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Synthesis of β-Arylethenesulfonyl Fluoride via Pd-Catalyzed Nondirected C−H Alkenylation

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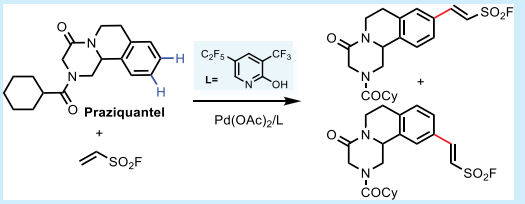
Supporting Information

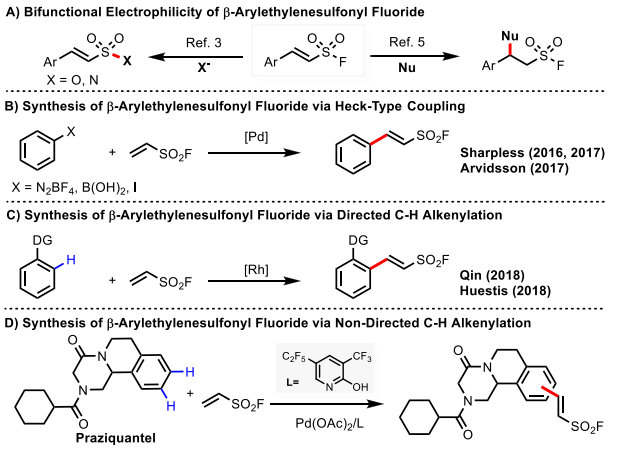
ABSTRACT: A rapid synthesis of β-arylethenesulfonyl fluorides is realized using ligand-accelerated Pd(II)-catalyzed nondirected C−H alkenylation of simple arenes. The newly developed electron-deficient 2-pyridone ligand is crucial for this transformation with arenes as limiting reagent. This protocol features a broad substrate scope and good functional group tolerance. Late-stage functionalization of various pharmaceuticals and their further click manipulations demonstrate this procedure to be highly valuable.



Nondirected C(sp²)−H activation using arene as the limiting reagent remains a significant challenge: electron-deficient arenes are significantly less reactive, and the diversity and scope of transformation is rather limited.[1,2] We have recently developed a pyridone-based ligand that can enable C−H olefination and carboxylation using 1 equiv of arenes.[2a] However, extending this initial finding to broad synthetic applications remains to be demonstrated. β-Arylethenesulfonyl fluoride derivative, one irreplaceable scaffold in sulfur(VI) fluoride exchange (SuFEx) chemistry,[3,4] has been documented as a unique bifunctional electrophile. Michael addition[5] or SuFEx chemistry[3] could take place in a selective fashion depending on suitable reaction conditions (Scheme 1A). Typically, β-arylethenesulfonyl fluoride motifs can be synthesized via sulfonylation of styrene derivatives[7] or via Horner−Wadsworth−Emmons approach from benzaldehyde.[8] More recently, the Sharpless group and the Arvidesson group have adopted a Pd-catalyzed Heck-type alkenylation to access the title compounds by using diazonium salts,[6a] aryl boronic acids,[6b] or aryl iodides[6c] as starting materials (Scheme 1B). Notably, Qin and Huetis recently reported several Rh(III)-catalyzed directed C−H olefinations with vinyl sulfonyl fluoride using different directing groups which provide a new entry to β-arylethenesulfonyl fluorides (Scheme 1C).[9] Taking account of wide appearance of sulfur(VI) containing moieties (sulfonate, sulfonamide, sulfone, etc.) in marketed drugs,[10] we became interested in developing a nondirected C−H olefination reaction with vinyl sulfonyl fluorides. Herein, we report a practical procedure to access β-arylethenesulfonyl fluoride via ligand-accelerated Pd-catalyzed nondirected C−H fluorosulfonylvinylation of simple arenes using arene as limiting reagent (Scheme 1D). This direct C−H fluorosulfonylvinylation of simple arenes substantially broadens the diversity of β-arylethenesulfonyl fluorides that can be used to access unique SuFEx precursors.

