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A regio- and stereoselective Heck–Matsuda process for construction of γ-aryl allylsulfonyl fluorides†

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A highly efficient regio- and stereoselective Heck–Matsuda method was developed employing aryl diazoniums and allylsulfonyl fluorides for the construction of a class of novel γ-aryl allylsulfonyl fluorides in the presence of $Pd(OAc)_2$ and PPh_3. The method features excellent regio- and stereoselectivity (up to 100% *E*-selectivity), broad substrate scope and mild reaction conditions. Further application of γ-aryl allylsulfonyl fluoride in SuFEx reactions was achieved to provide their corresponding sulfonates and sulfonamides in excellent yields.

Sulfur(VI) fluoride exchange (SuFEx), firstly developed by K. B. Sharpless and co-workers in 2014,[1] has gained burgeoning attention in the fields of drug discovery,[2] protein target identification,[3] bioconjugation,[4] surface chemistry,[5] and polymer chemistry.[6] The sulfonyl fluoride moiety as a vital functionality of SuFEx chemistry is widely applied in many fields based on the unique balance between aqueous stability and chemical reactivity of the S^{V}–F bond.[7] Aliphatic sulfonyl fluorides, as a class of representative sulfonyl fluoride molecules have been utilized as privileged "warheads" in enzyme inhibitors for decades,[8] involving MSF,[9] AM3506,[10] AM-374,[11] and PMSF[12] (Fig. 1). Allylic sulfones also have emerged as important building blocks in organic synthesis,[13] which widely present in a large variety of biologically active compounds (Fig. 1a).[14]

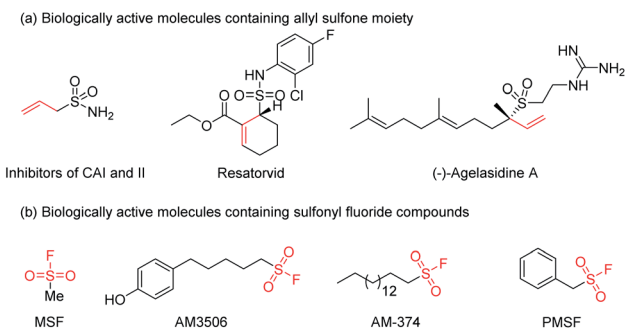
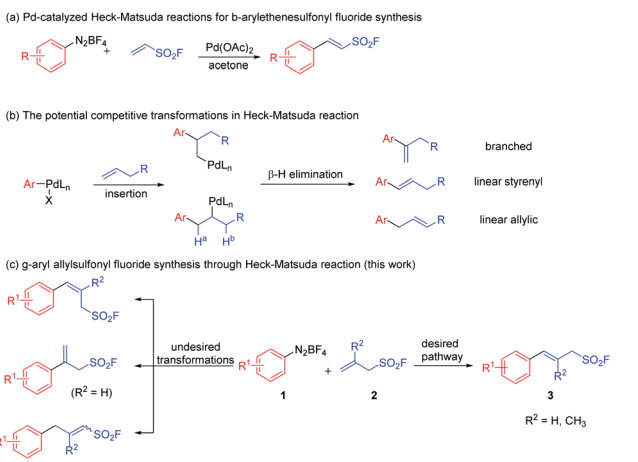


Fig. 1 Biologically active compounds containing allyl sulfones and sulfonyl fluorides.

Considering the increasing importance of allyl sulfone moiety and sulfonyl fluoride functionality in various fields, the simultaneous introduction of these two moieties into one molecule is highly desirable. However, due to the lack of efficient methods, access to γ-substituted allyl sulfonyl fluoride derivatives still remains less explored. Hence, it is of great significance to design and synthesize various sulfonyl fluoride compounds for the further SuFEx reactions.

The Heck–Matsuda reaction has been recognized as one of the most versatile and powerful synthetic tools for the construction of C–C bond since its discovery by Matsuda.[15] Palladium-catalyzed Heck–Matsuda reaction for the synthesis of β-arylethenesulfonyl fluorides from aryl diazonium tetrafluoroborates with exclusive regio- and stereoselectivity has been well studied (Scheme 1a).[16] Inspired by this seminal work, we assumed that the Heck–Matsuda reaction would also offer a feasible approach to construct unprecedented γ-aryl



Scheme 1 Palladium-catalyzed cross-coupling reactions.

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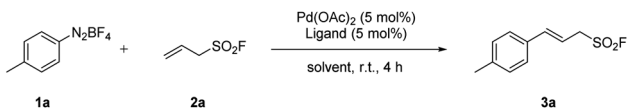
allylsulfonyl fluoride molecules. However, controlling regioselectivity and stereoselectiveity of Heck–Matsuda reaction with allylsulfonyl fluoride is still challenging.[17] The low selectivity mainly results from the uncontrollable migratory insertion into the olefins (branched *vs.* linear olefin products) and indiscriminate β-hydride elimination with either H^a or H^b (styrenyl *vs.* allylic linear olefin products) (Scheme 1b).[18] Herein, we report our recent progress of palladium-catalyzed highly regio- and stereoselective Heck–Matsuda reaction for the construction of γ-aryl allylsulfonyl fluorides (**3**) (Scheme 1c).

