# A novel, facile route to β-fluoroamines by hydrofluorination using superacid HF–$SbF_5$†

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**A range of unsaturated amines and sulfonamides were converted to β-fluoro nitrogen analogues after hydrofluorination in superacid HF–$SbF_5$, based on the formation of highly reactive electrophilic intermediates.**

Introduction of fluorine atom(s) may significantly improve the pharmacodynamic and pharmacokinetic profiles of a drug through simultaneous alteration of its electronic, lipophilic and steric characteristics as well as its metabolic stability,[1] mainly due to a fluorine atom's unique specificities.[2] As a consequence, selectively (poly)fluorinated analogues, in particular fluorinated nitrogen analogues,[3] of biologically active compounds are regarded as tools of relevant interest for pharmaceutical research.[4,5] Consequently the discovery of new methods to access fluoroamines remains a major challenge in synthetic chemistry. Few methods are reported in the literature to give β-fluoro nitrogen compounds.[6] The most commonly used strategy is the nucleophilic substitution of an amino alcohol using (diethylamino)sulfur trifluoride and derivatives, but this method suffers from the formation of rearranged and dehydrated products, a difficulty already encountered by Middleton.[7a] The ring opening of aziridines with various fluorine sources provides an alternative route to β-fluoroamines, but this technology lacks generality and requires starting materials that are not readily available.[7b] Halofluorination or hydrofluorination of unsaturated amines using a combination of Olah's reagent and an electrophile source could be an alternative route. However, to the best of our knowledge, few examples are mentioned in the literature, probably due to the strong electronic deactivation of the double bond after protonation of the amino group.[8] During the past decades Jacquesy *et al.* performed extensive studies on the reactivity of nitrogen compounds in superacid media (HF–$SbF_5$) showing the ability to perform reactions that cannot occur in usual conditions.[9] Among these results, bromofluorination of the allylic part of tabersonine and simple allylamine have been performed using an NBS–HF–$SbF_5$ system leading to γ-bromo-β-fluoroamines[10] and confirming the possibility of performing additions on *N*-allylic systems in superacid.

In this communication, we demonstrate a new and facile approach for the synthesis of β-fluoro nitrogen building blocks by a simple hydrofluorination of unsaturated nitrogen compounds in superacid HF–$SbF_5$, based on the dramatic reactivity of superelectrophilic ammonium dication intermediates.

The hydrofluorination reaction was attempted firstly on *N*-allylpiperidine as a model substrate, under various conditions. The reaction of compound **1a** in HF–$SbF_5$ (7 : 1 molar ratio) at −20 °C afforded the expected β-fluoroamine **2a** as the major product.‡ In order to determine the influence of the acidity on the conversion, the reaction was carried out with various amounts of Lewis acid. When substrate **1a** was used in pure HF, no reaction occurred. When the HF–$SbF_5$ molar ratio was lowered to 4 : 1, we observed the formation of a large amount of undesired products. A decrease in conversion at lower temperatures and no improvement at higher ones led us to set the reaction temperature to −20 °C. In optimized conditions (HF–$SbF_5$ 7 : 1 molar ratio, −20 °C, 60 min) *N*-allylpiperidine gave 72% of product **2a** after purification using column chromatography. This result prompted us to submit a series of *N*-allylic amines to reaction (Table 1). Expected β-fluoroamines **2b–g** were obtained in good yields (Table 1, entries 2–7), confirming the generality of the reaction to give fluorinated nitrogen building blocks. It should be pointed out that *N*-allylbenzylamine **1h** gave only a complex mixture of compounds, whatever the conditions. In optimized conditions, compound **1i** yielded desired fluorinated product **2i** in 45% yield, but also cyclized product **2i′**, issued from intramolecular cyclization, in 24% yield. These results are in accordance with a Friedel–Crafts reaction already observed in superacid starting from amides.[11] It is notable that, in our case, a weakly nucleophilic *para*-nitro substituted arene could trap the dicationic ammonium intermediate, confirming its highly electrophilic character.

