JOC*Note*

gem-Difluorination of Aminoalkynes via Highly Reactive Dicationic Species in Superacid $HF-SbF_5$: Application to the Efficient Synthesis of Difluorinated Cinchona Alkaloid Derivatives

Anne-Céline Cantet, Hélène Carreyre, Jean-Pierre Gesson, Marie-Paule Jouannetaud, and Brigitte Renoux*

Laboratoire "Synthèse et Réactivité des Substances Naturelles", University of Poitiers, CNRS, 40 Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France

brigitte.renoux@univ-poitiers.fr

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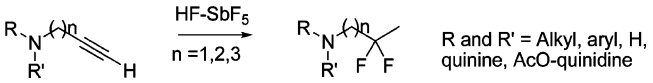

A variety of alkynylated amines, amides, and imides are reacted in the superacid system $HF-SbF_5$ to give regioselectively new *β-gem*-difluoroamines. The reaction, which is not observed in pure HF, is consistent with the formation of a dicationic intermediate (i.e., both vinylic and adjacent protonated *N*-ammonium cations). Application to the regioselective and efficient synthesis of difluorinated cinchona alkaloid derivatives is described.

As the most important electronegative element, fluorine has played a key role in recent pharmaceutical, agrochemical, and materials science.[1] The introduction of fluorine atoms in a given molecule often dramatically alters its chemical properties and its pharmacological profile in the case of biologically active compounds.[2] Recently, we have developed in our laboratory a powerful fluorinating methodology in superacid. Under these conditions ($HF-SbF_5$), unusual reactivity of functionalized organic substrates is observed.[3−7] While attempting to synthesize potentially new bioactive fluorinated compounds, Jacquesy et al. previously reported a novel oxidative *gem*-difluorination of vinca alkaloids in superacid $HF-SbF_5$, in the presence of either *N*-bromosuccinimide (NBS) or chloromethanes ($CHCl_3$ or CCl_4). This resulted in the preparation of vinflunine,[8] a new difluoro derivative which has shown promising antitumor activity and is currently in phase III clinical trials. More recently, hydrofluorination of these substrates was investigated to afford the corresponding *β*-fluoroamines.[9] Taking into account the interest in difluorinated building blocks of high synthetic value, we would like to report the behavior of alkyne nitrogen substrates as potential precursors of *β-gem*-difluoroamino derivatives in acidic and/or superacidic conditions.

The *gem*-difluorination of alkynes has been described by Olah[10] using HF/pyridine and by Henne[11] with hydrogen fluoride to give the corresponding *gem*-difluoroalkanes. Recently, Klumpp reported the reactivity of aminoalkynes and proposed for the first time the possible formation of dicationic electrophiles (or superelectrophiles) in the Brønsted superacid CF_3SO_3H (triflic acid) which form new products in Friedel−Crafts-type reactions.[12]

In the following note, we describe our studies of the superacid-catalyzed $HF-SbF_5$ chemistry of alkynes bearing an N-heterocycle or amine functional groups and their ability to regioselectively form new *β-gem*-difluoro nitrogen compounds. Starting materials **1**−**9** were easily synthesized in one step by direct alkylation of the corresponding amines under basic conditions (**2**, **5**, **6**, and **9**: NaH, THF;[13] **3** and **4**: K_2CO_3, acetone;[14] **7**: Cs_2CO_3, DMF;[15] **1** and **8**: K_2CO_3, 18-crown-6, benzene[16]) in the presence of alkynylic bromide in variable yields (19−89%).

Initial experiments were performed using pure HF (0 °C, 5 h). The expected addition of hydrogen fluoride by an electrophilic mechanism with Markovnikov's rule orientation on piperidine **2** afforded the difluoro derivative **12** as the sole product. Under the same conditions of acidity and temperature, phthalimide **1** yielded a *gem*-difluoro compound **10** as the major product (Table 1) and minor amounts of methylketone **11**. Surprisingly, all propargylic amino derivatives **3**−**9** remained unchanged under these conditions. It may be assumed that the basic nitrogen atom must be irreversibly protonated, thus decreasing the nucleophilicity of the adjacent triple bond and completely deactivating it toward electrophilic reagents. The use of more acidic conditions ($HF-SbF_5$) was then considered. In optimized conditions ($HF-SbF_5$: 7/1 molar ratio, −40 to −60 °C), the starting materials were fully transformed within 2 to 15 min. Results are summarized in Table 2. Under these conditions, primary, secondary, tertiary, and aromatic amines afforded the corresponding *β-gem*-difluoroamines in good yields

