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Exploring Superacid-Promoted Skeletal Reorganization of Aliphatic Nitrogen-Containing Compounds

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Abstract: Here we report a method to reorganize the core structure of aliphatic unsaturated nitrogen-containing substrates exploiting polyprotonation in superacid solutions. The superelectrophilic activation of *N*-isopropyl systems allows for the selective formal C_{sp³}-H activation / cyclization or homologation / functionalization of nitrogen-containing substrates. This study also reveals that this skeletal reorganization can be controlled through protonation interplay. The mechanism of this process involves an original sequence of C–N bond cleavage, isopropyl cation generation and subsequent C–N bond and C–C bond formation. This was demonstrated through in situ NMR analysis and labelling experiments, also confirmed by DFT calculations.

Introduction

Essential to drug discovery,^[1] the exploration of chemical space is dependent on the development of novel synthetic strategies and their associated methods.^[2] As a consequence, a closely related challenge is the necessity to perform efficiently chemical transformations in a concise and chemospecific fashion, especially on elaborated promising leads.^[3] Recent efforts in the direction of designing synthetic methods to rapidly build and modulate complex molecules through insertion, deletion, exchange of atoms (or group of atoms) or through reorganizing molecular frameworks were recently coined as “molecular editing” strategies.^[4] Bond breaking/bond forming sequences allowing to selectively reorganize molecular skeletons can also be targeted to diversify leads, as recently shown with cation-promoted reactions.^[5] Cation behavior can be dramatically modified through the generation of an additional (or multiple) charge at proximity, through “superelectrophilic activation”^[6] in superacid.^[7] Promoted by charge-charge repulsive effects, specific and selective functionalization or skeletal reorganization of elaborated molecules can occur (Figure 1A).^[8] Exploiting superelectrophilic activation by drawing pioneering work from the groups of Olah-Prakash,^[9] Ohwada^[10] and Klumpp,^[11] a current focus of our interest resides in the fluorination of aliphatic amines in superacid.^[12] In this context, an unexpected result caught our attention (Figure 1B). Substrate **1a**, which bears an isopropyl group, generated traces amount of the product **2a**^[13] after

treatment with HF/SbF₅ superacid. The mechanistic ambiguity^[14] associated with the original route to *N*-sulfonylpyrrolidine^[15] prompted us to further study this serendipitous discovery.

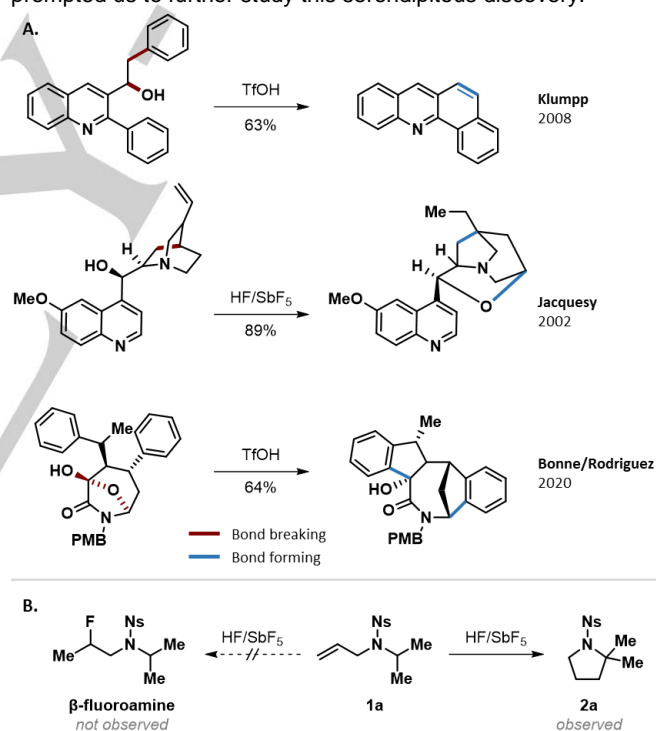


Figure 1. A) Skeleton reorganization of elaborated molecules in superacid solutions (PMB = *p*-methoxybenzyl). B) Reaction design and unexpected outcome of the reaction of **1a** in HF/SbF₅.