Our efforts to develop the C−H alkenylation with vinyl sulfonyl fluorides is based on our recent finding that 2-pyridone ligand can accelerate Pd(II)-catalyzed nondirected C−H functionalization of simple arenes with high efficency.[2a] A series of inert simple arenes, heterocycles, and functional molecules can be tolerated with our procedure relying on the development of 2-pyridone ligand. Taking account of the step-economy of C−H activation reactions, it will be highly desired if the nondirected C−H fluorosulfonylvinylation can be

Scheme 1. Synthesis of β-Arylethenesulfonyl Fluoride



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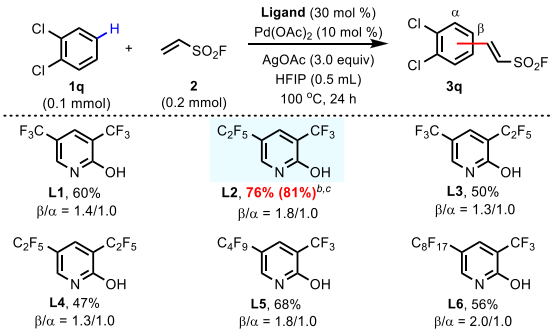
realized in this regard. However, this hypothesis faces several challenges according to the known literature. First, the direct Friedel–Crafts reaction of simple arene with ESF (ethenesulfonyl fluoride) might occur under acidic conditions.[6a] Second, ESF is less reactive than normal ethyl acrylate under Pd-catalyzed Heck-type reaction conditions,[3b] although ESF is a superior Michael acceptor.[5c]

We chose the less active 1,2-dichlorobenzene (**1q**) substrate to test our previous ligand-accelerated Pd-catalyzed nondirected C–H functionalization conditions. Gratifyingly, 60% yield of desired olefinated products (**3q**) with a selectivity of 1.4/1.0 (β/α) was obtained. After systematic evaluation of different reaction parameters, such as palladium sources, solvents, oxidants, and 2-pyridone-type ligands, 3,5-bistrifluoromethyl-2-pyridone **L1** still served as the best ligand employing HFIP as solvent and AgOAc as oxidant. We then turned our attention to develop more efficient 2-pyridone ligands (Scheme 2). We were pleased to find that a slightly

Scheme 2. Ligand Evaluation[a]



[a]The yield was determined by ^{1}H NMR using CH_2Br_2 as the internal standard. [b]The reaction was conducted on a 0.2 mmol scale, HFIP (0.25 mL). [c]73% isolated yield, β/α = 2.0/1.0.

more electron-deficient ligand **L2** gave us improved yield and selectivity (76% yield, β/α = 1.8/1.0), in which C5-CF_3 was replaced by electron-withdrawing C_2F_5 group. Neither placing the C_2F_5 at the C3 position in the ligand scaffold (**L3**) nor 3,5-di-C_2F_5 substituted ligand **L4** gave promising yields. Other modifications with long-chain perfluoroalkyl groups at the C5 position (**L5**,**6**) were also investigated, providing lower yields. The yield was further improved to 81% NMR yield (73% isolated yield) with a selectivity of 2.0/1.0 (β/α) by concentrating the reaction system in the presence of optimal ligand **L2**. Notably, the newly developed ligand **L2** is crucial for this ligand-accelerated Pd-catalyzed nondirected C–H fluorosulfonylvinylation of simple arenes. The kinetic study using **L1** and **L2** under the standard conditions showed that the initial reaction rate with **L2** is 1.6 times faster than that with **L1** (see the Supporting Information). According to our previous study,[2a] the ligand might be capable of accelerating the C–H cleavage step as an inner base and stabilizing the active palladium catalyst.

Under the optimal conditions, the scope of simple arenes was systematically examined employing **L2** as ligand. As summarized in Scheme 3, both electron-rich and electron-deficient aromatics were tolerated with this procedure, providing the monofluorosulfonylvinylated products in moderate to excellent yields (**3a–l**). In addition, this protocol features good functional group tolerance. Alkyl (**3b–d**), MeO (**3e**), F (**3g**), Cl (**3h**), CF_3 (**3i**), aldehyde (**3j**), ketone (**3k**), ester (**3l**), and NO_2 (**3v**) were all compatible with this procedure. When high active arenes were employed, a small amount of dialkenylated products were also observed (see the Supporting Information). For instance, benzene gave the monoproduct **3a** in 65% yield and diolefinated products in about 10% yield using HFIP as solvent. It is noteworthy that the major alkenylation reaction for electron-rich monosubstituted arenes occurred at the *meta* position in good yields (**3b–f**). This observation is inconsistent with the previous system employing ethyl acrylate as coupling partner for Pd-catalyzed nondirected C–H functionalization in which the *para* position product predominates as the major isomer. Primary study indicates the selectivity difference is caused by the unique properties of ESF, although the detailed reason is unclear so far (see control experiments in the Supporting Information). Not surprisingly, less reactive electron-deficient arenes were alkenylated using this catalytic system to afford the corresponding products in moderate to good yields with synthetically useful *meta* selectivity (**3g–l**). Moreover, naphthalene also provided the mono-olefinated product (**3m**) in 61% yield with a 14.0/1.0 (β/α) selectivity ratio by steric control. Disubstituted and trisubstituted aromatics were then examined. Generally, the selectivity of symmetric 1,2-disubstituted arenes was primarily governed by steric (**3n–q**), whereas substrates with less sterically hindered substituents such as 1,2-difluorobenzene (**3p**) and 1,2-dichlorobenzene (**3q**) provided a mixture of α- and β-olefinated products with the latter one as the major isomer. Fluorosulfonylvinylation of *m*-xylene led to the β isomer selectively (**3r**), but the 1,3-dichlorobenzene (**3s**) gave the α isomer as the major products probably due to the electronics. Symmetric 1,4-disubstituted aromatics (**3t**) and 4-substituted anisoles (**3u**,**v**) were also suitable substrates for this reaction and generally underwent monofunctionalization in high yield and selectivity. 1,3,5- and 1,2,3-trisubstituted arenes also reacted smoothly, providing the desired products in high yields (**3w**,**x**). We then investigated heterocyclic aromatics using this catalytic system. Heterocycles, including indoline (**1y**), 1,2,3,4-tetrahydroquinoline (**1z**), thiophene (**1aa**), furan (**1ab**), (benzo)thiophene (**1ac**), and 1,3-dimethyluracil (**1ad**), underwent this nondirected C–H fluorosulfonylvinylation reaction efficiently to give the corresponding heteroarylethenesulfonyl fluorides in moderate to good yields (**3y–ad**). However, electron-deficient heterocyclic aromatics, like pyridine and quinoline, cannot tolerate the current conditions.

