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Selective Synthesis of *gem*-Chlorofluorinated Nitrogen-Containing Derivatives after Superelectrophilic Activation in Superacid HF/SbF_5

Fei Liu,[†] Agnès Martin-Mingot,[†] Marie-Paule Jouannetaud,[†] Christian Bachmann,[‡] Gilles Frapper,[‡] Fabien Zunino,[§] and Sébastien Thibaudeau*,[†]

[†]*Laboratoire "Synthèse et Réactivité des Substances Naturelles", UMR 6514, 40 avenue du Recteur Pineau, F-86022 Poitiers Cedex, France,* [‡]*UMR 6503, 40 avenue du Recteur Pineau, F-86022 Poitiers Cedex, France, and* [§]*@rtMolecule, 40 avenue du Recteur Pineau, F-86022 Poitiers Cedex, France*

sebastien.thibaudeau@univ-poitiers.fr

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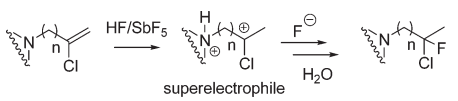
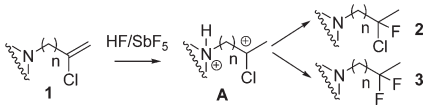


The first direct selective synthesis of novel *gem*-chlorofluorinated nitrogen-containing building blocks in superacid is reported. The dramatic role of the chlorine atom on the reaction is shown by in situ NMR experiments and allows the involvement of a novel original superelectrophilic activation process in superacid HF/SbF_5 to be postulated.

The importance of fluorine in medicinal chemistry,[1] which is mainly due to a fluorine atom's unique properties, is well-recognized.[2] Among fluorine substitution consequences, the strong inductive withdrawing effect of fluorine on the acidity or basicity of neighboring functional groups is especially evident,[3] making the incorporation of nitrogen-containing organofluorine cores very popular in medicinal chemistry.[4] While *gem*-difluorinated amines have been exploited, surprisingly little attention has been given to *gem*-chlorofluorinated analogues. The intriguing combination of the two different geminal halogens might interfere with both the gauche fluorine effect and the NH···FC dipole orientation effect,[5] with a concomitant effect on the conformation and basicity of the amines. In addition, their ability to be used as precursors of fluorinated nitrogen-containing functionalized building blocks[6] make them excellent candidates for SAR studies. However, their synthesis has been scarcely studied to date.[7] Herein, we report the first direct selective synthesis of *gem*-chlorofluorinated nitrogen-containing derivatives after reaction in HF/SbF_5.

SCHEME 1. Selective Synthesis of *gem*-Chlorofluorinated or *gem*-Difluorinated Nitrogen-Containing Derivatives in HF/SbF_5



In the course of the synthesis of the difluorinated anticancer agent vinflunine (Javlor),[8] we recently proposed that the *gem*-difluorination of unsaturated amines in superacid is strongly based on the ability to form superelectrophilic[9] ammonium-α-chloronium intermediates.[10] Despite the very weak nucleophilic character of the solvated fluorine in the polymeric anionic form $Sb_nF_{5n+1}^-$ of the superacidic medium,[11] it was postulated that the ammonium ion plays a critical role in activating the nearby electrophilic site, allowing its fluorination and subsequent formation of the difluorinated product. On the basis of these previous investigations, we postulated that ammonium-α-chloronium intermediates **A** should easily be formed in superacid starting from chlorinated olefins **1** (Scheme 1).

By modification of the reaction conditions and especially the cationic and anionic composition of the superacid medium,[11] *gem*-chlorofluorinated and/or *gem*-difluorinated derivatives **2** and/or **3** should be selectively obtained (Table 1). With substrate **1a** as a model substrate, the first attempt confirmed our initial hypothesis, with the formation of a mixture of products **2a** and **3a** (Table 1, entry 1). When performed at 0 °C, the reaction led to the selective formation of difluorinated product **3a** (Table 1, entry 2). Decreasing the temperature afforded chlorofluorinated product **2a** selectively, but the reaction was not complete in this case (Table 1, entry 3). The influence of the acidity of the medium[11] on the selectivity of the reaction was dominant and allowed the selective formation of product **2a** (Table 1, entry 4).

