

Designer HF-Based Fluorination Reagent: Highly Regioselective Synthesis of Fluoroalkenes and gem-Difluoromethylene Compounds from Alkynes

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Supporting Information

ABSTRACT: Hydrogen fluoride (HF) and selected nonbasic and weakly coordinating (toward cationic metal) hydrogen-bond acceptors (e.g., DMPU) can form stable complexes through hydrogen bonding. The DMPU/ HF complex is a new nucleophilic fluorination reagent that has high acidity and is compatible with cationic metal catalysts. The gold-catalyzed mono- and dihydrofluorination of alkynes using the DMPU/HF complex yields synthetically important fluoroalkenes and gem-difluoromethlylene compounds regioselectively.

espite its usefulness, the incorporation of fluorine into organic molecules remains a synthetic challenge. Fluorination reagents can be classified as electrophilic or nucleophilic. Nucleophilic fluorination reagents are usually less expensive than their electrophilic counterparts (e.g., Selectfluor, NFSI). Most, if not all, fluorinating reagents (electrophilic or nucleophilic) are made from hydrogen fluoride (HF). Thus, an HF-based reagent would be ideal in terms of cost and atom economy, but HF itself is a hazardous gas at room temperature and is very difficult to handle. Complexes of HF with organic bases such as Olah's reagent (pyridine/HF complex)² and triethylamine/HF complex³ are liquids at room temperature, so they are easier to handle. Pyridine/HF and triethylamine/HF have been explored extensively as nucleophilic sources of fluorine, ^{2a} but these organic bases are not without problems: they reduce the acidity of the system and may interfere with many metal catalysts. For example, pyridine can complex strongly with many transition metals and therefore reduce their activities.

We propose that HF and selected nonbasic, non-nucleophilic, and weakly coordinating (toward cationic metal) hydrogen-bond acceptors can form stable complexes through hydrogen bonding. These HF complexes can act as new nucleophilic fluorination reagents. In 2009, Laurence and co-workers reported a comprehensive database of hydrogen-bond basicity (measured by p $K_{\rm BHX}$). For most compounds, p $K_{\rm BHX}$ is in the range of 1 to 5, where a bigger number indicates higher hydrogen-bond basicity. We used this database as a guideline to select an ideal hydrogenbond acceptor. Among many hydrogen-bond acceptors in Laurence's database, we considered 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as an ideal hydrogen-bond acceptor to form a complex with HF. DMPU is inexpensive and readily available. Even more important, DMPU (p K_{BHX} = 2.82) is a better hydrogen-bond acceptor than pyridine (p $K_{BHX} = 1.86$)

and $\rm Et_3N$ (p $K_{\rm BHX}$ = 1.98)⁴ and at same time is much less basic than pyridine and $\rm Et_3N$ (Figure 1). Thus, the DMPU/HF

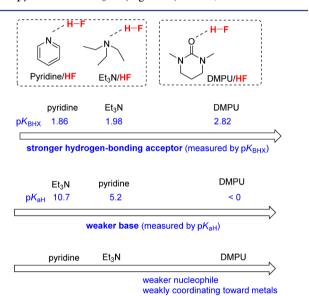


Figure 1. Comparison of DMPU/HF with pyridine/HF and Et₃N/HF.

complex should have higher acidity than the pyridine/HF and triethylamine/HF complexes. Also, DMPU is weakly coordinating to most metal catalysts, so it is unlikely to interfere strongly with most transition-metal catalysts. Moreover, DMPU is a very weak nucleophile, so it will not compete with HF in nucleophilic reactions. Therefore, the HF/DMPU complex should be an ideal fluorination reagent,⁵ especially in transition-metal-catalyzed reactions. Herein we are glad to report a proof of concept application of the DMPU/HF complex in the gold-catalyzed, highly regioselective mono- and dihydrofluorination of alkynes.

