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Solventless and Metal-free Regioselective Hydrofluorination of Functionalized Alkynes and Allenes: An Efficient Protocol for the Synthesis of *gem*-Difluorides

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Abstract

The combination of two easily handled, highly acidic liquid HF complex reagents, DMPU-12HF and KHSO₄-13HF, generated a highly acidic fluorination system that facilitated exclusive Markovnikov addition of HF to widely functionalized alkynes, including alkyne tethered drugs, or allenes to produce *gem*-difluorides with high atom economy, and with an easy workup.

Introduction

The value of fluorine in improving the pharmacokinetic and pharmacodynamic properties of active pharmaceutical ingredients, such as enhanced membrane permeation and superior metabolic stability¹ has contributed to the explosive growth of synthetic strategies for the selective fluorination of organic molecules.^{2–8} More specifically, molecules with a *gem*-difluoride moiety have received widespread coverage in drug development. A case in point is vinflunine, a *gem*-difluoromethylenated derivative of a vinca alkaloid, currently used as second-line chemotherapy for advanced transitional cell carcinoma.^{9–11}

There are three primary strategies for the synthesis of *gem*-difluorides from the perspective of the substrates (Scheme 1).¹² The first strategy is the direct dihydrofluorination of alkynes using hydrogen fluoride reagents (Scheme 1a). This method is one of the most straightforward and atom-economical protocols. Linn¹³ and Plueddeman¹⁴ pioneered this approach using anhydrous hydrogen fluoride (HF), but they only investigated non-

[†]Footnotes relating to the title and/or authors should appear here.

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Conflicts of interest

The authors declare no conflict of interest.

functionalized alkynes. To avoid the inconvenience of handling HF gas, Olah^{15–18} developed a pyridine-based HF reagent and achieved hydrofluorination with a limited scope of alkyne substrates. Later, Renoux utilized a superacid system HF-SbF₅ to *gem*-difluorinate aminoalkynes (Scheme 1a).¹⁹ The second strategy is the *gem*-difluorination of carbonyl compounds with various fluorinating reagents such as gaseous SF₄,²⁰ diethylaminosulfur trifluoride (DAST),²¹ bis(2-methoxyethyl) aminosulfur trifluoride (Deoxo-Fluor),²² aminodifluorosulfonium tetrafluoroborate (XtalFluor)²³, and 2,2-difluoro-1,3-dimethylimidazolidine (DFI) (Scheme 1b).²⁴ A third strategy encompasses various tactics such as the indirect fluorination of carbonyl derivatives with IF or BrF₃,²⁵ or the oxidative desulfurization-fluorination of ortho-thioesters, dithiolanes or thiocarbonyl derivatives with electrophilic halonium species^{26, 27} (Scheme 1c). Recently, Szabó utilized a fluoro-benziodoxole reagent on styrene substrates to accomplish the *gem*-difluorination.²⁸ All these methods have serious limitations such as poor substrate scope, low atom-economy and safety concerns about the fluorination reagents.

We have recently reported a stable and easily handled HF complex, KHSO₄-13HF. The high acidity and high fluoride nucleophilicity of this reagent made possible the direct hydrofluorination of alkenes via a bi-functional activation of hydrogen fluoride.^{29, 30} Given the ease of its addition to the double bond, we predicted a similar behavior with other unsaturated systems such as alkynes or allenes. We are pleased to report a neat and metal-free alkyne and allene hydrofluorination protocol using an easily handled, highly acidic liquid HF complex with an unmatched substrate scope, good functional group tolerance and very simple workup—calcium carbonate neutralization followed by chromatography.

