## Synthesis of $\beta$ -Tosyloxylated *gem*-Difluoroalkanes via Elusive [2,3]-Sulfonyloxy Migration

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**Abstract:** *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, which has been rarely known, is involved as a key step. The OTs group within the products enables a divergent and modular synthesis of a wide variety of functionalized *gem*-difluoroalkanes via simple and reliable S<sub>N</sub>2 reactions. Notable features of this protocol include mild reaction conditions, high efficiency and remarkably good functional group tolerance. Theoretical mechanistic studies were conducted, supporting a rate-determining [2,3]-sulfonyloxy shift is involved.

The rapid preparation and biological evaluation of small-molecule library consisting of structurally relevant analogues are key to lead compounds discovery in modern drug development.<sup>1-3</sup> Consequently, synthetic methods that allow the installation of medicinally important pharmacophore with 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 SN2 reactions. The recent years have witnessed the great success of organofuorines in pharmaceuticals and agrochemicals.<sup>4-5</sup> In this respect, gem-difluoroalkanes with unique steric and electronic properties are particularly interesting (Figure 1).<sup>6-8</sup> As bioisosteres of polar functional groups such as alcohols and thiols, the incorporation of gem-difluoromethylene moiety could potentially bring about improved bioavailability, lipophilicity and/or binding affinity to a target molecule.<sup>9-10</sup> The synthesis of gem-difluoroalkanes has therefore received considerable attention in recent years.<sup>11-15</sup>



Figure 1. Representative bioactive molecules containing a CF2 moiety.

Among those efforts, the hypervalent iodine-mediated oxidative gem-difluorination of alkenes with anionic fluoride sources has become an attractive tool due to the easy availability of both the substrates and regents.<sup>16-22</sup> In a generic reaction mechanism,<sup>23</sup> the initial 1,2-fluoroiodination of alkene forms a hypervalent iodine adduct I (Scheme 1a). The profound leaving group ability of the iodo moiety could then trigger an intramolecular rearrangement and by trapping with a fluorine anion, the gem-difluorinated product is furnished. Previously, [1,2]-aryl<sup>17-19</sup> and [1,2]-alkyl<sup>24-26</sup> 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 (Scheme 1b). For instance, starting from azide-substituted alkenes. Bi<sup>27-28</sup> observed an interesting [1,2]-azide migration and the reaction gave *gem*-difluoroalkanes bearing a valuable  $\beta$ -N<sub>3</sub> substituent. Independent works from Jacobsen<sup>29</sup> and  $us^{30}$  revealed a  $\beta$ -halo-*gem*-difluoroalkanes synthesis from simple vinyl halides featuring an exclusive [1,2]-halo migration event. Similar products were obtained via a [1,2]-aryl migratory fluorination of allyl bromide.<sup>31</sup> Very recently, a bora-Wagner-Meerwein rearrangement was also elegantly realized to give β-difluoroalkyl boronates.<sup>32</sup> Almost at the same time, we were able to construct the same type of products via an unusual 1,2-hydrogen shift enabled by boron substitution.<sup>33</sup>

We have been devoted to developing new methodology towards the synthesis of fluorine-containing building blocks.<sup>19,30,34-37</sup> To enable diverse and rapid synthesis of *gem*-difluoroalkanes, we recently realized the construction of  $\beta$ -boron and -halide *gem*-difluoroalkanes via a key [1,2]-aryl,<sup>19</sup> [1,2]-halo<sup>30</sup> or [1,2]-H<sup>33</sup> migration (as described above), respectively. Both the boryl and halide moiety serve as 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<sup>3</sup>)-B bond show reduced reactivity towards electrophiles.<sup>19,33</sup> Also, unexpectedly, the  $\beta$ -halide *gem*-difluoroalkanes are reluctant to undergo S<sub>N</sub>2 reaction probably due to the electron-withdrawing property of the adjacent CF<sub>2</sub> moiety.<sup>29-31</sup> In addition, alkyl halides are typically thermal/light unstable upon long-term storage.

a) hypervalent iodine-mediated gem-difluoroalkanes synthesis



b) reported gem-difluoroalkanes bearing a transformable FG via alkene gem-difluorination



c) Ag-catalyzed [2,3]-migration of sulfonyloxy group



d) this work: [2,3]-sulfonyloxy migratory gem-difluorination of vinyl sulfonates



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

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 and better substrates for diverse  $S_N2$  reactions, and are generally more stable than their halide counterparts.<sup>38</sup> 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  $\beta$ -difluoroalkyl sulfonates (**Scheme 1d**). This is, however, challenging as [2,3]-sulfonyloxy migrations were only scatteredly reported which could be attributed to the low basicity of the sulfonyloxy oxygen,<sup>39-41</sup> although the [2,3]-acyloxy migrations were well established.<sup>42-44</sup> An inspiring 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**).<sup>41</sup>

To start, we examined the feasibility of this sulfonyloxy migratory gem-difluorination by employing vinyl tosylate **1a** as the model substrate (**Table 1**).<sup>45-46</sup> Following our previous conditions with PIDA (diacetoxyiodobenzene) as oxidant and Py·HF (60 equiv.) as fluorine source in DCM at room temperature<sup>19, 30</sup>, we obtained the desired [2,3]-sulfonyloxy migration product **2a** in 56% <sup>1</sup>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<sub>3</sub>N·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 mCPBA (meta-chloroperbenzoic acid) resulted in a low yield of 47% (entry 10). And the use of a combination of hypervalent fluoroiodane OX14 and AgBF<sub>4</sub> failed to give any desired product (entry 11).<sup>18</sup>