Results and Discussion

Sulfonamide **1a** was thus initially employed as the model substrate and first, various acidic conditions were explored at 0 °C for 10 min reaction time. While no reaction occurred using HF or CF₃SO₃H, using HF/SbF₅ (with 2 mol% SbF₅ concentration) allowed to afford the pyrrolidine **2a** in 47% yield. This confirms the necessity to use HF/SbF₅ superacid solutions to perform the

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reaction (Table 1, entries 1-3). Increasing the acidity of the media by rising the concentration of SbF_5 ,^[16] proves beneficial to the reaction. The absence of significant effect of using 22 mol% SbF_5 compared to 12 mol% SbF_5 let us consider this concentration for further optimization (Table 1, entries 3-6). Decreasing the temperature to -40°C led to the formation of the β -fluorinated secondary sulfonamide **3a** as the major product (Table 1, entry 8). This hydrofluorination observed at low temperature suggests that this reaction could interfere with the formation of the pyrrolidine. Even more intriguing is the absence of isopropyl group on product **3a**, confirming that the mechanism of this transformation is not trivial. The formation of the desired pyrrolidine in respectively 53% and 56% yields after 1 min or 60 min reaction at 0°C (Table 1, entries 9-10) confirmed the efficiency of the process.

Table 1. Optimization of the superacid-promoted formation of **2a**.

Entry	Superacid ^[a]	t (min)	T ($^\circ\text{C}$)	Yield (%) ^[b]	
				2a	3a
1	HF	10	0	-	-
2	TfOH	10	0	-	-
3	HF/SbF ₅ (2 mol%)	10	0	47	-
4	HF/SbF ₅ (4 mol%)	10	0	52	-
5	HF/SbF ₅ (12 mol%)	10	0	60	-
6	HF/SbF ₅ (22 mol%)	10	0	59	-
7	HF/SbF ₅ (12 mol%)	10	-20	58	-
8	HF/SbF ₅ (12 mol%)	10	-40	19	45
9	HF/SbF ₅ (12 mol%)	1	0	53	-
10	HF/SbF ₅ (12 mol%)	60	0	56	-

Ns = *p*-nosyl. [a] Used as solvent (molar concentration of SbF_5 relative to HF in parenthesis). [b] Isolated yield.

To gain more insights into the mechanism of this curious rearrangement, a series of control experiments were carried out (Figure 2). First, to verify whether cyclic products arise directly from an acyclic cationic precursor, a series of quenching experiments were conducted. Using an excess of benzene allowed the formation of the corresponding acyclic arylated product **4a** in 61% yield after reacting **1a** in standard conditions (Figure 2a). Similarly, when **1a** was reacted in superacid followed by quenching with cyclohexane-*d*₁₂, the reduced product **5a** was obtained in 71% yield with 0.8 D incorporation (Figure 2b). As deuterium transfer reaction in these conditions occurs via an ionic mechanism,^[17] the formation of the deuterated product **5a** must come from an open-chain cationic intermediate. The same product **5a** was obtained in 97% yield by reacting **2a** under similar conditions, indicating that **2a** must be in equilibrium with an acyclic cationic intermediate in superacid solution (Figure 2c).^[18] To gain more information about the transfer of the isopropyl moiety along the reaction, substrate **1a_D** was prepared and submitted to superacid conditions (Figure 2d). The reaction led to the unique formation of a **2a_D** exhibiting 0.5 D incorporation in position 4,

suggesting that an electron-deficient center may be developed in this position at an intermediate stage of the reaction which is then reduced by hydride transfer coming from the isopropyl moiety. In addition, *N*-isopropyl-4-nitrobenzenesulfonamide and *N*-allyl-4-nitrobenzenesulfonamide were submitted in superacid solution to test an intermolecular isopropyl transfer. The formation of the product **2a** in 47% yield suggests that isopropyl cation must be generated in solution (Figure 2e).