Results and discussion

We used the hydrofluorination of alkyne **1a** as our model system (Table 1). We first tested the reactivity of KHSO₄-13HF (Table 1, entry 1). This reagent produced 9% of the *gem*-difluoride product but forming nearly equal amounts of dialkenylsulfate **3a** and ketone **4a**. This result showed that the HSO₄[−] anion enhances the reactivity of the HF complex but also introduces competitive side reactions (nucleophilic attacks of HSO₄[−] and water). For comparison, we tested other HF reagents, but no reactions took place (Table 1, entries 2, 3, 4). Using toluene as the solvent did not improve the outcome (Table 1, entry 5). We switched to HFIP since it can form a hydrogen bonding network which may further enhance the reactivity of acids.³¹ The reaction afforded more difluoride product but also gave an equal amount of sulfate dimer **3a** and ketone **4a** (Table 1, entry 6). Mixing K₂SO₄-14HF with different acids, such as trifluoroacetic acid (TFA) and triflic acid (TfOH), did not improve the outcome (Table 1, entries 7, 8). This result confirmed the importance of dual bifunctional activation role of KHSO₄ in the system.^{29, 30} When we increased the reaction temperature to 50 °C, we managed to increase the conversion to product (Table 1, entry 9). To reduce the dialkenylsulfate product and augment the proportion of difluoride product, we introduced DMPU-12HF, an HF complex with high acidity developed in our laboratory,^{32–35} our reason for this experiment was to increase the concentration of the fluoride source without weakening the acidity of the system. We obtained a higher proportion of difluoride compared to the sulfate byproduct (Table 1, entry 10). To underscore the importance of the KHSO₄-13HF, we added KHSO₄ instead of KHSO₄-13HF with DMPU-12HF and we found

that no reaction had occurred (Table 1, entry 11). When we conducted the reaction solventless, we obtained a higher yield of *gem*-difluoride product (Table 1, entry 12). We then varied the relative amounts of HF reagents and found that one equivalent of KHSO₄-13HF and two equivalents of DMPU-12HF (Table 1, entries 12, 13, 14) gave the best results. When we extended the reaction time to 3 hours, we obtained optimal conversion and yield (Table 1, entry 15).

Having established the optimal conditions for the hydrofluorination of an alkyne, we explored the substrate scope and functional group tolerance (Table 2). The distance between the location of the triple bond and the electron withdrawing substituent had a significant effect on the yield (**2a-2d**). This could be explained by the fact that electron withdrawing substituents reduce the electronic density of the alkyne, making it more inert to activation by protonation. Terminal and internal alkynes showed good yield (**2e** vs **2f**). A wide range of functional groups such as esters (**2a-2f**, **2h-2j**), ether (**2g**), nitro group (**2e-2g**, **2i**), aldehyde (**2h**), amide (**2j**, **2k**) and alcohol (**2n**) were well tolerated. The tolerance of the mesylate (**2l**) and tosylate groups (**2m**) enhanced the possibility of further functionalization. Furthermore, the hydrofluorination of a readily available iodoalkyne³⁶⁻³⁸ gave a good yield of the synthetically important β -iodo-difluoride (**2i**), which can be further functionalized for the synthesis of various *gem*-difluorides. The L-phenylalanine derivative **1j** afforded the desired product **2j** in 68% isolated yield.

Our protocol worked satisfactorily well with substrates with a thiophene moiety (Table 2, 2a-2d). We explored other heterocycles, as illustrated in Table 3. We obtained acceptable to very good yields with different heterocyclic substrates including furan (**2aa**), thiazole (**2ab**), pyridine (**2ac**), pyrrole (**2ad**), indazole (**2ae**, **2af**), benzotriazoles (**2ag**, **2ah**) and indoles (**2ai**, **2aj**, **2ak**). Substrates containing basic functional groups (**2ac**, **2ae-2ah**) needed longer reaction times. Our *gem*-difluorination protocol is an easy-to-use tool for the modification of drug molecules with diverse functional groups (Table 4). For example, we obtained a derivative of Probenecid (**2al**) in 83% yield. Probenecid is a prototypical uricosuric agent used to treat patients with renal impairment. On the other hand, a Febuxostat-tethered alkyne produced the corresponding difluoro product **2am** in 71% yield. Febuxostat is used to treat hyperuricemia. This reaction tolerated an ester, nitrile, ether, and a thiazole ring present in Febuxostat. Telmisartan is used to manage hypertension; the *gem*-difluorination of its alkyne derivative furnished **2an** in 71% yield, without affecting the benzoimidazole ring. These examples, using current drugs, demonstrate that our *gem*-difluorination protocol is suitable for the late-stage, protecting-group-free modification of biologically interesting molecules.

To further prove the expediency of our method, we conducted a gram scale synthesis. Both terminal (eq 1) and internal (eq 2) alkyne substrates gave good yields of products — the reaction was completed in only 30 minutes without heating and using less amount of HF reagents. Our protocol also exhibited very high regio-selectivity in the hydrofluorination of an internal alkyne (**2f-1:2f-2** = 32:1, eq 2). The regio-selectivity could be easily predicted by NBO charge density via a simple DFT calculation of starting material **1f**. The calculation shows the C1 is more electron rich than the C2 (eq 2). As predicted, the protonation occurred at C1 and fluorine atoms were added to the electron deficient carbon (C2 in **1f**).