(1) (a) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (b) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992. (c) Purse, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(3) Morgenthaler, M.; Schweiser, E.; Hoffman-Roder, F.; Benini, F.; Martin, R. E.; Jaeschke, G.; Wagner, B.; Fisher, H.; Bendels, S.; Zimmerili, D.; Schneider, J.; Hiedrich, F.; Kansy, M.; Muller, K. *ChemMedChem* **2007**, *2*, 1100.

(4) Hagmann, W. H. *J. Med. Chem.* **2008**, *51*, 4359.

(5) Buissonneaud, D. Y.; van Mourik, T.; O'Hagan, D. *Tetrahedron* **2010**, *66*, 2196 and references cited therein.

(6) Shibatomi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5796.

(7) To the best of our knowledge, only two articles have reported the synthesis of *gem*-chlorofluorinated amines. See: (a) Verniest, G.; Colpaert, F.; Van Hende, E.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 8569. (b) Van Hende, E.; Verniest, G.; Surmont, R.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 2935.

(8) (a) Fahy, J.; Duflos, A.; Ribert, J.-P.; Jacquesy, J.-C.; Berrier, C.; Jouannetaud, M.-P.; Zunino, Z. *J. Am. Chem. Soc.* **1997**, *119*, 8576. (b) Jacquesy, J.-C. *J. Fluorine Chem.* **2006**, *127*, 1484.

(9) Olah, G. A.; Klumpp, D. In *Superelectrophiles and Their Chemistry*; John Wiley and Sons: New York, 2008.

(10) Zunino, F.; Liu, F.; Berrier, C.; Martin-Mingot, A.; Thibaudeau, S.; Jouannetaud, M.-P.; Jacquesy, J.-C.; Bachmann, C. *J. Fluorine Chem.* **2008**, *129*, 775.

(11) (a) Bonnet, B.; Mascherpa, G. *Inorg. Chem.* **1980**, *19*, 785. (b) Mootz, D.; Bartmann, K. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 391. (c) Culmann, J.-C.; Sommer, J. *J. Am. Chem. Soc.* **1990**, *112*, 4057. (d) Culmann, J.-C.; Fauconet, M.; Jost, R.; Sommer, J. *New J. Chem.* **1999**, *23*, 863. (e) Sommer, J.; Canivet, P.; Schwartz, S.; Rimmelin, P. *New J. Chem.* **1981**, *5*, 45.

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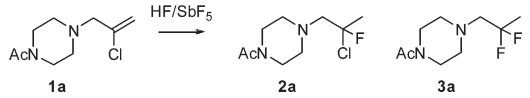
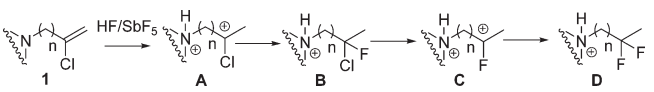
TABLE 1. Substrate 1a Behavior in HF/SbF_5[a]



entry	acidity (mol % SbF_5)	temperature (°C)	product (yield)[b]	
1	13.6	−20	**2a** (40)	**3a** (24)
2	13.6	0	**2a** (0)	**3a** (70)
3	13.6	−50	**2a** (45)	**3a** (0)[c]
4	3.8	−20	**2a** (74)	**3a** (0)

[a]Reaction conditions: substrate (1 mmol), HF/SbF_5 (3 mL), 10 min. [b]Yield obtained after flash chromatography. [c]Starting material remaining.

SCHEME 2. Proposed Mechanism for the Fluorination Process



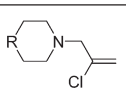
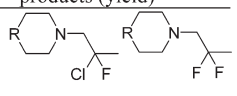
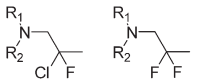
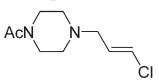
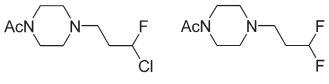
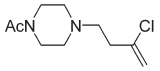
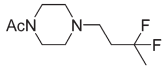
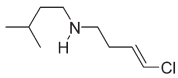
To explain these preliminary results, we postulated the mechanism shown in Scheme 2. Protonation of the amine and the double bond in superacid should give dication **A**, which after fluorination should give ammonium **B**, the precursor of the chlorofluoro product. After 10 min of reaction in HF/SbF_5 (13.6 mol % SbF_5) at 0 °C starting from chlorofluorinated amine **2a**, product **3a** was formed quantitatively, confirming that ion **B** could be considered as an intermediate in the difluorination process. After protonation of ion **B** and HCl elimination, α-fluoronium intermediate **C**, a precursor of difluorinated ammonium **D** (ion **D** could also come from **B** via an S_N2-type mechanism) should be formed to give the difluorinated product **3a** after hydrolysis.

