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 tosylated 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 S2 reactions. Notable features of this protocol include mild reaction conditions, high efficiency and remarkably good functional-group tolerance.

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.[11] Consequently, synthetic methods that allow the installation of a latent functional group (FG) are of significant value. Ideally, the latent FG should be easily and diversely transformable into other FGs through reliable chemistry, for example, the classic S2 reactions. The recent years have witnessed the great success of organofluorines 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 CF2 moiety.](image)

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-fluorodination 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 fluoride anion, the gem-difluorinated product is furnished (Scheme 1a). Previously, [1,2]-aryl[8-10] and [1,2]-alkyl[11] 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[12] observed an interesting [1,2]-azide migration and the reaction gave gem-difluoroalkanes bearing a valuable β-N3 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.[11] 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.[12]

![Scheme 1. Hypervalent iodine-mediated gem-difluoroalkane synthesis and reaction design.](image)
We have been devoted to developing new methodology towards the synthesis of fluorine-containing building blocks.

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[8] [1,2]-halo[11] or [1,2]-H[13] 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(sp³)-B bond show reduced reactivity towards electrophiles.[6d,13]

Also, unexpectedly, the β-halide gem-difluoroalkanes are reluctant to undergo Sn2 reaction probably due to the electron-withdrawing property of the adjacent CF₂ moiety.[10,11] In addition, alkyl halides 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 and better substrates for diverse Sn2 reactions, and are generally more stable than their halide counterparts.[15] 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 are only scatteredly reported which could be attributed to the low basicity of the sulfonyloxy oxygen,[16] although the [2,3]-acyloxy migrations were well established.[17]

An inspiring example was disclosed by Gevorgyan wherein a sulfonyloxy migration product was obtained in 56% yield (entry 1). Screening of other solvents revealed that DCM was the solvent of choice (entries 2–4). Interestingly, lowering the amount of Py-HF to 20 equiv. led to an improved yield of 73%. (entries 5, 6). Other anionic fluorine sources such as EtSN-HF, AgF, CsF and TBAF turned out to be completely ineffectives (entries 7, 8). Efforts were thus paid to identify an optimal oxidant. It was found that a broad range of hypervalent fluoroiodanes were only scatteredly reported with drawing property of the adjacent CF₂ moiety.[10,11] In addition, alkyl halides are typically thermal/light unstable upon long-term storage.

To start, we examined the feasibility of this sulfonyloxy migratory gem-difluoroalkylation by employing vinyl tosylate 1a as the model substrate, which can be efficiently prepared via a gold catalyzed addition of sulfonic acid to alkynes (Table 1).[19] 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% 1H NMR yield (Table 1, entry 1). 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 EtSN-HF, AgF, CsF and TBAF turned out to be completely ineffective (entries 7, 8). Efforts were thus paid to identify an optimal oxidant. It was found that a broad range of hypervalent iodine-based oxidants with varying acyloxy or ary1 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 floriodioine OX14 and AgBF₄ failed to give any desired product (entry 11).[9c]

The influence of the migrating group on the reactivity was also explored (listed below). The methylsulfonyloxy (OM1, 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 unidentified by-products, with no fluorine incorporated as determined by 19F NMR.

### Table 1. Optimization of the reaction conditions.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>F⁻ (x equiv)</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Py HF (60)</td>
<td>PIDA</td>
<td>DCM</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>Py HF (60)</td>
<td>PIDA</td>
<td>DCE</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>Py HF (60)</td>
<td>PIDA</td>
<td>Toluene</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Py HF (60)</td>
<td>PIDA</td>
<td>CH₂CN</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Py HF (10)</td>
<td>PIDA</td>
<td>DCM</td>
<td>70¹</td>
</tr>
<tr>
<td>6</td>
<td>Py HF (20)</td>
<td>PIDA</td>
<td>DCM</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>EtSN-HF (20)</td>
<td>PIDA</td>
<td>DCM</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>CsF or AgF</td>
<td>PIDA</td>
<td>DCM</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Py-HF (20)</td>
<td>OX6</td>
<td>DCM</td>
<td>81 (75)²</td>
</tr>
<tr>
<td>10</td>
<td>Py HF (20)</td>
<td>mCPBA</td>
<td>DCM</td>
<td>47</td>
</tr>
<tr>
<td>11</td>
<td>AgBF₄</td>
<td>OX14</td>
<td>DCM</td>
<td>0</td>
</tr>
</tbody>
</table>

*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-tolualdehyde as an internal standard. ¹48 h. ²Yield of isolated products. ³Phi (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...
vinylic (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 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 \( \alpha \)-difluorination product could be obtained in moderate yields (2ad-2ae).

Scheme 2. Scope of [2,3]-sulfonyloxy migratory gem-difluorinations. *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. *the 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 Sn2 reactions, the C–I(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[19] with 1-m-tolylmagnesium regent, or be reduced to alkylfluoride 12 with element zinc[20]. 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 sulphonate 2u furnished a \( \beta \)-difluoroalkyl alcohol 15 in good yield, which can be further oxidized[21] to \( \alpha \)-difluorocarboxylic acid 16 or converted to \( \beta \)-difluoroalkyl sulfonic acid 17[22], a potential surfactant[23], efficiently.
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.

Acknowledgements

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


Entry for the Table of Contents

[Chemical Reaction Diagram]

[Chemical Structures]

valuable building block

[2,3]-sultenyloxy migration