Synthesis of β-Tosyloxylated *gem*-Difluoroalkanes via Oxidative Fluorination of Vinyl Sulfonates Featuring A [2,3]-Sulfonyloxy Migration

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Abstract: The *gem*-difluoroalkanes widely exist in pharmaceuticals, agrochemicals and materials. Reported herein is a facile synthesis of tosyloxylated *gem*-difluoroalkanes via an oxidative fluorination of readily available vinyl sulfonates. An intriguing [2,3]-sulfonyloxy migration is involved as a key step. The OTs group in the product enables a divergent and modular synthesis of a wide variety of functionalized *gem*-difluoroalkanes via reliable S_N2 reactions. Notable features of this protocol include mild reaction conditions, high efficiency and remarkably good functional-group tolerance.

Keyword: *gem*-difluorination, [2,3]-sulfonyloxy migration, vinyl sulfonate, hypervalent iodine, late-stage modification.

The rapid preparation and biological evaluation of small-molecule library consisting of structurally relevant analogues is key for lead compounds discovery in modern drug development.[1] Consequently, synthetic methods that allow the installation of medicinally important pharmacophore and simultaneously introducing a latent functional group (FG) are of significant value. Ideally, the latent FG should be easily and diversely transformable to other FGs through reliable chemistry, for example, the classic S_N2 reactions. The recent years have witnessed the great success of organofuorines in pharmaceuticals and agrochemicals.[2] In this respect, *gem*-difluoroalkanes with unique steric and electronic properties are particularly interesting (Figure 1).[3] As bioisosteres of polar functional groups such as alcohols and thiols, the incorporation of *gem*-difluoromethylene moiety could potentially bring about improved bioavailability, lipophilicity or binding affinity to a target molecule.[4] The synthesis of *gem*-difluoroalkanes has therefore received considerable attention in recent years.[5]