Fluoroalkenes are important synthetic building blocks and targets, but they are made from a shallow pool of fluoroalkene synthons⁸ or their preparation requires lengthy procedures that are not functional-group-friendly.⁹ Typical synthetic methods of fluoroalkenes include tandem addition—reduction,^{9a} tandem addition—elimination,¹⁰ Shapiro reaction,^{7b} Julia—Kocienski olefination, 11 and Peterson olefination. 12 Sadighi and co-workers have reported a SIPr-Au catalyzed monohydrofluorination of alkynes using ${\rm Et_3N/HF},^{13}$ but because of the low acidity of the

Received: August 14, 2014 Published: September 26, 2014 Et₃N/HF system, stoichiometric amounts of acid and acidic cocatalyst have to be used. Also, this method works only for internal alkynes, where there is no reliable way to control the regioselectivity. By taking advantage of the unique properties of our DMPU/HF reagent, we were able to mono- and dihydrofluorinate both terminal and internal alkynes in a highly regioselective fashion.

We used the monohydrofluorination of alkyne **1a** as our model reaction. The fluorination agents alone were not able to fluorinate **1a** (Table 1, entries 1–3), and a strong acid (TfOH)

Table 1. Optimization of the Reaction Conditions for Monohydrofluorination of Alkynes a

entry	HF source ^a	catalyst	t (h)	$\frac{2a}{(\%)^b}$	3a (%)
1	pyridine/HF	_	24	0	0
2	$Bu_4N^+OTf^-/HF$	_	48	0	0
3	DMPU/HF	_	48	0	0
4	pyridine/HF	TfOH (100%)	24	0	0
5	DMPU/HF	TfOH (100%)	24	0	0
6	pyridine/HF	Au-1 (5%)	5	13	3
7	DMPU/HF	Au-1 (5%)	5	48	52
8	DMPU/HF	Au-1 (5%)	24	32	68
9	DMPU/HF (1.2 equiv)	Au-1 (5%)	3	99	<1
10	DMPU/HF (1.2 equiv)	Au-1 (2%)	3	99	<1
11	DMPU/HF (1.2 equiv)	Au-1 (1%)	5	83	0

^aConcentrations of HF sources: pyridine/HF (70%), DMPU/HF (65% w/w). ^bDetermined by GC–MS.

$$Au-1 = L-Au-N$$

$$L = (JohnPhos)$$

was not an effective mediator either (entries 4-5). The HF/ DMPU complex we prepared contains 65 wt % HF, corresponding to an HF:DMPU molar ratio of around 11.8:1.14 We recently reported acid-assisted activation of an imidogold precatalyst as a superior way to generate cationic gold compared with the common silver-based methodology. 15 We found that our DMPU/HF system is acidic enough to activate the imidogold precatalyst (Au-1). Indeed, the DMPU/HF system is much more efficient in the fluorination of 1a than the commonly used pyridine/HF complex (entries 6 and 7). The DMPU/HF/Au-1 system is highly reactive but it gave a mixture of monofluorinated product 2a and difluorinated product 3a (entry 8). We were able to achieve selective monofluorination by reducing the amount of fluorination reagent from 3 to 1.2 equiv (entry 9), and the good yield and selectivity of product 2a were maintained even at lower gold precatalyst loadings of 2% and 1% (entries 10 and 11).

With the optimized conditions in hand, we investigated the scope of the monohydrofluorination of alkynes (Table 2). Clean and regioselective transformations were observed for all of the terminal alkynes tested (Table 2, entries 1–8). The reaction also worked well for internal alkynes, although longer reaction times and higher loadings of gold catalyst were needed (entries 9–11). This reaction also has good functional group tolerance: an alkyne with a strong electron-withdrawing group (entry 9) and an alkyne with an acidic C–H group and an ester group (entry 12)

Table 2. Substrate Scope for Monohydrofluorination of Alkynes $\mathbf{1}^a$

 $^a\mathrm{Conditions}$: Alkyne 1 (0.5 mmol) and DMPU/HF (65 wt %, 1.2 equiv) in DCE at 55 $^\circ\mathrm{C}$ for 3 h. $^b\mathrm{Isolated}$ yields (other yields are $^{19}\mathrm{F}$ NMR yields).

gave the corresponding fluoroalkenes in good yields and selectivity.

We found that in the monohydrofluorination of acceptorsubstituted terminal alkyne 1m, the DMPU/HF/Au-1 system yielded a completely different regioisomer compared with the literature report, where no catalyst was used. Thus, the uncatalyzed addition of HF to 1m gave the Michael addition product 4 (Scheme 1b), 16 whereas our DMPU/HF/Au-1 system reversed the tendency toward Michael addition to give 2m instead as the only isomer (Scheme 1a).