(1) Dolbier, W. R., Jr. *J. Fluorine Chem.* **2005**, *126*, 157−163.
(2) (a) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3−11. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231.
(3) Berrier, C.; Jacquesy, J. C.; Jouannetaud, M. P.; Lafitte, C.; Vidal, Y.; Zunino, F.; Fahy, J.; Duflos, A. *Tetrahedron* **1998**, *54*, 13761−13770.
(4) Gesson, J. P.; Jacquesy, J. C.; Jacquesy, R. *Tetrahedron Lett.* **1971**, *49*, 4733−4736.
(5) Martin, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **1996**, *37*, 2967−2970.
(6) Debarge, S.; Violeau, B.; Bendaoud, N.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2003**, *44*, 1747−1750.
(7) Moine, A.; Thibaudeau, S.; Martin, A.; Jouannetaud, M. P.; Jacquesy, J. C. *Tetrahedron Lett.* **2002**, *43*, 4119−4122.
(8) (a) Fahy, J.; Duflos, A.; Ribet, J. P.; Jacquesy, J. C.; Berrier, C.; Jouannetaud, M. P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *119*, 8576−8577. (b) Jacquesy, J. C.; Berrier, C.; Jouannetaud, M. P.; Zunino, F.; Fahy, J.; Duflos, A.; Ribet, J. P. *J. Fluorine Chem.* **2002**, *114*, 139−141. (c) Jacquesy, J. C.; Fahy, J. *Biomedical Chemistry: Applying Chemical Principles to the Understanding and Treatment of Disease*; Wiley-Interscience: New York, 2000; pp 227−245.
(9) Thibaudeau, S; Martin-Mingot, A.; Jouannetaud, M. P.; Karam, O.; Zunino, F. *Chem. Commun.* **2007**, 3198−3200.
(10) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* **1973**, 779.
(11) (a) Henne, A. L.; Zimmerschied, W. J. *J. Am. Chem. Soc.* **1947**, *69*, 281−283. (b) Henne, A. L.; Plueddeman, E. P. *J. Am. Chem. Soc.* **1943**, *65*, 587−589.
(12) Klumpp, D. A.; Rendy, R.; Zhang, Y.; McElrea, A.; Gomez, A.; Dang, H. *J. Org. Chem.* **2004**, *69*, 8108−8110.
(13) Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 1361−1367.
(14) Kundu, N. G.; Nandi, B. *J. Org. Chem.* **2001**, *66*, 4563−4575.
(15) Perrez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Gonzalez-Perez, P.; Perez-Castells, J. *Synthesis* **2002**, *13*, 1810−1812.
(16) Cousson, A.; Gazeau, C.; Gesson, J. P.; Jacquesy, J. C.; Rambaud, D.; Renoux, B. *Bull. Soc. Chim. Fr.* **1994**, *131*, 95−104.

10.1021/jo702441p CCC: $40.75
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TABLE 1. Reactivity of Aminoalkynes in Pure HF

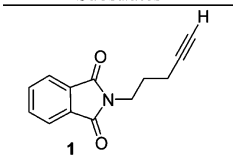
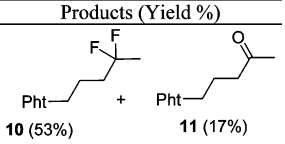
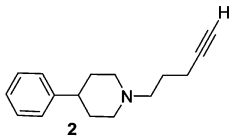
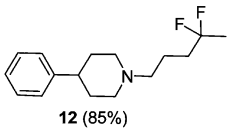
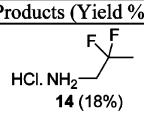
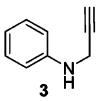
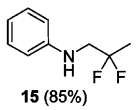
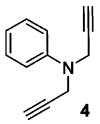
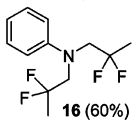
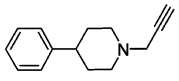
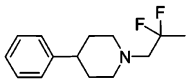
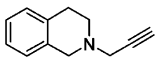
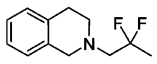
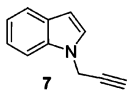
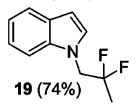
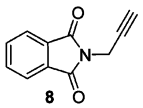
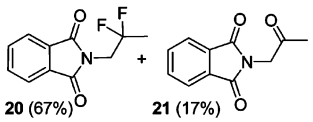
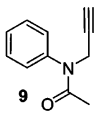
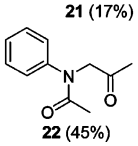
Substrates	Products (Yield %)
 **1**	 **10** (53%) + **11** (17%)
 **2**	 **12** (85%)
3-9	Starting materials