Taking advantage of this novel protocol, several amino acid derivatives and drugs were evaluated under the ligand-accelerated Pd-catalyzed nondirected C–H fluorosulfonylvinylation conditions (**5a–f**). Both phenylalanine derivative **5a** and *O*-methyltyrosine derivative **5b** delivered the corresponding olefinated products in 76% and 60% yields, respectively. Pharmaceuticals and their derivatives, such as clofibrate (**5c**), praziquantel (**5d**), metalaxyl (**5e**), and estrone (**5f**), were compatible with this protocol, providing corresponding products in moderate to good yields (Scheme 4). Notably, gram-scale reaction with praziquantel gave the desired olefinated products **5d** in 70% yield. The late-stage fluorosulfonylvinylation of those complex structures demonstrated the versatility of this reaction.

The unique reactivity of β-arylethenesulfonyl fluoride were tested choosing fluorosulfonylvinylated *O*-methyltyrosine derivative **5b**. Amidation of **5b** with morpholine provided the desired product sulfonamide **6** in 81% yield. Vinylsulfone **7**

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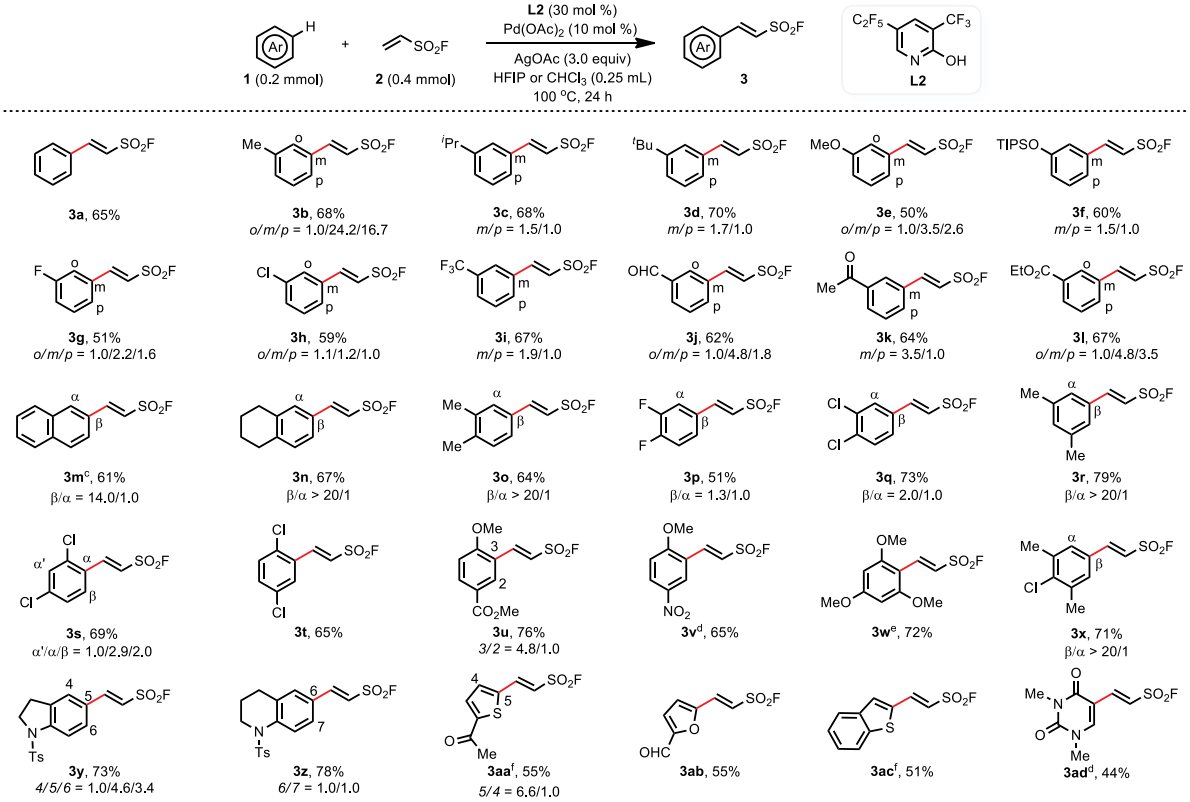
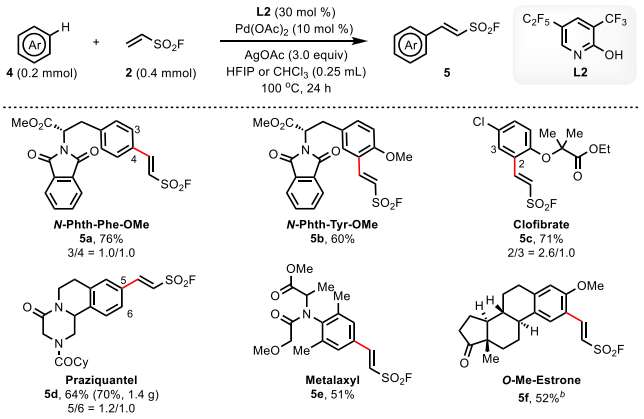
Scheme 3. Substrates Scope of Simple Arenes[a,b]