To an approximation, superelectrophilic activation decreases with increasing separation of the charge centers.[9] To verify the ability to use ammonium-α-chloronium superelectrophilic activation as a new synthetic tool, a scope and limitations study focused on the influence of the distance between the charge centers on the reaction course was needed (Table 2).

Through the use of reaction conditions A or B, *gem*-chlorofluorinated or *gem*-difluorinated amines, amides, imides, or sulfonamides were selectively obtained in good yields (Table 2, entries 1−12). Increasing the distance between the amino group and the chlorine atom allowed the formation of γ,γ-chlorofluorinated and -difluorinated amines (Table 2, entries 13−15). It also should be noted that the reaction of substrate **1i** led to a complex mixture of compounds, regardless of the conditions used. At this stage, the behavior of substrates **1e** and **1f** intrigued us. In a previous study,[12] we showed that dicationic carboxonium−carbenium ions $\mathbf{B_1}$ and $\mathbf{B_2}$ are not superelectrophilic enough to react with fluoride ions (Scheme 3).

In α-chloronium ions, the chlorine atom becomes both a π- and σ-donor substituent.[13] As a consequence, we could have expected that the stabilizing effect of the chlorine atom in intermediates $\mathbf{C_1}$ and $\mathbf{C_2}$, which reduces their electrophilic character, should prevent them from fluorination. To understand and verify this intriguing effect of chlorine substitution on the reactivity of amides and imides, a screening of various substrates was investigated (Table 3).

TABLE 2. Synthesis of *gem*-Chlorofluorinated and *gem*-Difluorinated Nitrogen-Containing Compounds in Superacid HF/SbF_5

entry	substrate	conditions[a]		products (yield)[b]	
					
1	**1a** R=NAc	A	-20	**2a** (74)	**3a** (0)
2	**1a** R=NAc	B	0	**2a** (0)	**3a** (70)
3	**1b** R=CH_2	A[c]	-20	**2b** (68)	**3b** (0)
4	**1b** R=CH_2	B	0	**2b** (0)	**3b** (64)
					
5	**1c** R_1=*p*NO_2Bn R_2=H	A	-20	**2c** (73)	**3c** (0)
6	**1c** R_1=*p*NO_2Bn R_2=H	B	0	**2c** (0)	**3c** (66)
7	**1d** R_1=*p*ClPhSO_2 R_2=H	A[c]	0	**2d** (68)	**3d** (0)
8	**1d** R_1=*p*ClPhSO_2 R_2=H	B	0	**2d** (0)	**3d** (81)
9	**1e** NR_1R_2=Phtal	A[c]	-20	**2e** (77)	**3e** (0)
10	**1e** NR_1R_2=Phtal	B	0	**2e** (0)	**3e** (83)
11	**1f** R_1=*p*-NO_2Bz R_2=H	A	-78	**2f** (70)	**3f** (0)
12	**1f** R_1=*p*-NO_2Bz R_2=H	B	-50	**2f** (0)	**3f** (60)
					
13	**1g**	A[c]	-20	**2g** (60)	**3g** (16)
14	**1g**	B	0	**2g**(0)	**3g** (80)
					
15	**1h**	A	-50	**3h** (71)	
					
16	**1i**	A	-20	/[d]	

[a]Reaction conditions A: SbF_5 (3.8 mol %), 10 min, *T* (°C). Reaction conditions B: SbF_5 (13.6 mol %), 10 min, *T* (°C). [b]Yield obtained after flash chromatography. [c]Reaction time = 1 min. [d]Complex mixture.

Under difluorination conditions (conditions B), we showed above that imide **1e** and amide **1f** led exclusively to difluorinated products (Table 2, entries 10 and 12). However, starting from amide **1f**, oxazole **4f** was selectively synthesized after reaction at 0 °C (Table 3, entry 1). Increasing the distance between the imide function and the chlorine atom led to the formation of carbonyl compounds **4j** and **4k** (Table 3, entries 2 and 4). To form the corresponding difluorinated product **3j**, a longer reaction time was needed, and only a small amount of the desired product could be synthesized (Table 3, entry 3). The limit of the reaction was found with the formation of a complex mixture of compounds after reaction of substrate **1m** in superacid (Table 3, entry 6). The exclusive formation of oxazole **4f**

(12) Thibaudeau, S.; Martin-Mingot, A.; Jouannetaud, M.-P.; Karam, O.; Zunino, F. *Chem. Commun.* **2007**, 3198.
(13) Christe, K. O.; Zhang, X.; Ban, R.; Hegge, J.; Olah, G. A.; Prakash, G. K. S.; Sheety, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 481.