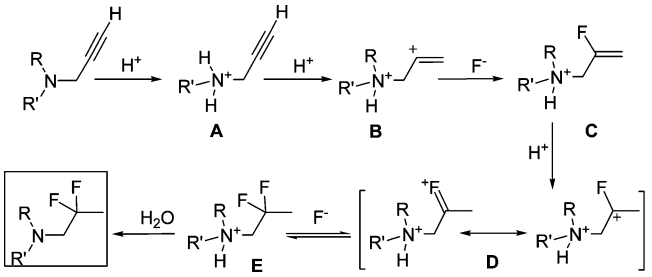
TABLE 2. Reactivity of Aminoalkynes in HF−SbF_5

Substrates	Products (Yield %)
 **13**	 **14** (18%)
 **3**	 **15** (85%)
 **4**	 **16** (60%)
 **5**	 **17** (87%)
 **6**	 **18** (61%)
 **7**	 **19** (74%)
 **8**	 **20** (67%) + **21** (17%)
 **9**	 **22** (45%)

(60−87%) with the exception of the volatile primary amine **14** (18%). Special behavior was observed for imide **8**: in addition to the expected *gem*-difluoro derivative **20**, methylketone **21** was also formed as the minor product (17%). It should be pointed out that amide **9** gave only ketone **22**.

We propose a general mechanism that involves reactive dicationic intermediates composed of vinylic cations and adjacent protonated N-base sites. The intermediate is consistent with the formation of *β-gem*-difluoro compounds or methylketones starting from propargylic amino derivatives (Scheme 1). In pure HF, first protonation occurs on the nitrogen atom to give a monocationic intermediate **A** which is unreactive toward protonation of the triple bond. Addition of a Lewis acid such

SCHEME 1. Proposed Mechanism



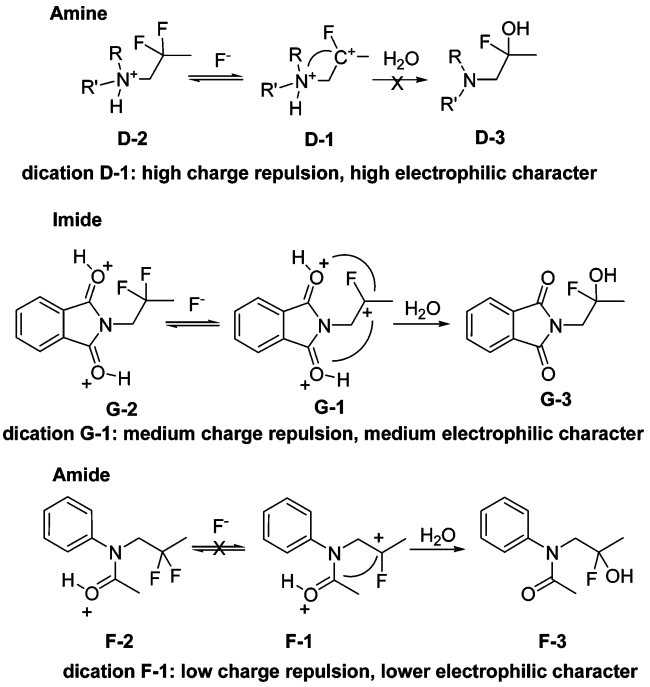
as SbF_5 results in an increase in acidity, allowing the formation of the 1,3-dication **B** (vinylic cation with adjacent ammonium center) which is trapped by a fluoride ion to give monocation **C**. Further protonation furnishes 1,3-dication **D** which is highly stabilized by mesomerism.[17−19] Its high electrophilic character enables its fluorination in the presence of the poor nucleophile, the complex fluoride ion (SbF_6^- or $Sb_2F_{11}^-$),[20] to give ammonium ion **E**, precursor of *β-gem*-difluoroamines **14**−**20**. Particular behavior was observed for the amide **9** with the exclusive formation of the corresponding methylketone. This result can be accounted for by considering the O-protonation of amides, previously described by Gillepsie et al.[21] The resulting carboxonium-α-fluoronium dication **F-1** is not sufficiently electrophilic to be trapped by a fluoride ion in contrast with the ammonium−carbenium dication **D-1** where charge repulsion is higher (Scheme 2).