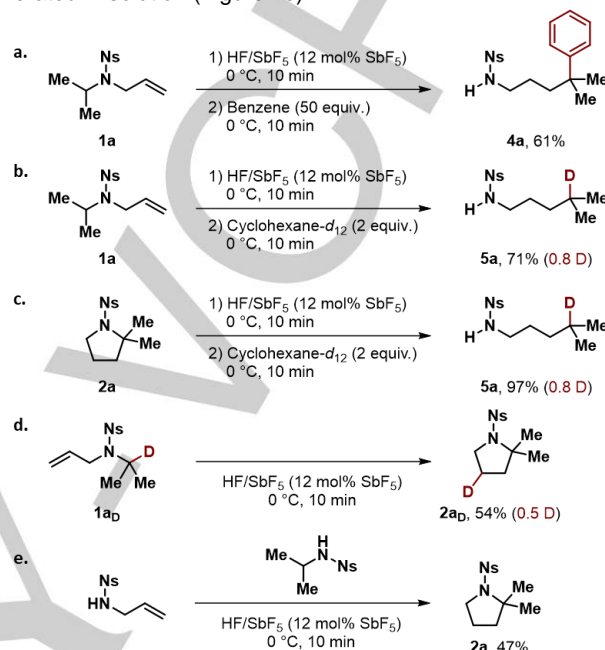


Figure 2. Control and labeling experiments (D ratio determined by ¹H NMR analysis, See SI).

To further demonstrate the intermediacy of some ions, *in situ* NMR experiments were conducted at low temperature. First, substrate **1a** was subjected to HF/SbF₅ solution in standard conditions (Figure 3).

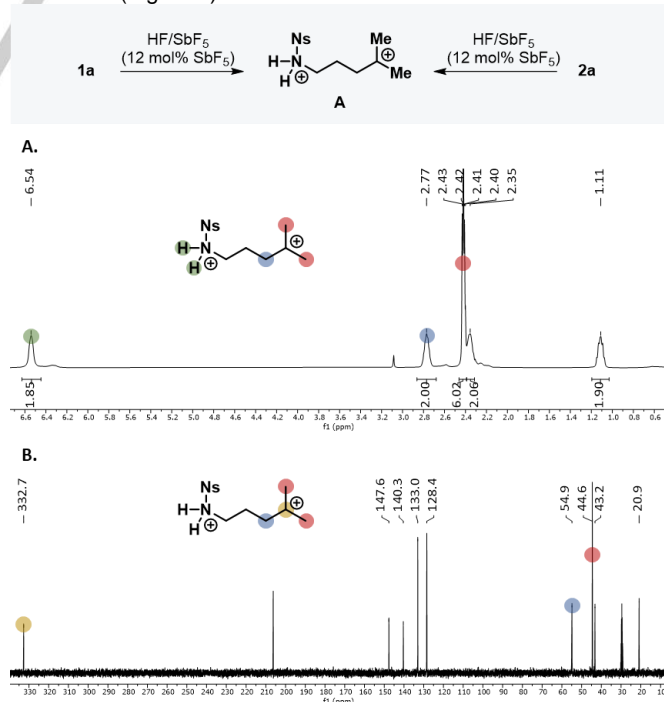
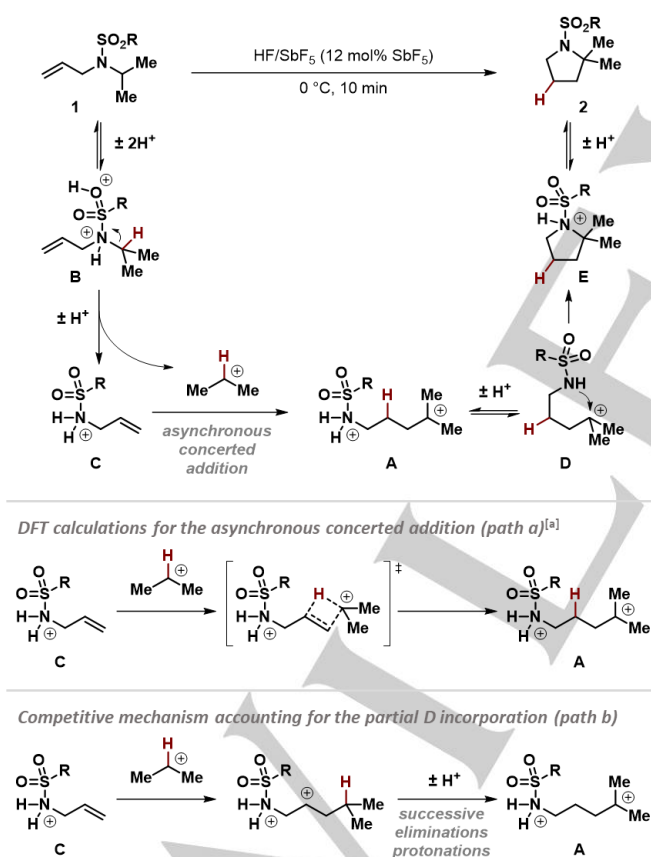