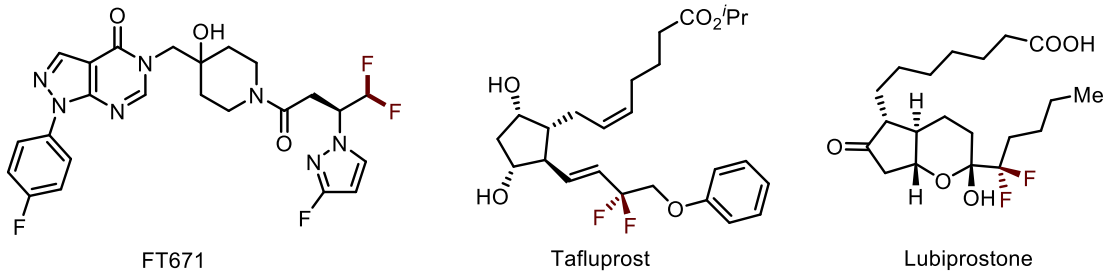
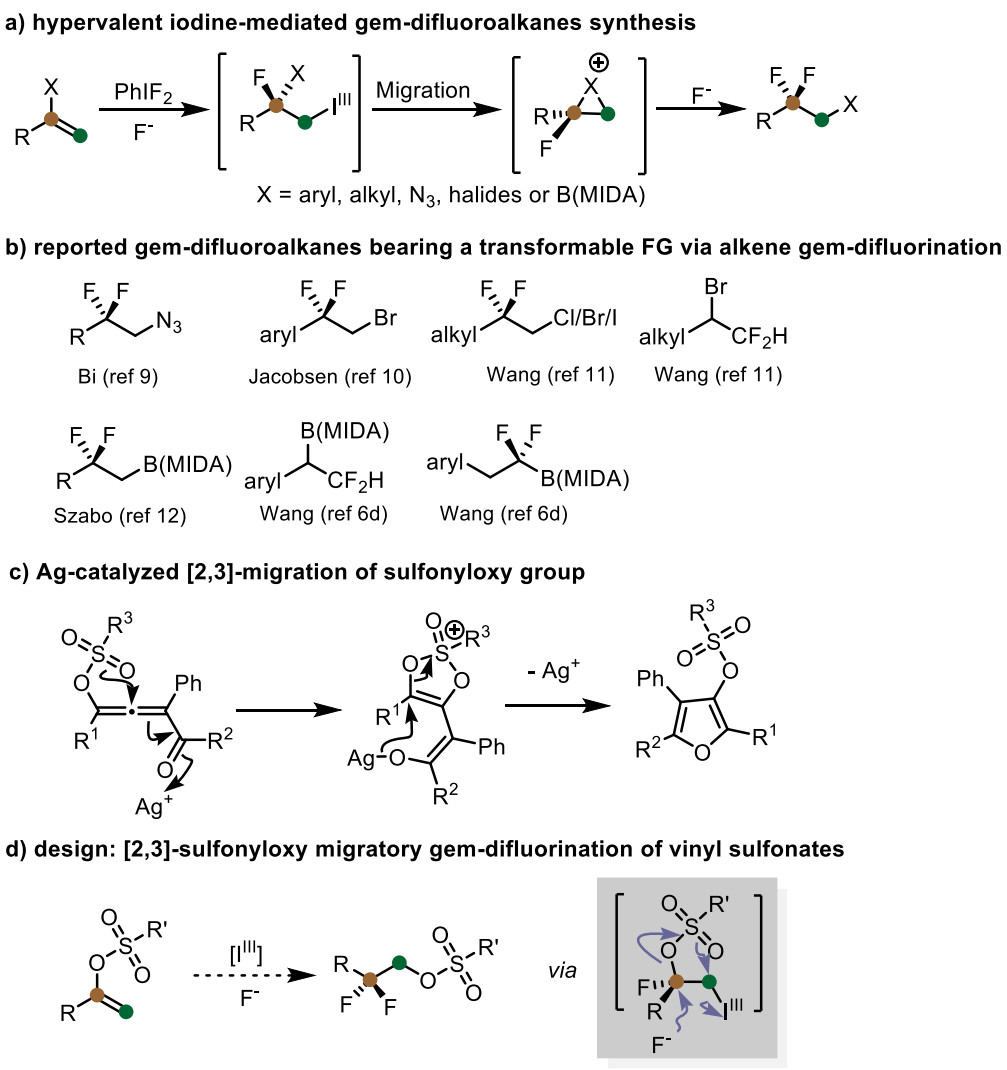


Figure 1. **Representative bioactive molecules containing a CF_2 moiety.**



Scheme 1. Hypervalent iodine-mediated *gem*-difluoroalkane synthesis and reaction design.

Among these efforts, the hypervalent iodine-mediated oxidative *gem*-difluorination of alkenes has become an attractive tool given the easy availability of both the substrates and regents.[6] In a generic reaction mechanism,[7] the initial 1,2-fluoroiodination of alkene forms a hypervalent iodine adduct. The profound leaving group ability of the iodo moiety could then trigger an intramolecular rearrangement to give a carbon cation stabilized by the α fluorine atom. Upon trapping with a fluorine anion, the *gem*-difluorinated product is furnished (Scheme 1a). Previously, [1,2]-aryl[6b-d] and [1,2]-alkyl[8] migration were typically involved and well established. Recent efforts uncovered that with proper substitution pattern on the double bond, [1,2]-heteroatom migration was also feasible. For instance, starting from azide-substituted alkenes, Bi[9] observed an interesting [1,2]-azide migration and the reaction gave *gem*-difluoroalkanes bearing a valuable β-N_3 substituent. Independent works from Jacobsen[10] and us[11] revealed a β-halo-*gem*-difluoroalkanes synthesis from simple vinyl halides. The reaction featured an exclusive [1,2]-halo migration and the halide within the products allowed diverse follow-up derivatizations. Very recently, a bora-Wagner-Meerwein rearrangement was also realized elegantly to

give β-difluoroalkyl boronates.[12]