Hydrolysis leads to the intermediate **F-3**, precursor of the methylketone. In the chemistry of dicationic electrophiles, the proximity of charge influences the reactivity of the intermediates. Proximity effects were also observed in two other recent studies involving dicationic species.[22,23]

An intermediate reactivity is observed for the imide series as the result of a di-O-protonation. The α-fluorocarbenium ion **G-1** can be partially fluorinated to afford a mixture of *gem*-difluoro compound and methylketone. This trend may reflect the relative reactivities of the dicationic intermediates. Therefore, the 1,3-dication **D-1** from the amine substrate is more reactive and electrophilic than its 1,5-dication **F-1** and trication **G-1** analogues formed from the amide and imide derivatives, respectively (Scheme 2). These results illustrate the influence of the distance between charge centers and the increasing electrophilic character for dications **D-1**, **G-1**, and **F-1**. We have demonstrated that, in the highly acidic medium HF−SbF_5 at low temperature, aminoalkynes undergo exclusive and regioselective *gem*-difluorination to afford the corresponding *β-gem*-difluoroamines in good yields. Extension of this reaction to other

(17) Olah, G. A.; Heiliger, L.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8020−8021.
(18) Shaler, T. A.; Morton, T. H. *J. Am. Chem. Soc.* **1989**, *111*, 6868−6870.
(19) Olah, G. A.; Mo, Y. K.; Halpern, Y. *J. Org. Chem.* **1972**, *37*, 1169−1174.
(20) (a) Culmann, J. C.; Fauconet, M.; Jost, R.; Sommer, J. *New J. Chem.* **1999**, *23*, 863−867. (b) Esteves, P. M.; Ramirez-Solis, A.; Mota, C. J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2672−2677.
(21) (a) Gillepsie, R. J.; Birchall, T. *Can. J. Chem.* **1963**, *41*, 148−151. (b) Olah, G. A.; Schleyer, P. v. R. *Carbonium Ions*; John Wiley & Sons: New York, 1973; Vol. IV, ISBN 0-471-65337-3. (c) Moodie, A. B.; Thomas, P. N.; Schofield, K. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1693−1705.
(22) Klumpp, D. A.; Sanchez, G. V.; Aguirre, S. L.; Zhang, Y.; DeLeon, S. *J. Org. Chem.* **2002**, *67*, 5028−5031.
(23) Klumpp, D. A.; Beauchamp, P. S.; Sanchez, G. V.; Aguirre, G. S.; DeLeon, S. *Tetrahedron Lett.* **2001**, *42*, 5821.

SCHEME 2. Relative Reactivities of the Dicationic Intermediates

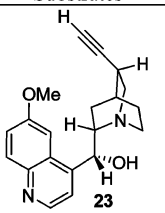
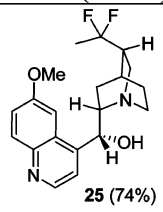
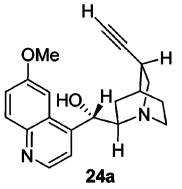
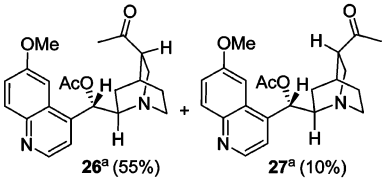
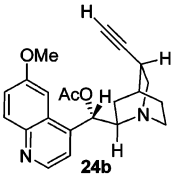
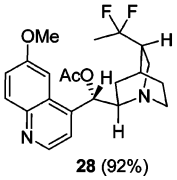


polyfunctional bioactive products and more elaborate targets such as cinchona alkaloid derivatives has been studied.