SCHEME 3. Reaction of Amides and Imides in Superacidic HF/SbF_5

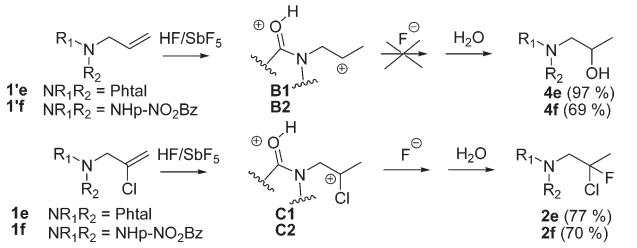
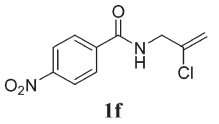
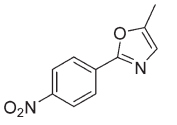
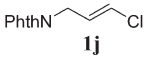
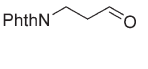
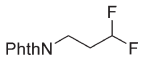
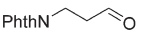
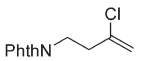
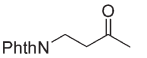
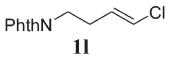
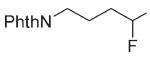
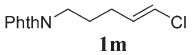


TABLE 3. Reactivity of Unsaturated Imides and Amides[a]

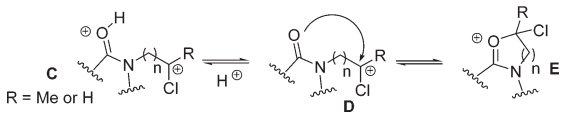
entry	substrate	temperature	products (yield)[b]
1	 **1f**	0	 **4f** (97)
2	 **1j**	-20	 **4j** (91)
3	**1j**	0[c]	 **3j** (18)  **4j** (66)
4	 **1k**	-20	 **4k** (78)
5	 **1l**	-20	 **3l** (65)
6	 **1m**	-20	/[d]

[a]Reaction conditions B: SbF_5 (13.6 mol %), 10 min. [b]Yield obtained after flash chromatography. [c]Reaction time = 24 h. [d]Complex mixture.

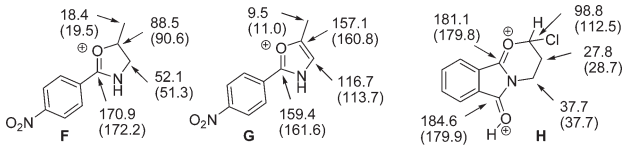
after reaction of amide **1f** at 0 °C and the observed nonlinear effect of the distance between the function and the reactive double bond on the reactivity of the substrates encouraged us to postulate the mechanism shown in Scheme 4.

Amides and imides exist as neutral and O-protonated forms in strongly acidic solutions.[14] If a fast equilibrium between these species in superacid and potent intramolecular participation of the carbonyl group in the stabilization of the formed carbenium ion are assumed,[15] carboxonium ions of type **E** could be considered as the reactive intermediates in the reactions of chlorinated amides and imides. To confirm the involvement of these novel monocationic superelectrophilic intermediates in the fluorination process, amides and

SCHEME 4. Proposed Reaction Mechanism Involving Cyclic Carboxonium Ions



SCHEME 5. Results from Low-Temperature (−20 °C) ^{13}C NMR Studies of Amides 1′f and 1f and Imide 1j Dissolved in HF/SbF_5 (Compared to Theoretical Values in ppm)



imides were dissolved in HF/SbF_5 (21.6 mol % SbF_5) and studied by ^{13}C NMR and DEPT experiments at −20 °C. To compare experimental NMR chemical shift values with those from theory, model calculations on the postulated intermediates were also performed at the B3LYP/cc-pVTZ level.[16] For example, the cyclic carboxonium ions **F**, **G**, and **H** are the sole intermediates respectively detected from low-temperature ^{13}C NMR studies of amides **1′f** and **1f** and imide **1j** dissolved in superacid (Scheme 5).