Scheme 1. Selectivity of the DMPU/HF/Au-1 Fluorination System

The DMPU/HF/Au-1 system is highly effective for alkyne hydrofluorination, but it is not a good catalyst for hydrofluorination of alkenes (Scheme 1c). In other words, alkene groups are well-tolerated. For example, a 1:1 mixture of 1-octene (5) and 1-octyne (1b) gave only alkyne hydrofluorination product 2b under the conditions of our model reaction.

gem-Difluoromethylene (CF₂)-containing compounds are important building blocks and targets in organic synthesis. 7a,17 In this regard, dihydrofluorination of an alkyne is a straightforward and atom-economical way to synthesize CF₂containing compounds 3. Olah and co-workers reported a synthesis of difluorinated alkanes with limited scope and selectivity. 2b As shown above (Table 1, entry 8), we observed the formation of 3a during our search for optimal conditions for the synthesis of 2a. We believed that further hydrofluorination of fluoroalkenes 2 would give the dihydrofluorination products 3, but as we saw in Scheme 1c, our DMPU/HF/Au-1 system is not a good catalytic system for the hydrofluorination of alkenes, so complete conversion of 2 to 3 is difficult. We then explored the possibility of using a cocatalyst or additive that could catalyze the further hydrofluorination of 2 to give the desired product 3 (Table 3). Additional nucleophilic fluorine sources (CsF and

Table 3. Optimization of the Conditions for Dihydrofluorination of Alkynes 1

AgF; entries 1 and 2) were moderately effective, but could not convert all of the **2a** to **3a**. The weak Lewis acid KCTf₃ (entry 3) was not effective either, but the stronger acids Ga(OTf)₃ and KHSO₄ (entries 4–5) helped to produce **3a** with very good selectivity. Because KHSO₄ is relatively inexpensive and readily available, we selected KHSO₄ as our cocatalyst for the synthesis of **3**.

To get a clearer understanding of the role of a Lewis acid like $Ga(OTf)_3$ in the formation of *gem*-difluoromethylene compounds **3** we conducted a control experiment (eq 1). DMPU/HF alone can convert **2a** to **3a** without any catalyst, but this reaction is sluggish (eq 1, condition 1). However, a Lewis acid like

2a	condition DCE, 55°C	+	F F	(eq 1)
condition 1	DMPU/HF (1 equiv)	time 1 h 2 h	conversi 16% 18%	ion
condition 2	DMPU/ <mark>HF</mark> (1 equiv), Ga(OTf) ₃ (10%)	1 h 2 h	47% 56%	

 $Ga(OTf)_3$ can significantly speed up this conversion (eq 1, condition 2).

With the optimized conditions for dihydrofluorination of alkynes in hand, we investigated the substrate scope of this transformation (Table 4). This reaction worked very well for both terminal and internal alkynes.

Table 4. Substrate Scope for Dihydrofluorination of Alkynes 1^a

 a Alkyne 1 (0.5 mmol), DMPU/HF (65 wt %, 3.0 equiv), and KHSO $_4$ (1.5 equiv) in DCE at 55 $^{\circ}$ C for 12 h. b Isolated yield (other yields are 19 F NMR yields).

The usefulness of our method was further validated by the synthesis of fluorocarbocycles via ring-closing metathesis (RCM) reactions (Scheme 2).⁸ Because fluoroalkenes can be prepared

Scheme 2. Synthesis of Fluorocarbocycles

F
$$CO_2Me$$
 1. NaHMDS CO_2Me 2. CO_2Me CO_2

efficiently using our new method and alkene groups are well-tolerated, we can envision a diverse set of fluorocycles made by the combination of alkyne monohydrofluorination and RCM reactions.

In summary, our new fluorination reagent DMPU/HF not only is easily handled but also is an efficient fluorination system for the regioselective mono- and dihydrofluorination of alkynes. Further applications of this new fluorination reagent as well as commercialization discussions are currently being conducted in our laboratory.

ASSOCIATED CONTENT

S Supporting Information

Experimental procedures and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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