We have been devoted to developing new methodology towards the synthesis of fluorine-containing building blocks.[6d, 13] To enable diverse and rapid synthesis of *gem*-difluoroalkanes, we recently realized the construction of β-boron and -halide *gem*-difluoroalkanes via a key [1,2]-aryl[6d] and [1,2]-halo[11] migration (as described above), respectively. Both the boryl and halide moiety serve as valuable latent FGs for the modular synthesis of functionalized *gem*-difluoroalkanes via FG manipulations. Still, however, some improvements are necessary. For examples, unlike the aromatic borons, alkyl borons with a C(sp^3)-B bond show reduced reactivity towards electrophiles.[6d] While the alkyl halides display fruitful reactivity, they are typically thermal/light unstable upon long-term storage. To overcome these limitations, we envisioned the installation of an oxygen-centered leaving group (for example, OTs, where Ts is *p*-toluenesulfonyl) could be a viable solution. Alkyl sulfonates are well-known to be reliable substrates for diverse S_N2 reactions, and are generally more stable than their halide counterparts.[14] Following the previous success of [1,2]-halide/azide migration processes starting from halide/azide substituted alkenes, we expected the use of vinyl sulfonates may have the opportunity to realize a [2,3] rearrangement of the sulfonyloxy group, thereby delivering interesting β-difluoroalkyl sulfonates (Scheme 1d). This is, however, challenging as [2,3]-sulfonyloxy migrations were only scatteredly reported,[15] although the [2,3]-acyloxy migrations were well established.[16] An elegant example was disclosed by Gevorgyan wherein a sulfonyloxy migration of tosyl allene was promoted by a silver catalyst towards the synthesis of tetrasubstituted furan (Scheme 1c).[15c]

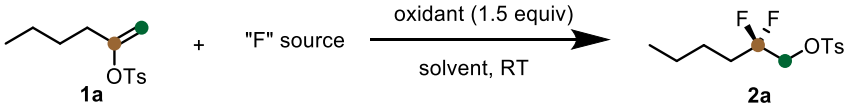
Result and discussion

To start, we examined the feasibility of this sulfonyloxy migratory *gem*-difluorination by employing vinyl tosylate **1a** as the model substrate, which can be efficiently prepared via a gold-catalyzed addition of sulfonic acid to alkyne.[17] (Table 1). Following our previous protocol with PIDA (diacetoxyiodobenzene) as oxidant and Py·HF (60 equiv.) as fluorine source in DCM at room temperature,[6d, 11] we obtained the desired [2,3]-sulfonyloxy migration product **2a** in 56% ^{1}H NMR yield (Table 1, entry1). Screening of other solvents revealed that DCM was the solvent of choice (entries 2–4). Interestingly, lowering the amount of Py·HF to 20 equivalent led to an improved yield of 73%. (entries 5, 6). Other anionic fluorine sources such as Et_3N·HF, AgF, CsF and TBAF turned out to be completely ineffective (entries 7, 8). Efforts were than paid to identity an optimal oxidant. It was found that a broad range of hypervalent iodine-based oxidants with varying acyloxy or aryl groups (**OX1-OX14**, listed below) were applicable to the reaction. Still, **OX6** with an *ortho*-methyl substituent on the phenyl group proved to the best to give a good yield of 81% (entry 9). Attempt to use PhI as a catalyst in combination with stoichiometric amounts of *m*CPBA (meta-chloroperbenzoic acid) resulted in a low yield of 47% (entry 10). And the use of a combination of hypervalent fluoroiodane **OX14** and $AgBF_4$ failed to give any desired product (entry 11).[6c]