The observed signals at 170.9 and 181.1 ppm in addition to the CH signals observed respectively at 88.5 and 98.8 ppm for **F** and **H** confirmed the presence of CH groups that are strongly deshielded and proximal to carboxonium ions, consistent with the proposed cyclic carboxonium ions.[17] Interestingly, the quaternary carbon at 157.1 ppm and a CH signal at 116.7 ppm proved the presence of a formed double bond after reaction of **1f** under these conditions (21.6 mol % SbF_5). These observations, combined with the shielded conjugated carboxonium ion (159.4 ppm), are in accordance with the structure of oxazolinium ion **G**. It should be noted that for all of the postulated intermediates, the observed chemical shift values are in good agreement with the calculated data.[16] On the basis of this study, the involvement of the cyclic carboxonium ions shown in Scheme 6 can be postulated. Whereas five-membered-ring carboxonium ion **F** is not electrophilic enough to be fluorinated, the withdrawing effect of the chlorine atom in **G′** makes possible the superelectrophilic activation,[18] and fluorination occurs. Interestingly, the effect of the cyclic shape of the chlorinated cyclic carboxonium ions on the fluorination process is dramatic. Whereas five- and seven-membered-ring carboxonium ions (intermediates **I** and **K**) give fluorinated products, making them superelectrophiles, the corresponding six-membered rings (intermediates **H** and **J**) cannot be fluorinated (or are fluorinated very slowly in the case of dication **H**) and cannot be considered as superelectrophiles. To the best of our knowledge, this is the first time that the relative superelectrophilic character of polycationic intermediates has been shown to be influenced by their geometry in addition to charge repulsion. In

(14) (a) Cox, R. A.; Druet, L. M.; Klausner, A. E.; Modro, T. A.; Wan, P.; Yates, K. *Can. J. Chem.* **1981**, *59*, 1568. (b) Perrin, C. L.; Lollo, C. P.; Johnston, E. R. *J. Am. Chem. Soc.* **1984**, *106*, 2749. (c) Olah, G. A.; Schlosberg, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 6464. (d) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770. (e) Bagno, A.; Bujnicki, B.; Bertrand, S.; Comuzzi, C.; Dorigo, F.; Janvier, P.; Scorrano, G. *Chem.—Eur. J.* **1999**, *5*, 523.

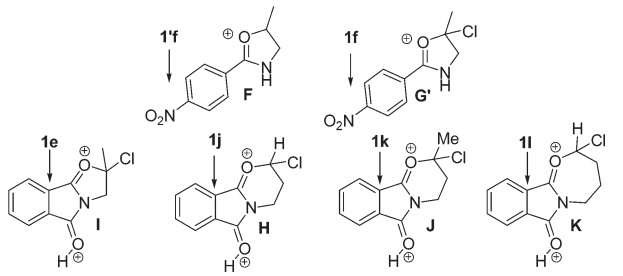
(15) Similar intramolecular stabilization in superacid has already been postulated. Please see: Thibaudeau, S.; Martin-Mingot, A.; Jouannetaud, M.-P.; Jacquesy, J.-C. *Tetrahedron* **2002**, *58*, 6643 and references cited therein.

(16) Please see the Supporting Information.

(17) Olah, G. A.; Laali, K. K.; Wang, Q.; Prakash, G. K. S. In *Onium Ions*; Wiley-Interscience: New York, 1998.

(18) In superacid HF/SbF_5 (21.6 mol % SbF_5), after protonation and HCl elimination, **G′** gives oxazolinium **G**.

SCHEME 6. Cyclic Carboxonium Ions Involved in Superacid



addition, even if it should be recognized that "electrophilic assistance" (solvation, association) by the superacidic medium could occur in this context,[19] the involvement of a monocationic intermediate such as cyclic carboxonium ion **G′** has not been reported to date in a superelectrophilic activation process.