In all cases, even after prolonged reaction time, a small amount of starting material remained in the crude reaction mixture. After submitting fluorinated compound **2c** to the reaction conditions, a mixture of alkene **1c** and fluorinated product **2c** was obtained in a 5 : 95 molar ratio (determined by $^1$H NMR spectroscopy of the crude reaction mixture). These results provided evidence of equilibrium in the mechanism (Scheme 1). Recently, Klumpp *et al.* performed the arylation of unsaturated amines in superacid $CF_3SO_3H$ in the presence of benzene[12] and showed the ability of unsaturated piperidine to react with poorly nucleophilic arenes after formation of a superelectrophilic[13] ammonium dication. Similarly, we postulate that, after protonation of the nitrogen atom, the strong acidity of the medium allows the formation of superelectrophilic dication **A**. The ammonium cation plays a

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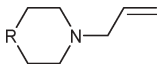
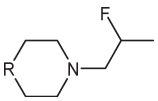
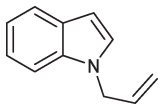
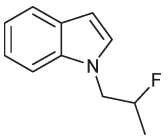
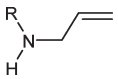
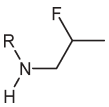
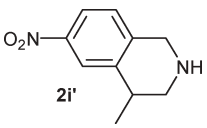
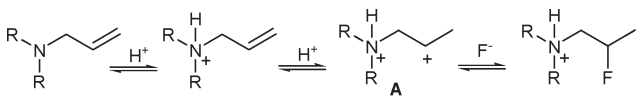
**Table 1** Hydrofluorination of *N*-allylic amines

| Entry | Substrate | Product | Yield (%)[a] |
|---|---|---|---|
| |  |  | |
| 1 | R = $CH_2$ | **1a** | **2a** | 72 |
| 2 | R = NH | **1b** | **2b** | 57 |
| 3 | R = NBn | **1c** | **2c** | 85 |
| 4 | R = NAc | **1d** | **2d** | 69 |
| 5 | R = O | **1e** | **2e** | 61 |
| 6 | R = CO | **1f** | **2f** | 70 |
| |  |  | |
| 7 | | **1g** | **2g** | 40 |
| |  |  | |
| 8 | R = Bn | **1h** | —[b] | —[b] |
| 9 | R = *p*-$NO_2$-Bn | **1i** | **2i** | 45 |
| | | | | 24 |
| | |  | |
| | | **2i'** | | |

[a] Chemical yield after column chromatography. [b] Complex mixture.



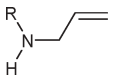
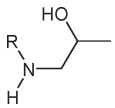
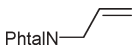
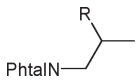
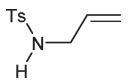
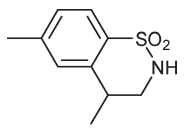
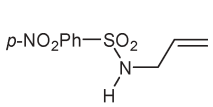
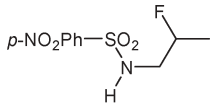
**Scheme 1**

critical role in activating the nearby electrophilic site[12] and the intermediate can be fluorinated, even in the presence of a poor nucleophile such as solvated fluorine in the polymeric anion form, $Sb_nF_{5n+1}^-$, of the superacidic medium.[14]

To explore the generality of the hydrofluorination, amides, sulfonamides and carbamates have been submitted to the reaction conditions (Table 2).

Reaction of carbamate **3a** was unsuccessful and no material could be extracted after hydrolysis of the crude product. This result could be explained by an alkyl–oxygen cleavage of protonated carbamate leading to carbamic acids, already observed by Olah in superacid.[15] The behaviour of amides and amines appeared to be different. After reaction in the usual conditions, amides **3b–c** gave only corresponding hydroxy products **4b–c** in good yields. Starting from phthalimide **3d**, when fluorinating agent HF–pyridine was added to reaction mixture (Table 2, entry 5), we observed the formation of fluorinated product **4d′** in 31% yield, beside the hydroxy derivative (34% yield). It should be noticed that no intramolecular reaction occurs starting from amide **3c**, whereas such a reaction was observed with compound **1i** (Table 1, entry 9), results which further strengthen the hypothesis of the relative reactivities of dicationic intermediates. Sulfonamide behaviour was different. Indeed, compound **4e** was obtained in 64% yield after reaction of **3e** by intramolecular Friedel–Crafts reaction. When the