Figure 3. Generation of dication **A** from substrate **1a** and product **2a** in HF/SbF₅. **A)** ¹H NMR spectra of dication **A** at 0°C . **B)** ¹³C NMR spectra of dication **A** at 0°C .

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The good quality of the recorded spectra enabled us to identify the dication **A** as the unique species generated under these conditions. In the ^1H NMR spectrum, two clean doublets at 7.57 ppm and 7.25 ppm confirm aromatic protons of the nosyl group (not shown, full spectrum in SI). A singlet of 2H at 6.54 ppm is characteristic of the protonated nitrogen atom of the sulfonamide function. A singlet of 6H accounting for both methyl groups is also observed at 2.42 ppm suggesting the formation of a tertiary carbocation. This is confirmed in the ^{13}C NMR spectrum with a very characteristic signal at 332.7 ppm. The signal at 54.9 ppm (CH_2) corresponds to the methylene in α position of the carbocation. The equilibrium between this dication and the cyclic product is also confirmed as the exact similar spectra was obtained when **2a** was submitted to the same conditions (see SI). When *N*-isopropyl-nosylamide was submitted to HF/SbF_5 at low temperature, clean ^1H and ^{13}C NMR spectra corresponding to protonated 4-nosylamide were obtained, confirming that C–N bond cleavage does not necessitate the prior generation of a carbocationic intermediate that could have come from the protonation of the allyl moiety and that it must occur at an early stage of the reaction (see SI). A proposed mechanism based on these observations is depicted in Scheme 1 to rationalize this unusual process.



Scheme 1. Proposed mechanism for the formation of pyrrolidine **2** from sulfonamide **1**. [a] Computed at the B3LYP/aug-cc-pvtz//B3LYP/cc-pvdz level of theory with a PCM solvation model (R = 4- NO_2 - C_6H_4).

We believe that this reaction begins with superacid *N*-protonation of the sulfonamide.^[19] A second protonation of the sulfonamide function could generate a superelectrophilic 1,3-dication **B**. The ability to generate long-lived cationic species in superacid solutions^[20] and the destabilization of dication **B** through charge

repulsion could act as a driving force for C–N bond cleavage leading to the generation of intermediate **C** (or its diprotonated analogue) after prototropy and isopropyl cation liberation. The need for a second protonation during this step is reinforced by DFT calculations (see the supporting information for all computational details), which reveal that no cleavage is possible with **1aH⁺** (monoprotonated either on the nitrogen or the oxygen), whereas a clear transition state for the C–N bond breaking can be evidenced with **B**, and with a very low activation energy (4.4 kcal/mol for R = 4- NO_2 - C_6H_4). The isopropyl cation could then react with the alkene moiety of **C**. Here, while a two-step sequence of electrophilic addition and hydride transfer could have been envisioned, DFT calculations suggest instead that both chemical events occur in a single asynchronous concerted step, the formation of the C–C bond inducing the transfer of the proton and ultimately leading to key dication **A** (path a). Note this concerted mechanism, very similar to the text-book concerted addition involved in hydroboration (it is useful to remind that isopropyl cation is isoelectronic to dimethylborane)^[21] allows to account for the clean formation of **2a_D** (*vide supra*). The deprotonated function would then act as the intramolecular nucleophile to finalize the process occurring during reaction quenching or being in equilibrium in the reaction conditions (**D-E-2**). A competitive mechanism must also be postulated, taking into account that only 50% of deuterium incorporation is observed in product (Figure 2d). A non-concerted electrophilic addition would generate a secondary carbocation that after successive elimination/protonation steps would generate the non-deuterated intermediate **A** (path b).