We next turned our attention to the synthetic opportunity provided by these new *gem*-chlorofluorinated derivatives (Scheme 7). First, a new chlorofluorinated amine building block **5** was synthesized in 62% yield after treatment of phtalimide **2e** with hydrazine. Alternatively, imide **2e** could also be used to access original fluoroenimide **6** after basic elimination. Interestingly, Woodward recently reported an elegant synthesis of β-functionalized hydroxylamines via the Owari rearrangement of β-chloro-*N*-oxides.[20] With chlorofluorinated amines, we thought that the strongly inductive withdrawing effect of the fluorine atom in the geminal position should activate this transformation. Gratifyingly, after in situ formation of the corresponding *N*-oxide, ring closure, and nucleophilic ring opening with the formed benzoate, fluorinated *N*-oxide **7** could be obtained in 77% yield under optimized conditions. It should be pointed out that no C−F bond cleavage occurred under our conditions.[21]

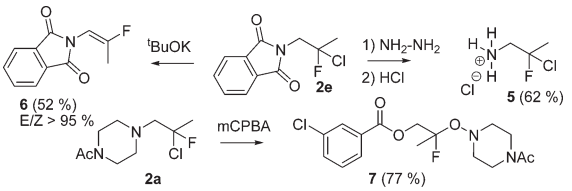
In summary, we have described a new, selective, one-step synthetic route to novel *gem*-chlorofluorinated and *gem*-difluorinated nitrogen-containing compounds starting from easily accessible starting materials. In addition, for the first time, we have proved the involvement of a monocationic superelectrophile in a fluorination reaction in superacid. Furthermore, the cyclic shape of the cyclic chlorinated carboxonium ions has been proved to be crucial for this new superelectrophilic activated fluorination process in the superacid HF/SbF_5. We believe that this novel, powerful synthetic methodology, which is based on cationic α-chloronium ion activation, allows access to a new class of fluorinated organic molecules that will prove to be useful building blocks for many applications in the life sciences. As already proved by the recent development of Javlor, such a process could also be used on more elaborated substrates.

(19) Olah, G. A. In *A Life of Magic Chemistry*; John Wiley and Sons: New York, 2001.

(20) Wefelscheid, U. K.; Woodward, S. *J. Org. Chem.* **2009**, *74*, 2254.

(21) Intramolecular nucleophilic substitution of alkyl fluorides was recently achieved with phenolate ions. Please see: Zhang, L.; Zhang, W.; Liu, J.; Hu, J. *J. Org. Chem.* **2009**, *74*, 2850.

SCHEME 7. Synthetic Applications of Chlorofluorinated Derivatives



Experimental Section

The authors draw the reader's attention to the dangerous features of superacid chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all of the necessary safety arrangements in place.

Synthesis of *gem*-Chlorofluorinated Compounds. Optimized Procedure: Conditions A. To a HF/SbF_5 mixture (3 mL, 3.8 mol % SbF_5) was added substrate (1 mmol). The mixture was magnetically stirred at the same temperature for 10 min of reaction time, after which the reaction mixture was neutralized with water/ice/Na_2CO_3 until pH 9 was attained and then extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Products were isolated by column chromatography over silica gel.

Compound 2a: 1-(4-(2-Chloro-2-fluoropropyl)piperazin-1-yl)-ethanone. The optimized procedure (maintained at −20 °C) was followed. Purification by flash column chromatography [99.5/0.5 dichloromethane/NH_3(aq)] gave 164 mg of the title compound (74%).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.93 (d, $^3J_{H-F}$ = 19.4 Hz, 3H, H-3″), 2.06 (s, 3H, H-2), 2.57 (m, 4H, H-3′), 2.78 (dd, $^3J_{H-F}$ = 24.2 Hz, $^2J_{H-H}$ = 14.3 Hz, 1H, H-1″), 2.94 (dd, $^3J_{H-F}$ = 14.3 Hz, $^2J_{H-H}$ = 14.3 Hz, 1H, H-1″), 3.42 and 3.57 (2 m, 4H, H-2′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 21.7 (s, CH_3, C-2), 28.4 (d, $^2J_{C-F}$ = 25 Hz, CH_3, C-3″), 41.9 and 46.8 (2 s, $2CH_2$, C-2′), 54.4 and 54.6 (s, CH_2, C-3′), 67.8 (d, $^2J_{C-F}$ = 22 Hz, CH_2, C-1″), 114.3 (d, $^1J_{C-F}$ = 243 Hz, 1C, C-2″), 169.3 (s, C-1). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −99.3. MS (GCT, CI^+) *m*/*z* (relative intensity %): 222 (2), 224 (5), 187 (80). HRMS (ESI) *m*/*z*: calcd for $C_9H_{16}N_2OF\ ^{35}Cl$, 222.0935; found, 222.0930.

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Supporting Information Available: Experimental procedure, characterization of products, computational data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.