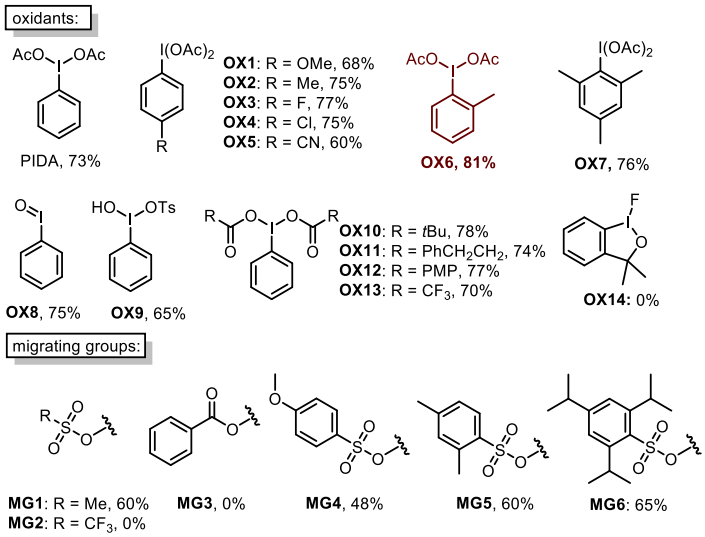
The influence of the migrating group on the reactivity was also explored (listed below). The methylsulfonyloxy (OMs, **MG1**) group gave good yield (60%) of the corresponding

product. The (trifluoromethyl)sulfonyloxy (OTf, **MG2**) group, however, showed no reactivity in this transformation. Arylsulfonyloxy groups bearing different electronic and steric properties, including the bulky triisopropylphenylsulfonyloxy, were found to be generally tolerated (**MG4-MG6**). Although [2,3]-acyloxy migration were more common than that of sulfonyloxy group, the use of vinyl benzoate (**MG3**) led to the formation of some unidentifiable by-products, with no fluorine incorporated as determined by ^{19}F NMR.

Table 1. Optimization of the reaction conditions.[a]