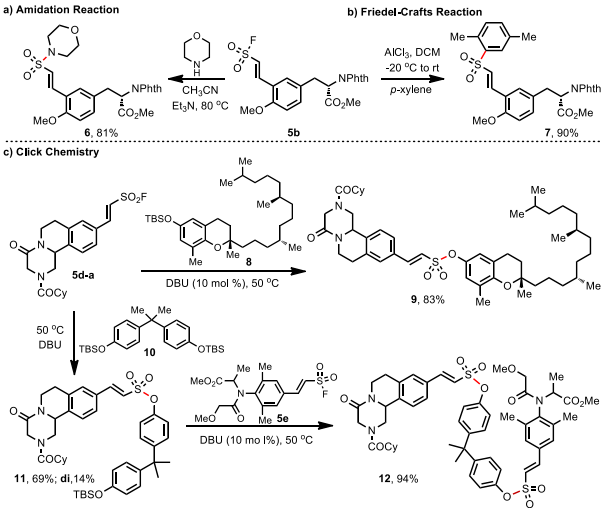
[a]For detailed reaction conditions, see the Supporting Information. [b]Isolated yield; the regioselectivity was determined by ^{1}H NMR. [c]$CHCl_3$ (0.25 mL) was used instead of HFIP. [d]$Pd(OAc)_2$ (20 mol %), **L2** (60 mol %), and ESF (4.0 equiv) were used. [e]**L1** (13.9 mg, 30 mol %) and $CHCl_3$ (0.25 mL), 10 h. [f]Ag_2CO_3 (1.5 equiv) was used instead of AgOAc, 16 h.

Scheme 4. Late-Stage Functionalization[a]



[a]Isolated yield; the regioselectivity was determined by ^{1}H NMR. [b]$Pd(OAc)_2$ (20 mol %), **L1** (60 mol %), ESF (4.0 equiv), and $CHCl_3$ (0.25 mL) were used.

Scheme 5. Applications of β-Arylethenesulfonyl Fluoride



was obtained in 90% yield under the typical Friedel−Crafts reaction conditions. More importantly, two bioactive fragments can be easily assembled to one complex functional molecule via SuFEx chemistry. As summarized in Scheme 5c, TBS-protected (+)-δ-tocopherol **8** can be easily installed on fluorosulfonylvinylated praziquantel **5d-a** in 83% yield under the standard SuFEx conditions. Assembly of fluorosulfonylvinylated metalaxyl (**5e**) and **5d-a** by a bisphenol A linkage led to the desired product **12** in 65% total yield after two sequential manipulations.

In summary, practical and rapid synthesis β-arylethenesulfonyl fluoride has been achieved using ligand-accelerated Pd-catalyzed nondirected C−H alkenylation for the first time. The key to the success of this protocol is the development of an electron-deficient 2-pyridone ligand. Moreover, this protocol features broad substrate scope and functional group tolerance. The late-stage fluorosulfonylvinylation of several amino acid derivatives and drugs demonstrates the versatility of this procedure and will open a new avenue for drug discovery via SuFEx click chemistry.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, complete characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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