Our initial investigation started with the reaction of 4-methylbenzenediazonium tetrafluoroborate (**1a**, 0.2 mmol) and allylsulfonyl fluoride (**2a**, 0.4 mmol) in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 ligand at 25 °C in DMF (Table 1, entry 1).

To our delight, the ^1H NMR of crude product indicated that the (*E*)-styrenyl product **3a** was formed exclusively, while the possible isomeric products were not observed. Subsequently, a variety of ligands such as triphenylphosphine, 1,4-bis(diphenylphosphino) butane (dppb), 1,1′-bis(diphenylphosphino) ferrocene (dppf) were screened, and triphenylphosphine was found to be the optimal ligand for this process (Table 1, entry 1–3). The screening of the solvent indicated that methanol was the best choice (Table 1, entry 4–6). Subsequent examination on the loading of catalyst and ligand revealed that 3 mol% $Pd(OAc)_2$ and 3 mol% PPh_3 were essential (Table 1, entry 7–8). Reducing the amount of allylsulfonyl fluoride from 2.0 equivalents to 1.1 equivalents led to nearly identical yields of desired product **3a** (Table 1, entry 9–11). Therefore, $Pd(OAc)_2$ (3 mol%), PPh_3 (3 mol%), allylsulfonyl fluoride (1.1 equiv.) in MeOH (0.1 M) was eventually selected as the optimized conditions for the process.

With the optimized reaction conditions in hand, we next evaluated the substrate scope and functional group tolerance of this protocol using various aryldiazonium tetrafluoroborates (**1**) and allylsulfonyl fluorides (**2**). It turned out to be that our protocol was compatible with a broad range of substrates, delivering the desired products with excellent selectivity in most cases. Besides, the substrates bearing whether electron-donating groups (**1a**, **1c**, **1k**, **1n**, **1o**, and **1r**) or electron-withdrawing groups (**1d–1j**, **1l**, **1m**, **1q**, and **1v**) all worked well. In addition, *ortho*-, *meta*-, or *para*-mono-substituted and multi-substituted diazonium (**1r–1v**) salts all afforded their corresponding products in moderate to good yields. It is worth noting that the halogen atom on the aromatic rings of aryldiazonium tetrafluoroborates (**1d–1f**, **1l**, **1m**, **1p**, and **1v**) tolerated well and delivered their corresponding products in acceptable yields, while the C (sp^2)–X bond remained untouched during the transformations. Nitro-substituted (**1g**) diazonium salt was also successfully converted into the corresponding allyl sulfonyl fluoride with moderate yield (**3g**, 56% yield) (Table 2). Furthermore, the allylsulfonyl fluoride with a methyl

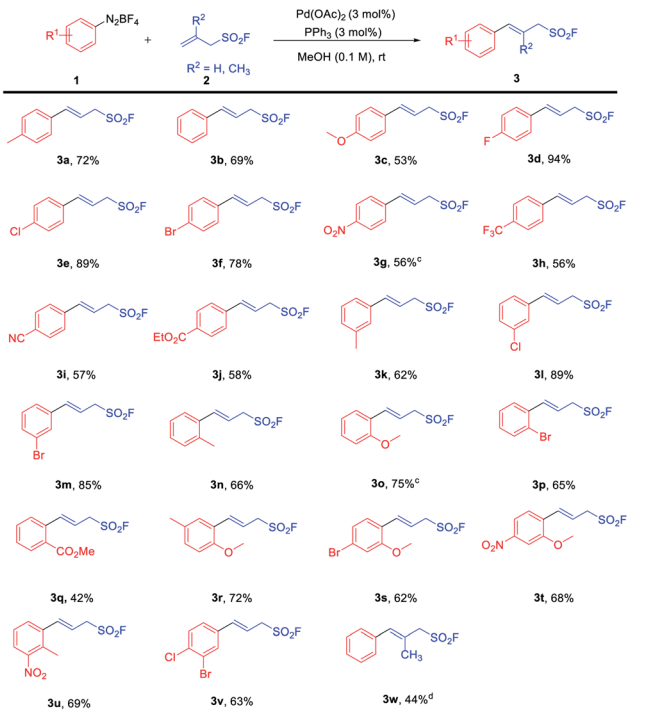
Table 1 Optimization of the reaction conditions[a,b]