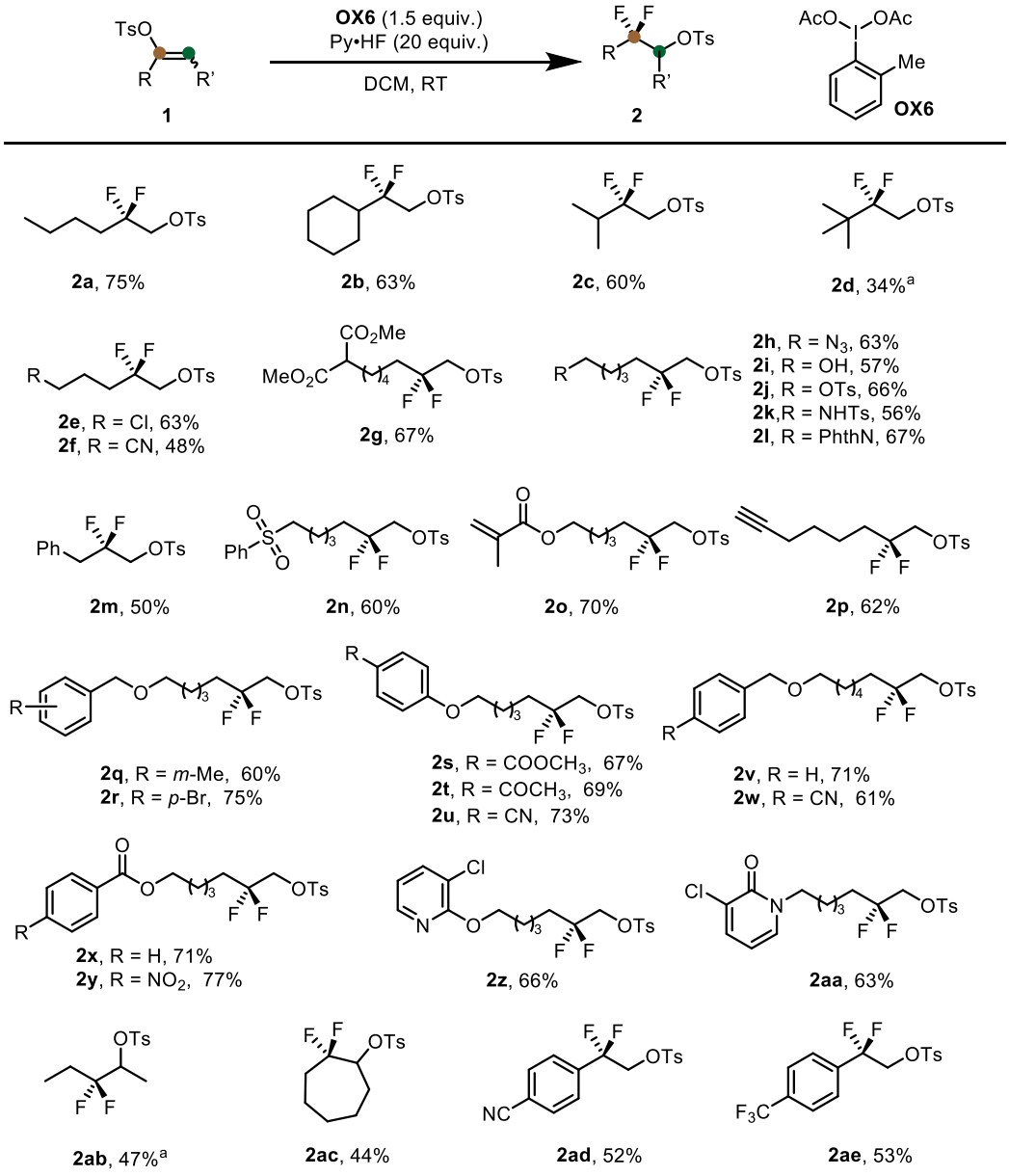
Entry	"F" (x equiv)	Oxidant	Solvent	Yield [%]
1	Py·HF (60)	PIDA	DCM	56
2	Py·HF (60)	PIDA	DCE	53
3	Py·HF (60)	PIDA	Toluene	33
4	Py·HF (60)	PIDA	CH_3CN	0
5	Py·HF (10)	PIDA	DCM	70[b]
6	Py·HF (20)	PIDA	DCM	73
7	Et_3N•HF (20)	PIDA	DCM	0
8	CsF or AgF or TBAF	PIDA	DCM	0
9	**Py·HF (20)**	**OX6**	**DCM**	**81(75)**[c]
10[d]	Py·HF (20)	*m*CPBA	DCM	47
11	$AgBF_4$	**OX14**	DCM	0



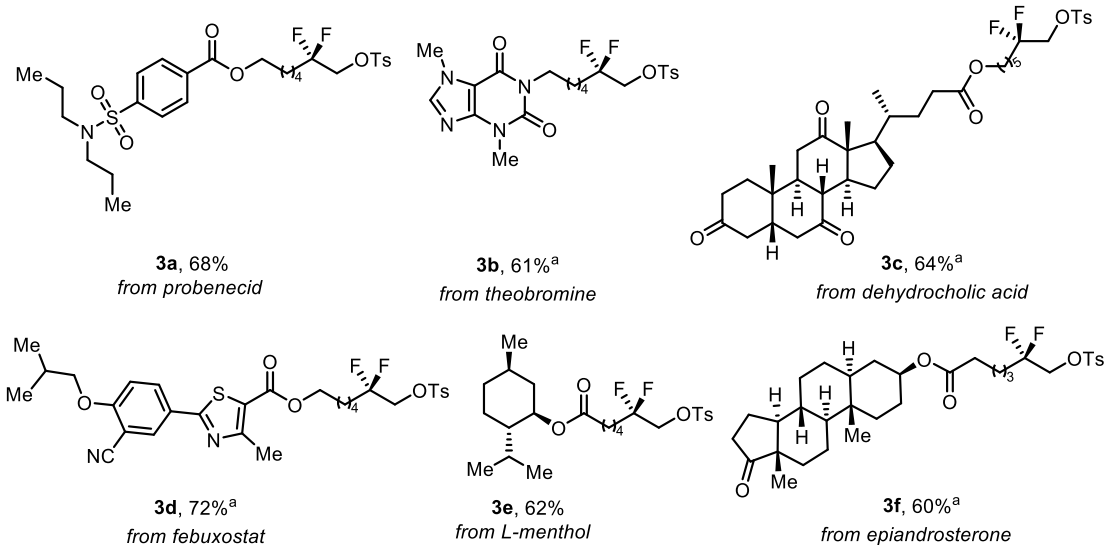
a, General reaction conditions: **1a** (0.1 mmol, 1.0 equiv), "F" source, oxidant (1.5 equiv), solvent (2.0 mL), RT, 8 min, yields were determined by ^1H NMR analysis using *p*-iodoanisole as an internal standard. b, 48 h. c, Yield of isolated products. d, PhI (20 mol%) was used. DCE = 1,2-dichloroethane