Regioselective and Easy Access to Difluorinated Cinchona Alkaloids. Cinchona alkaloids represent an extraordinarily versatile class of natural compounds and have been used as effective therapeutic agents. Indeed, the most representative quinine and quinidine display high activity as antimalaria and antiarrhythmic drugs.[24] Cinchona alkaloids and their derivatives have also demonstrated wide potential as chiral auxiliaries in asymmetric synthesis.[25] In superacid medium, such as HF−SbF_5, substrates undergo superelectrophilic activation to form highly reactive protosolvated species leading to new synthetic pathways.[26] We have previously reported a non-regioselective synthesis of a mixture of *gem*-difluoro derivatives starting from *O*-acetylquinine and *O*-acetylquinidine dihydrochlorides in HF−SbF_5.[27,28] With the postulated mechanism for the reactivity of simple alkynylated amines accounted for, a regioselective reaction may be envisioned starting from the alkynes quinine and quinidine derivatives. We have investigated the reactivity of such derivatives in HF−SbF_5.

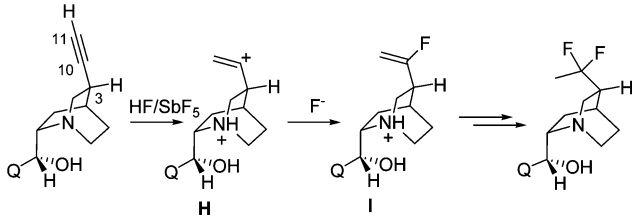
Substrates **23** and **24** were prepared from quinine and quinidine as described in the literature.[29] Formation of 10,11-dibromo derivatives (Br_2 in chloroform) followed by dehydrobromination in ethanolic KOH by heating under reflux[30] gave the desired free alkynes **23** and **24a** with 53 and 34% yield, respectively. Acetylation of **24a** with acetic anhydride in CH_2Cl_2 yielded **24b** (90%). All reactions have been performed in HF−SbF_5 at low temperature (between −25 and −40 °C) within 10 to 15 min. Table 3 shows that free alkynes **23** and **24b** gave a single *gem*-difluoro compound, whereas **24a** yielded two methylketones.

TABLE 3. Reactivity of Cinchona Alkaloid Derivatives in HF−SbF_5

Substrates	Products (Yield %)
 **23**	 **25** (74%)
 **24a**	 **26**[a] (55%) + **27**[a] (10%)
 **24b**	 **28** (92%)

[a] Products isolated after acetylation of crude mixture.

SCHEME 3. Postulated Mechanism



The postulated mechanism for the formation of the *gem*-difluoroquinine is similar to the one described in Scheme 1. The protonation of the C10−C11 triple bond gives ion **H**, which is trapped by complex fluoride ions (SbF_6^-, $Sb_2F_{11}^-$, etc.) to afford ion **I**, precursor of **25** (Scheme 3). Although the corresponding acetylated 10,10-difluoroquinine **25** has already been synthesized in superacid media from quinine acetate in the presence of chloride ions, it was obtained as a 50/50 mixture with its C3 epimer in a 60% total yield.[27]

Indeed these two epimers have been obtained due to the formation of the carbenium ion at C3. As we have previously noted, quinine and quinidine demonstrate different behaviors

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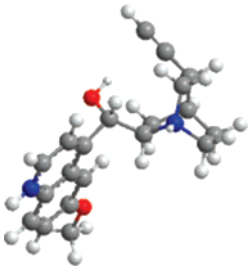
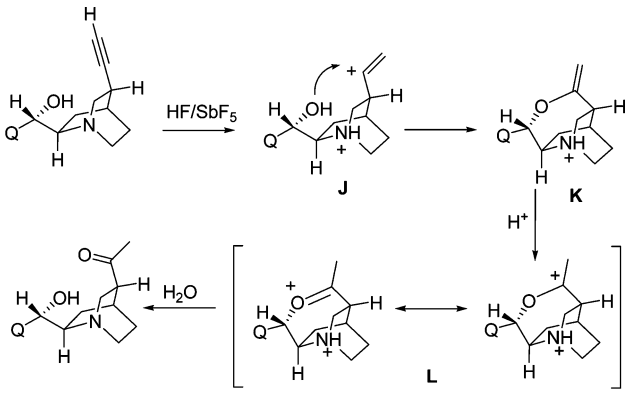


FIGURE 1. Preferred conformation of diprotonated 10,11-didehydroquinidine **24a**.