Aiming at exploring the ability to apply this peculiar rearrangement to various sulfonamides, inherent core of active ingredients,^[22] a series of *N*-alkyl-*N*-isopropyl substituted sulfonamides were tested in standard conditions (Figure 4). First, a gram scale experiment from **1a** was successfully conducted to generate product **2a** in 67% yield. Gratifyingly, the corresponding pyrrolidines **2b-2g** were generated in reasonable yields, confirming the ability to modulate the arenesulfonamide core substituent. In the case of tosyl derivative **1d**, the reaction is in competition with the intramolecular Friedel-Crafts type transformation which explains the moderate yield obtained.^[23] This reaction could be applied to the formation of a bis-pyrrolidine product from the designed bis-allylic substrate **1h** and also to aliphatic sulfonamide substrate as exemplified by the formation of **2i**. Considering the multi-purpose functions of vinylsulfones function in proteomics,^[24] the direct formation of product **2j** is also of interest. The reaction of substrates **1k** and **1l** bearing respectively a trisubstituted alkene and a homoallyl moiety afforded compounds **2k** and **2l** in reasonable yields, demonstrating that this reaction is not only limited to allyl derivatives. In the latter case, **2l** was obtained along with a minor proportion of **2k** which could indicate that **1l** might rearrange to **1k** prior to cyclization. However, when substrate **1n** bearing a 4-methyl-3-pentenyl function was engaged under the standard conditions, the reaction led exclusively to the formation of product **2a**. Interestingly, the reaction was also found efficient with *S*-allylsulfonamide **1m** affording sultam **2m** in 45% yield. While ethyl and cyclopropyl cleavage was observed when substrates **1o** and **1p** were subjected to superacid conditions, no alkyl transfer / cyclization occurred and only compound **3a** was obtained in both cases. On the other hand, no C–N bond cleavage was observed

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with *N*-methyl derivative **1q** which underwent alkene hydrofluorination as expected. This skeletal rearrangement was also found specific to sulfonamide derivatives as no pyrrolidines were obtained with amide **1r**, aniline **1s** or amine **1t**, products coming from alkene hydrofunctionalization being generated instead.^[25]