Having determined the optimized conditions (Table 1, entry 9), the substrate scope was subsequently explored (Scheme 2). The compatibility of α-alkyl vinyl sulfonates was firstly examined. As illustrated in scheme 2, in addition to primary alkyl (**1a**), vinyl tosylates with secondary alkyl substituents were also smoothly converted to the corresponding

products **(2b** and **2c)**. However, a sterically demanding *tert*-butyl substituent retarded the reaction, and a reduced yield of 34% was observed (**2d**). Many FGs, such as Chloro (**2e**), cyano (**2f**), ester (**2g**), azide (**2h**), free hydroxy (**2i**), sulfonate ester (**2j**), sulfonamide (**2k**), phthalimide (**2l**), and even vinyl (**2o**) and ethynyl (**2p**) remained untouched, suggesting a high chemoselectivity and the profound mildness of the protocol. Aromatic rings with diverse substitution patterns were also generally compatible, including pyridine (**2z**) and pyridinone (**2aa**). The protocol was also applicable to the trisubstituted vinyl tosylates (**2ab**-**2ac**), although slightly decreased yields were found. A limitation of this transformation is the incompatibility of electron-neutral and -rich aryls α to the OTs group. The undesired aryl ketones substituted with a α-OAc were formed instead without the participation of fluoride (not shown). Nevertheless, with electron-poor aryls, the *gem*-difluorination product could be obtained in moderate yields (**2ad**-**2ae**).