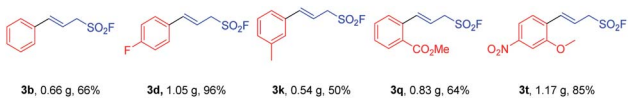
Entry	Ligand	**2a** (*x* equiv.)	Solvent	Yield (%)
1	PPh_3	2.0	DMF	66
2	Dppb	2.0	DMF	36
3	Dppf	2.0	DMF	Trace
4	PPh_3	2.0	DMA	51
5	PPh_3	2.0	MeOH	71
6	PPh_3	2.0	Acetone	16
7[c]	PPh_3	2.0	MeOH	61
8[d]	PPh_3	2.0	MeOH	72
9[d]	**PPh_3**	**1.1**	**MeOH**	**78**
10[d]	PPh_3	1.2	MeOH	78
11[d]	PPh_3	1.5	MeOH	76

[a] Reaction conditions: aryldiazonium tetrafluoroborate (**1a**, 0.2 mmol), $Pd(OAc)_2$ (5 mol%) and PPh_3 (5 mol%) were dissolved in solvent (0.2 M, 2.0 mL) before the subsequent addition of allylsulfonyl fluoride (0.4 mmol, 2.0 eq.). Then the resulting mixture was stirred at room temperature for 4 h. [b] The yields were determined by HPLC using pure **3a** as the external standard (t_R = 6.1 min, λ_{max} = 258.3 nm, acetonitrile/water = 80 : 20 (v/v)). [c] 2 mol% $Pd(OAc)_2$, 2 mol% PPh_3. [d] 3 mol% $Pd(OAc)_2$, 3 mol% PPh_3.

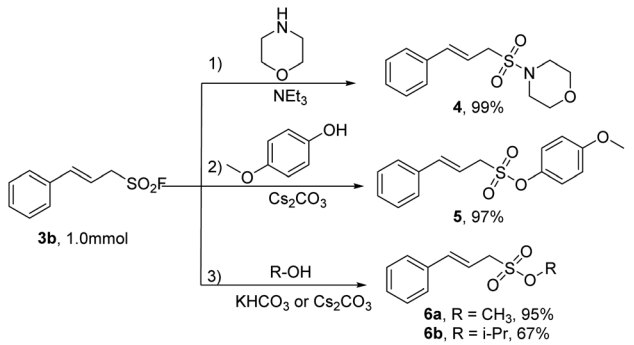
Table 2 Substrate scope of aryldiazonium tetrafluoroborates[a,b]



[a] Reaction conditions: aryldiazonium tetrafluoroborate (**1**, 1.0 mmol), $Pd(OAc)_2$ (3 mol%) and PPh_3 (3 mol%) were dissolved in MeOH (0.1 M), before the subsequent addition of allylsulfonyl fluoride (1.1 mmol, 1.1 eq.). The resulting mixture was stirred at room temperature under air. The selectivity for (*E*)-styrene was >20 : 1 unless otherwise noted. The selectivity is (*E*)-styrene: (all other isomers), as determined by ^1H NMR spectroscopy. [b] Isolated yields. [c] The selectivity for (*E*)-styrene was >10 : 1. [d] The selectivity for (*E*)-styrene was = 9 : 1.



Scheme 2 Gram-scale experiments.



Scheme 3 Transformations *via* SuFEx reactions.

substituent on the vinyl skeleton (**2b**) was also compatible with the reaction system, albeit a moderate yield of the product (**3w**) was achieved. And the *E* configuration of compound **3w** was confirmed by NOE analysis (see the ESI† for details).

To demonstrate the practicality of this method, a series of gram-scale reactions were performed under the optimal reaction conditions (Scheme 2). And the research results revealed that these reactions worked well to transform the corresponding aryldiazonium tetrafluoroborates (**1b**, **1d**, **1k**, **1q**, and **1t**) into their corresponding products (**3b**, **3d**, **3k**, **3q**, and **3t**) in moderate to excellent yields (50–96%).

Some extended work focusing on the chemical transformations of this class of novel sulfonyl fluoride molecules was carried out as described in the Scheme 3. (*E*)-3-Phenylprop-2-ene-1-sulfonyl fluoride (**3b**) was successfully converted into sulfonamide (**4**) in nearly quantitative yield (99%) when coupled with morpholine in the presence of Et_3N. Furthermore, the SuFEx reactions of (*E*)-3-phenylprop-2-ene-1-sulfonyl fluoride (**3b**) with phenol or alcohols also proceeded smoothly, delivering the sulfonates (**5**, **6a**, and **6b**) in good to excellent yields (67–97%).

Conclusions

In conclusion, we have successfully developed a mild, efficient, and robust Heck–Matsuda reaction for highly regio- and stereoselective construction of γ-aryl allylsulfonyl fluorides. The application of these novel molecules in SuFEx chemistry was also demonstrated. Further studies on the biological activity of these novel sulfonyl fluorides and chemical transformations of allylsulfonyl fluorides reagent are undergoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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