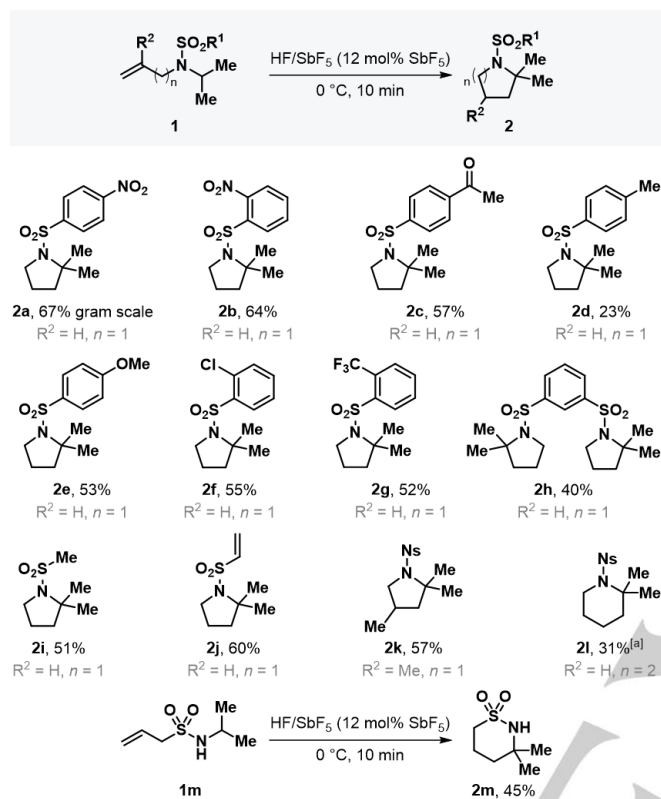
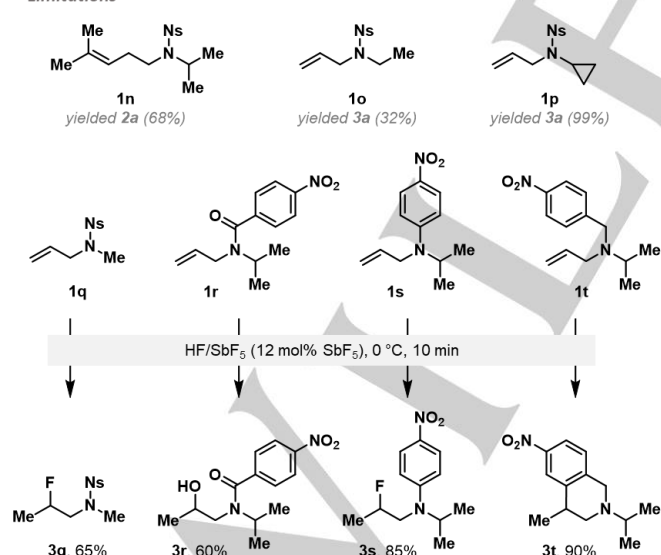
Limitations^[b]

Figure 4. Reaction scope for the skeletal rearrangement of **1**. Isolated yield. Ns = *p*-nosyl. [a] Calculated yield; obtained as a 65:35 **2l/2k** mixture (overall yield: 47%). [b] See SI for further information.

Secondary alcohols and alkyl halides have already been demonstrated to be ideal candidates for cation generation in HF/SbF₅ solutions.^[7] We thus consider exploring a bimolecular version of the process that we could consider appropriate in an early drug discovery campaign based on elaborated molecules

external adornment. Using external partner 2-chloropropane in the presence of allylamine **6a** allows the direct formation of the product **2a** in good yield. This confirmed that external source of isopropyl cation can be used with the same efficiency for the whole process. Thus, the application of this strategy to diversify allylamine-containing model molecules and elaborated targets was conducted in the presence of 2-chloropropane (Figure 5A). Starting from homoallylic substrate **6l**, the piperidine **2l** could also be formed as the major product and the dansyl derivative **6u** afforded efficiently the product **2u**.^[26] To further confirm the ability to explore this process in a medicinal chemistry context, inflammasome inhibitor analogue **2v** and anti-inflammatory Deracoxib analogue **2w** were cleanly produced with the same procedure,^[27] confirming the ability to use this intermolecular variant on polyfunctional substrates.