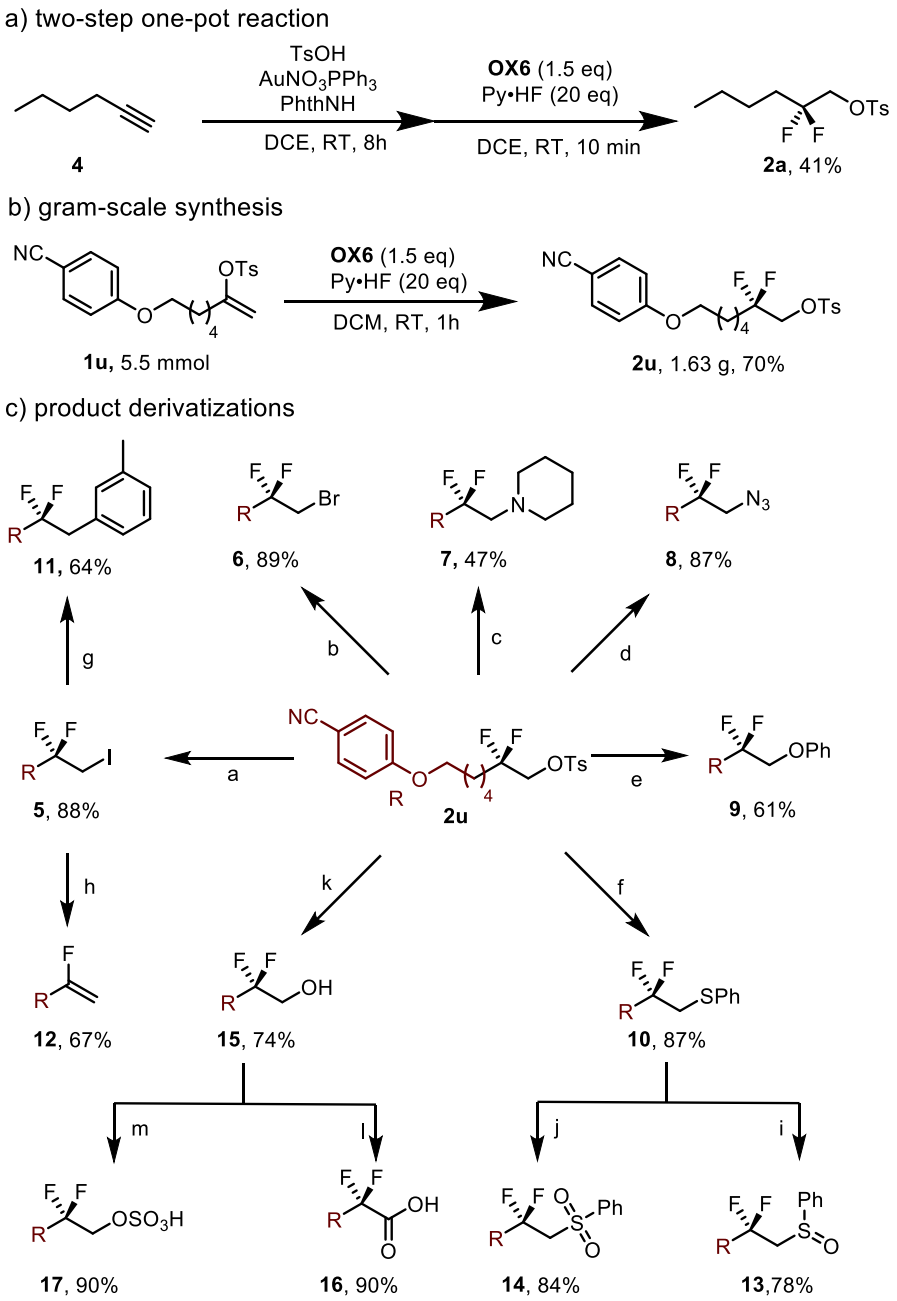
Scheme 2. Scope of [2,3]-sulfonyloxy migratory *gem*-difluorinations. a, **OX3** was used.



Scheme 3. [2.3]-sulfonyloxy migratory *gem*-difluorination of complex molecules. a, reaction time increased to 1 h.

To further challenge the robustness of the protocol, the late-stage modifications of complex natural product or drug derivatives were conducted. As shown in **scheme 3**, vinyl tosylates derived from probenecid (**3a**), theobromine (**3b**), dehydrocholic acid (**3c**), febuxostat (**3d**), L-menthol (**3e**) and epiandrosterone (**3f**) were also competent substrates, affording the corresponding products in good efficiency. These results demonstrated a potential utility of this methodology in direct derivatization of biologically active molecules.