$\sim \sim$	/ <b>F</b> " agurag	oxidant (1.5 equiv)		F F
	)Ts			OTs
1a ີ				2a
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	CH₃CN	0
5	Ру·НF (10)	PIDA	DCM	70 <sup>b</sup>
6	Py·HF (20)	PIDA	DCM	73
7	Et <sub>3</sub> N•HF(20)	PIDA	DCM	0
8	CsF or AgF or TBAF	PIDA	DCM	0
9	Py·HF(20)	OX6	DCM	81(75)°
10 <sup>d</sup>	Py·HF (20)	<i>m</i> CPBA	DCM	47
11	AgBF <sub>4</sub>	OX14	DCM	0

Table 1. Optimization of the reaction conditions.<sup>a</sup>



<sup>a</sup>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 <sup>1</sup>H NMR analysis using p-iodoanisole as an internal standard. <sup>b</sup>48 h. <sup>c</sup>Yield of isolated products. <sup>d</sup>PhI (20 mol%) was used. **DCE** = 1,2-dichloroethane

The influence of the migrating group on the reactivity was also explored (listed below). The methylsulfonyloxy (OMs, **MG1**) group gave a 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 <sup>19</sup>F NMR.

Having determined the optimized conditions (**Table 1**, entry 9), the substrate scope was subsequently explored (**Scheme 2**). The compatibility of  $\alpha$ -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 (**2b-2ac**), although slightly decreased yields were found. A limitation of this transformation is the incompatibility of electron-neutral and -rich aryls  $\alpha$  to the OTs group. The undesired aryl ketones substituted with a  $\alpha$ -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. <sup>a</sup>OX3 was used.

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.



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

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  $\beta$ -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<sub>N</sub>2 reactions, the C-I(5),38 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<sup>47</sup> with *m*-tolylmagnesium regent, or be reduced to alkenyl fluoride **12** with element zinc.<sup>48</sup> The  $\beta$ -difluoroalkylphenyl sulfide **10** could be selectively oxidized to either sulfoxide 13 or sulfone 14, depending on the loading of mCPBA oxidant. In another vein, the hydrolysis of  $\beta$ -difluoroalkyl sulfonate **2u** furnished a  $\beta$ -difluoroalkyl alcohol **15** in good yield, which can be further oxidized<sup>49</sup> to  $\alpha$ -difluorocarboxylic acid **16** or converted to  $\beta$ -difluoroalkyl sulfonic acid **17**.<sup>50</sup> a potential surfactant,<sup>51</sup> efficiently.

a) two-step one-pot reaction



b) gram-scale synthesis



c) product derivatizations



**Scheme 4.** Telescoped and gram-scale synthesis, product derivatizations. Conditions: a) Nal, DMF, 110 °C; b) LiBr, DMSO, 110 °C; c) Piperidine, K<sub>2</sub>CO<sub>3</sub>, DMSO, 95 °C; d) NaN<sub>3</sub>, DMSO, 110 °C; e) PhONa, DMSO, 90 °C; f) PhSNa, DMSO, 35 °C; g) *m*-tolylmagnesium bromide, CoCl<sub>2</sub>, TMEDA, THF; h) Zn, DMA/H<sub>2</sub>O, 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; I) TPAP, NMO, H<sub>2</sub>O/CH<sub>3</sub>CN. m) SO<sub>3</sub>·Py, THF, RT.



Scheme 5. Theoretical Mechanistic studies.

To understand the reaction mechanism, density functional theory (DFT) calculations were performed (see supporting information for details). In these modeling studies, isopropyl substituted vinyl tosylate (1c) was used as a model substrate and PhIF<sub>2</sub> formed in situ was selected as the starting point<sup>23, 52</sup> in combination of two molecules of HF as activator. As shown in Scheme 5, the active species INT-2 generated by the reaction of HF with PhIF<sub>2</sub> coordinates to vinyl tosylate (1c) to provide iodonium ion intermediate INT-3 ( $\Delta G =$ 6.1 kcal/mol). Then, a regioselective  $S_N2$ -like nucleophilic attack with  $-F(HF)_2$  via **TS-1** (with a barrier of 11.8 kcal/mol) results in the formation a 1,2-fluoroiodination intermediate INT-4. The formation of the C-I bond in INT-4 significantly weakens the I-F bond, which is elongated from 1.97 Å to 2.12 Å. Consequently, the I-F bond is prone to dissociate under the activation of HF to provide a more stable INT-5, which is exergonic by 25.1 kcal/mol from INT-4. Then, the intramolecular displacement of the C-I bond by the pendent sulfonyl oxygen leads to the formation of a five-membered ring INT-6. An S<sub>N</sub>2-like transition state **TS-2** with a barrier of 25.7 kcal/mol is involved. And finally, a second  $-F(HF)_2$  attacks the F-substituted carbon atom through TS-3 with a barrier of 9.2 kcal/mol to give the [2,3]-sulfonyloxy migrated and gem-difluorinated product ( $\Delta G = -59.9$  kcal/mol). In addition, unlike the SN2-like transition state TS-1, the metathesis-like transition state **TS-1a** is 2.0 kcal/mol higher in energy, suggesting it might be a competitive pathway (green lines). Nevertheless, the calculations indicate that [2,3]-sulfonyloxy migration is rate-determining overall.

In summary, an efficient synthesis of  $\beta$ -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  $\beta$ -C, -N, -O, -X and -S functionalities were easily

obtained. Considering the importance of  $\beta$ -difluoroalkanes in medicinal chemistry and the modular nature of the protocol, we anticipate it may find applications in modern drug discovery.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (22022114, 21971261), the Guangdong Basic and Applied Basic Research Foundation (2020A1515010624), the Fundamental Research Funds for the Central Universities (20ykzd12) and the Local Innovative and Research Teams Project of Guangdong Pearl River Talents Program (2017BT01Y093).

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

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