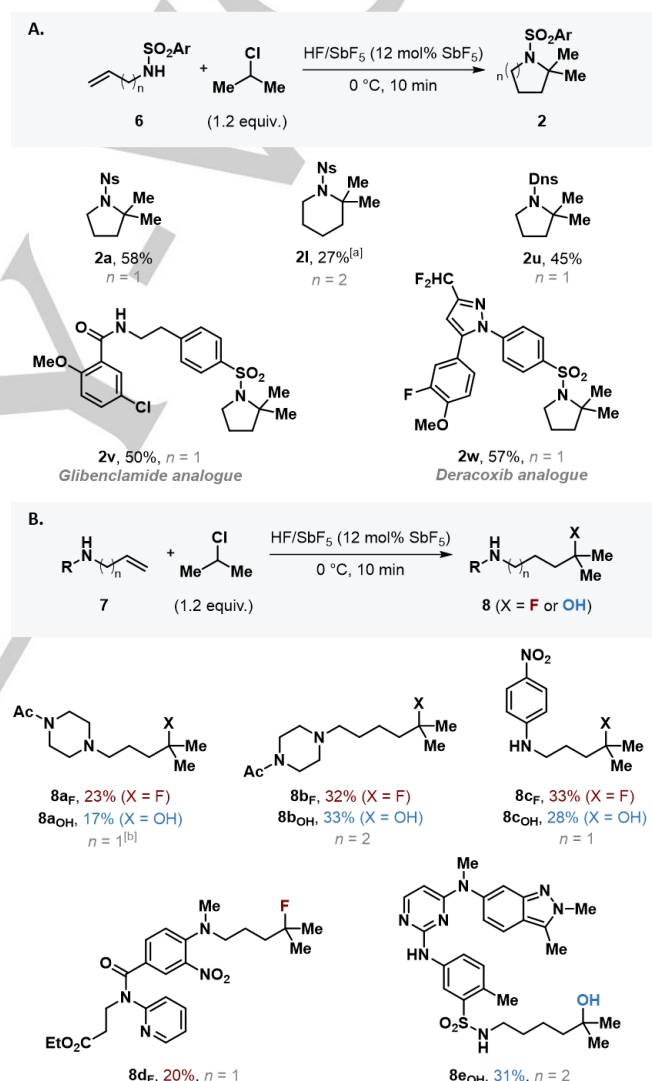


Figure 5. A) Intermolecular variant of the title reaction. B) Superacid-promoted gem-carbofunctionalization of unsaturated amines. Isolated yield. Ns = *p*-nosyl; Dns = dansyl. [a] Calculated yield; obtained as a 9:1 **2l/2k** mixture (overall yield: 31%). [b] Using 2.4 equiv. of 2-chloropropane at -20 °C for 20 min.

In superacid, amines being fully protonated, any intramolecular cyclization through cation trapping by neutral nitrogen atom should be avoided. In such conditions, the alkene moiety of unsaturated amines could thus undergo addition of isopropyl cation that would generate a carbocationic intermediate prone to react further by intermolecular nucleophilic trapping. This has

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been confirmed by submitting unsaturated substrates **7a-c** which afforded elongated fluorinated analogues **8a-c_F** and alcohols **8a-co_H** after fluoride ion trapping or hydrolysis (Figure 5B). This strategy was extended to polyfunctionalized substrates **7d** and **7e**^[28] with success, although with moderate yields in standard condition, probably due to a partial deactivation of the substrate by polyprotonation.

Conclusion

In summary, we have discovered a new skeletal reorganization process of unsaturated nitrogen-containing substrates that is promoted by polyprotonation in superacid solutions. It represents an original direct entry to modified scaffolds from simple substrates and can be extended to an intermolecular version affording expedient access to cyclic and acyclic analogues of elaborated products. Of note is the intriguing mechanism that was demonstrated to implicate C–N bond cleavage, isopropyl cation generation and subsequent C–C and C–N bonds formation. This study also reveals that skeletal reorganization in superacid can be controlled through protonation interplay.

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Keywords: Polycations • Rearrangement • Fluorine • Superacid • Heterocycles

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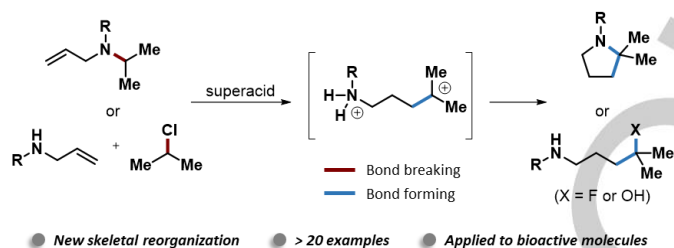
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Original rearrangement of isopropyl-containing nitrogen-containing compounds allows the skeletal reorganization to cyclic and elongated functionalized systems. An unprecedented tandem C–N bond cleavage / C–C and C–N bond formation through the generation of a dication is shown.



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Exploring Superacid-Promoted Skeletal Reorganization of Aliphatic Nitrogen-Containing Compounds

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