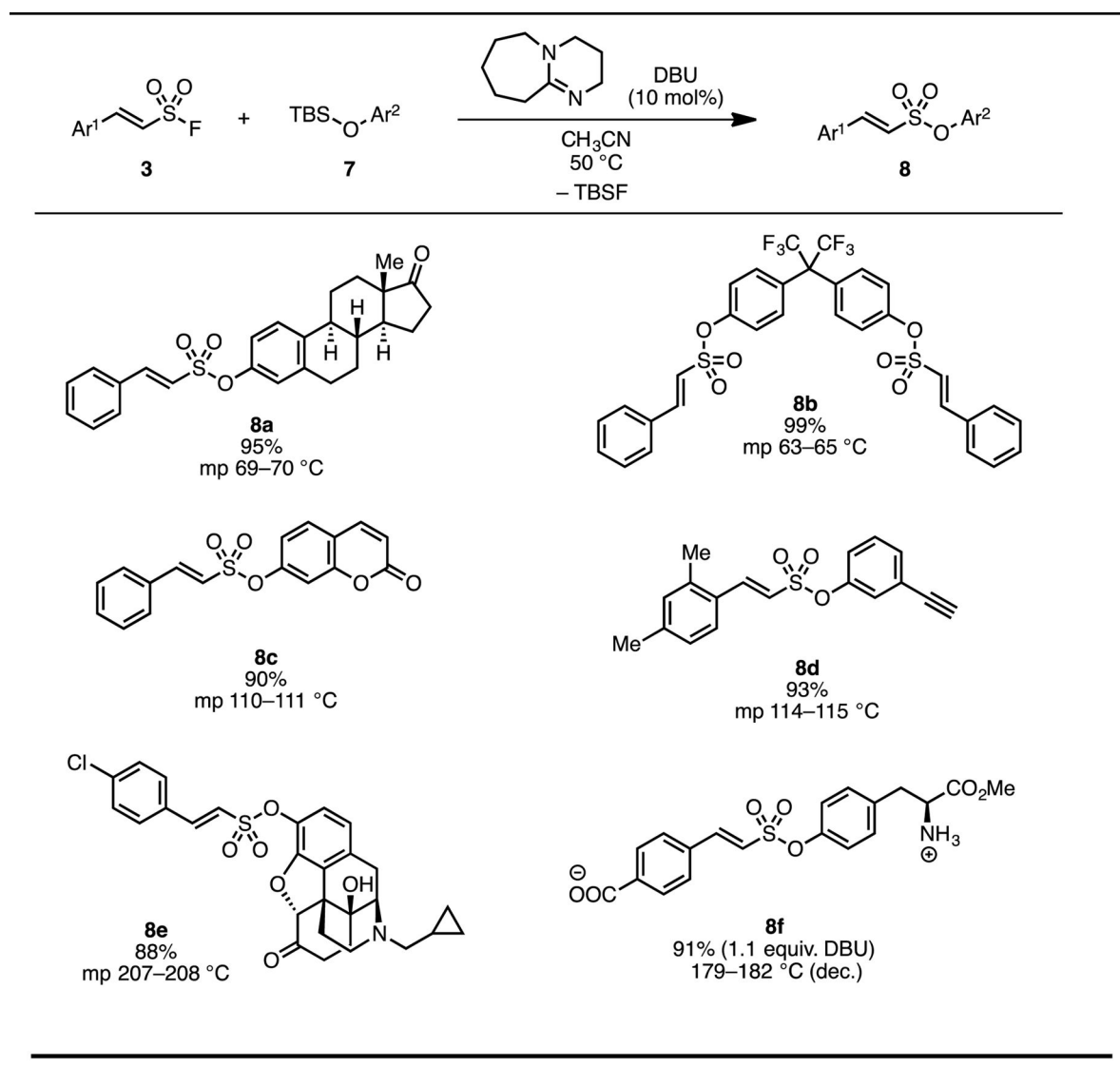
[a]Conditions: **3** (1.0 equiv.), **7** (1.0 equiv.), DBU (10 mol %), CH₃CN (0.5 M), 50 °C.