SCHEME 4. Postulated Mechanism



in $HF-SbF_5$.[28] Thus, it seemed interesting to study reactivity of 10,11-didehydroquinidine **24a** in superacid media. As we expected, 10,11-didehydroquinidine **24a** did not afford the corresponding *gem*-difluoro derivative in $HF-SbF_5$, but a mixture of 10-keto C3 epimers **26** (55%) and **27** (10%) (Table 3). These compounds have been isolated in a 65% overall yield after acetylation of the crude mixture.

According to molecular modeling of diprotonated 10,11-didehydroquinidine **24a** (protonation of both nitrogen atoms) carried out with Chem3D by applying the PM3 semiempirical methods in MOPAC (Figure 1), the most stable conformation of diprotonated **24a** has the "open" one, similar to that of diprotonated quinidine.[28] As the hydroxyl group is close to the alkyne in superacid media, **24a** is very favorable to intramolecular cyclization with formation of an ether bond.

Taking into account these data, the postulated mechanism is outlined in Scheme 4. Carbenium ion **J** is trapped by the hydroxyl group to give ion **K**, which after protonation affords a carboxonium ion **L**, precursor of methylketone **26**. This mechanism does not explain the formation of the other methylketone **27**, epimeric at C3. This compound could be obtained from epimerization of methylketone **26** during hydrolysis of the reaction mixture. In order to prevent intramolecular reactions, we decided to protect the hydroxyl group by acetylation. As expected, reaction of 10,11-didehydroquinidine acetate **24b** in $HF-SbF_5$ provided a single *gem*-difluoro derivative **28** in very good yield (Table 3). It should be noted that, as in the case of quinine, this compound has already been synthesized from *O*-acetylquinidine in the presence of chloride ions in superacid media in low yield (20%), isolated from a mixture of two supplementary *gem*-difluoro compounds.[28] The structure of **28** is in agreement with the spectral data reported for this product.

In conclusion, we have demonstrated that, in the highly acidic medium $HF-SbF_5$ at low temperature, aminoalkynes undergo exclusive and regioselective difluorination to afford, in good yields, the corresponding *gem*-difluoroamines. We have postulated a mechanism, accounting for the formation of these new difluoro derivatives, as a result of the electrophilic character of the intermediate dication which is modulated by the distance between charge centers, with this parameter being modified by the nitrogen substituents (amine, amide, or imide). The reactivity of such nitrogen substrates studied in superacid media showed the ability to perform reactions that cannot be observed in conventional acid. Extension of this novel reaction has been applied to other polyfunctional bioactive products and more elaborate targets such as cinchona alkaloid derivatives and allows the regioselective and efficient synthesis of *gem*-difluoro derivatives of quinine and quinidine. Starting from 10,11-didehydroquinine and 10,11-didehydroquinidine acetate, a single corresponding *gem*-difluoro derivative was obtained in good yield, demonstrating that neither epimerization nor rearrangement occurs in the course of the reaction. Our results highlight the interest of superacids in organic chemistry and their ability to carry out novel reactions, which are not observed with conventional acids.

Experimental Section

General Procedure for the Synthesis of Difluoro Compounds. In a typical experiment, to a stirred solution of HF (5 mL) and SbF_5 (2.5 mL) at low temperature in a Teflon reactor was added the substrate (1.8 mmol). The reaction was kept at a given temperature for 2−15 min according to the substrate. The mixture was then neutralized with $Na_2CO_3-H_2O$−ice. After extraction with dichloromethane, the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by silica gel chromatography gave the difluoro derivatives.

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Supporting Information Available: Detailed experimental procedures and characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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