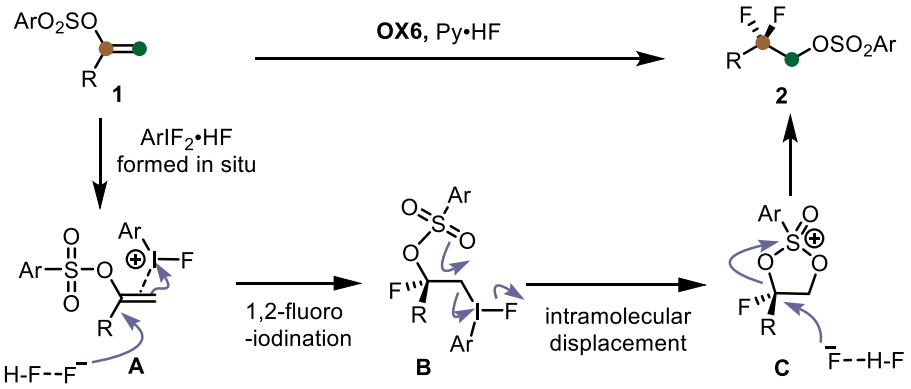
Considering the simplicity of conditions for substrate preparation and *gem*-difluorination, a telescoped synthesis was conducted. Thus, after the completion of the gold-catalyzed addition of sulfonic acid to alkyne **4**, hypervalent iodine **OX6** and Py·HF were added directly without isolating the vinyl tosylate intermediate. Gratifyingly, this one-pot two-step procedure allowed the synthesis of **2a** in 41% yield from terminal alkyne in a pot-economical manner (Scheme 4a). A gram-scale synthesis of β-difluorinated alkyl sulfonate **2u** gave a good yield of 70% (Scheme 4b), with minimal yield erosion compared to the milligram synthesis (73%, Scheme 2). The OTs served as valuable latent FG for diverse functionalized *gem*-difluoroalkanes synthesis. As expected, via simple S_N2 reactions, the C−I[14](**5**), C−Br (**6**), C−N (**7** and **8**), C−O (**9**), C−S (**10**) bond formations proceeded effectively (Scheme 4c). The iodide **5** could be further arylated through a cobalt(II)-catalyzed coupling reaction[18] with *m*-tolylmagnesium regent, or be reduced to alkenyl fluoride **12** with element zinc.[19] The β-difluoroalkylphenyl sulfide **10** could be selectively oxidized to either sulfoxide **13** or sulfone **14**, depending on the loading of *m*CPBA oxidant. In another vein, the hydrolysis of β-difluoroalkyl sulfonate **2u** furnished a β-difluoroalkyl alcohol **15** in good yield, which can be further oxidized[20] to α-difluorocarboxylic acid **16** or converted to β-difluoroalkyl sulfonic acid **17**[21], a potential surfactant[22] , efficiently.



Scheme 4. Telescoped and gram-scale synthesis, product derivatizations. Conditions: a) NaI, DMF, 110 °C; b) LiBr, DMSO, 110 °C; c) Piperidine, K_2CO_3, DMSO, 95 °C; d) NaN_3, DMSO, 110 °C; e) PhONa, DMSO, 90 °C; f) PhSNa, DMSO, 35 °C; g) *m*-tolylmagnesium bromide, $CoCl_2$, TMEDA, THF; h) Zn, DMA/H_2O, 80 °C; i) *m*CPBA (1.1 eq), DCM, 0 °C; j) *m*CPBA (2.2 eq), DCM, 0 °C; k) NaOH, EtOH, 70 °C; l) TPAP, NMO, H_2O/CH_3CN. m) SO_3·Py, THF, RT.

On the basis of literature precedents,[11, 23] a plausible mechanism for this [2,3]-sulfonyloxy migration was proposed and briefly depicted in Scheme 5. Initially, the coordination of vinyl sulfonate with aryl difluoroiodine (**A**) triggers a regioselective vicinal fluoroiodination to produce intermediate **B**. The observed regioselectivity can be understood by the neighboring stabilizing effect of oxygen to the developing positive

charge. Next, the intramolecular displacement of the C-I bond by the pendent sulfonyl oxygen lead to the formation of a five-membered ring (**C**), which would then be attacked by a second fluoride to give the [2,3]-sulfonyloxy migrated and gem-difluorinated product.



Scheme 5. Mechanistic proposal.

Conclusions

In summary, an efficient synthesis of β-difluoroalkyl sulfonates was realized via a hypervalent iodine-promoted gem-difluorination reaction of vinyl sulfonates. An interesting [2,3]-sulfonyloxy migration was involved as the key step for success. Broad substrate scope, good functional group compatibility, simple reaction conditions and generally good yields were found. By FG manipulation of the sulfonyloxy group, a broad range of *gem*-difluorinated molecules containing β-C, -N, -O, -X and -S functionalities were easily obtained. Considering the importance of β-difluoroalkanes in medicinal chemistry and the modular nature of the protocol, we anticipate it may find applications in modern drug discovery.

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