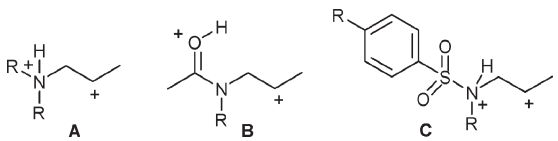
**Table 2** Hydrofluorination of *N*-allylic derivatives

| Entry | Substrate | Product | Yield (%)[a] |
|---|---|---|---|
| |  |  | |
| 1 | R = COOMe | **3a** | — | — |
| 2 | R = Bz | **3b** | **4b**[19] | 86 |
| 3 | R = *p*-$NO_2$-Bz | **3c** | **4c** | 69 |
| |  |  | | |
| 4 | | **3d** | R = OH | **4d**[20] | 97 |
| 5[b] | | **3d** | R = OH | **4d** | 34 |
| | | | R = F | **4d′** | 31 |
| |  |  | | |
| 6 | | **3e** | | **4e** | 64 |
| |  |  | | |
| 7 | | **3f** | | **4f** | 74 |

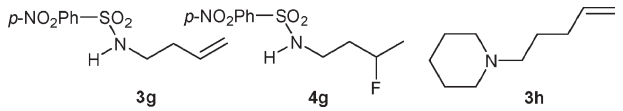
[a] Chemical yield after column chromatography. [b] Quenching with HF–pyridine 70 : 30 w/w (24 h, −20 °C) before hydrolysis.

nucleophilic character of the arene was decreased by the presence of the electron withdrawing nitro group in the *para* position, only hydrofluorination occurred, with 74% yield (Table 2, entry 7). The observed differences of reactivity between amines, amides and sulfonamides encouraged us to postulate that reactivities depend on the electrophilic character of the intermediates. The protonation of amides occurs on the oxygen atom[16] to give the monocation and a second protonation gives the reactive dication **B** (Scheme 2). In the chemistry of dicationic electrophiles, the proximity of the charge centers may influence the reactivity of the intermediates.[17] In the amide case, carboxonium–carbenium dication **B** seems to be less electrophilic than the ammonium–carbenium dication **A** where charge repulsion is higher. The dication **B** is insufficiently electrophilic to react with a fluoride ion in superacid and leads to hydroxy derivatives after hydrolysis. When fluorinating agent HF–pyridine is added, the intermediate can be partially fluorinated. After N-protonation of a sulfonamide group,[18] a second protonation gives the dicationic intermediate **C**, which can be trapped by the arene or fluoride ions, depending on the nucleophilic character of the aromatic ring, showing a similar reactivity of dicationic intermediates **A** and **C**.

We have also found that hydrofluorination presents some limitations, as only 30% of γ-fluorinated product **4g** was obtained after reaction of compound **3g** and no fluorinated product was



**Scheme 2**




**Scheme 3**

obtained starting from compound **3h**, which led to a mixture of undesired products (Scheme 3). Again it seems that increasing the distance between charges in the intermediate species makes the reaction less selective and isomerization possibly occurs.

In summary, we have found that *N*-allylic amines and sulfonamides react in the superacidic medium HF–$SbF_5$ to give β-fluoro nitrogen-containing compounds in good yields after a simple hydrofluorination reaction. We have also showed that β-hydroxy analogues can be obtained starting from corresponding amides. To reflect these relative reactivities we proposed a mechanism showing that this new reaction of hydrofluorination of *N*-allylic compounds is based on the strong electrophilic character of the carbenium ion formed in the β-position to the ammonium ion. The present work opens new possibilities for the direct and effective preparation of fluorinated building blocks of high synthetic value, starting from easily accessible starting materials. Evaluation of the scope and limitation of this novel methodology along with applications on more elaborated targets are in progress in our laboratory.

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## Notes and references

‡ *Procedure for the production of* ***2a***: to a mixture of HF–$SbF_5$ (9 ml, 7 : 1 molar ratio), maintained at −20 °C, was added 250 mg of *N*-allylpiperidine. The mixture was magnetically stirred at the same temperature for 1 h. The reaction mixture was then neutralized with water–ice–$Na_2CO_3$ and extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (97 : 2 : 1 $CH_2Cl_2$–MeOH–$NH_3$) gave the product as a colourless oil (209 mg, 72%). All experimental procedures and spectral data are reported in the ESI.†


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