Finally, we investigated the *gem*-difluorination of allenes using our protocol (Table 5). Compared with alkyne substrates, the allene substrates were more reactive, and their reaction only needed DMPU-12HF for *gem*-difluorination. It should be noted that two regioisomers were obtained, with the 2,2-difluoride as the main product.

Conclusions

We have developed a direct regioselective *gem*-difluorination protocol using easily-handled hydrogen fluoride reagents. We demonstrated the effectiveness of this tactic with variously functionalized alkynes, including alkynes tethered to natural products and drug molecules. The protocol offers incomparable broad functionality tolerance, exclusive Markovnikov addition regioselectivity, high atom economy, easy workup procedure, and scalability in the synthesis of *gem*-difluorides from alkynes or allenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a) Dihydrofluorination of alkynes

b) Direct gem-difluorination of carbonyl compounds

c) Indirect gem-difluorination of carbonyl derivatives

Scheme 1.
Strategies for the synthesis of *gem*-difluorides

Table 1.

Reaction condition optimization for hydrofluorination of alkyne.^a

entry	HF complex (A-xHF)	T (°C)	solvent	yield (1a / 2a / 3a / 4a) ^b
1	1 equiv KHSO ₄ -13HF	rt	DCE	75% / 9% / 11% / 5%
2	1 equiv K ₂ SO ₄ -14HF	rt	DCE	100% / 0 / 0 / 0
3	1 equiv Py-9HF	rt	DCE	100% / 0 / 0 / 0
4	1 equiv DMPU-12HF	rt	DCE	100% / 0 / 0 / 0
5	1 equiv KHSO ₄ -13HF	rt	Toluene	79% / 8% / 8% / 5%
6	1 equiv KHSO ₄ -13HF	rt	HFIP	29% / 23% / 20% / 28%
7 ^c	1 equiv K ₂ SO ₄ -14HF	rt	DCE	100% / 0 / 0 / 0
8 ^d	1 equiv K ₂ SO ₄ -14HF	rt	DCE	100% / 0 / 0 / 0
9	1 equiv KHSO ₄ -13HF	50	DCE	62% / 13% / 16% / 9%
10	1 equiv DMPU-12HF + 1 equiv KHSO ₄ -13HF	50	DCE	48% / 27% / 14% / 11%
11 ^e	2 equiv DMPU-12HF	50	DCE	100% / 0 / 0 / 0
12	2 equiv DMPU-12HF + 1 equiv KHSO ₄ -13HF	50	Neat	6% / 65% / 12% / 16%
13	1 equiv DMPU-12HF + 0.5 equiv KHSO ₄ -13HF	50	Neat	46% / 39% / 6% / 9%
14	2 equiv DMPU-12HF + 0.5 equiv KHSO ₄ -13HF	50	Neat	38 / 46% / 6% / 10%
15 ^f	2 equiv DMPU-12HF + 1 equiv KHSO ₄ -13HF	50	Neat	0 / 72% / 12% / 16%

^aReaction conditions: **1** (0.1 mmol), HF complex (1 equiv based on the complex A-xHF, equivalents of HF are x), solvent (0.1 mL), 1 hour.^bNMR yields with benzonitrile as internal standard;^c1 equiv TFA was added;^d1 equiv TfOH was added;^e1 equiv KHSO₄ was added;^f3 h reaction time;

Table 2.

Hydrofluorination of alkynes.^a ^aReaction conditions: **1** (0.2 mmol), 1 equiv KHSO₄·13HF, 2 equiv DMPU-12HF, neat, 50 °C, 3h. All yields are for the isolated product.^bregioisomer ratio.

Table 3. Hydrofluorination of alkynes with various heterocyclic substituents.^a ^aReaction conditions: **1** (0.2 mmol), 1 equiv KHSO₄·13HF, 2 equiv DMPU·12HF, neat, 50 °C, 3 h. All yields are for isolated products.^b15 h reaction time.

Table 4. Late-stage functionalization of known drugs.^a ^aReaction conditions: 1 (0.2 mmol), 1 equiv KHSO₄–13HF, 2 equiv DMPU–12HF, neat, 50 °C, 3h. All yields are for the isolated product.

Table 5.

gem-Difluorination of allenes.^a ^aReaction conditions: **3** (0.2 mmol), 2 equiv DMPU-12HF, neat, 50 °C, 5 h.^bNMR yield.^cisolated yield.