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Reaction Mechanisms

Accumulation, Characterization and Reactivity of Chiral Ammonium-Carboxonium Dications in Superacid

Emanuela Berrino, Thomas Cantin, Maxime Artault, Stefanie Beck, Christoph Jessen, Jérôme Marrot, Frédéric Guégan, Agnès Mingot, Andreas Kornath⁺,* and Sébastien Thibaudeau*

Abstract: The accumulation of chiral ammonium-oxocarbenium dications in superacid is evidenced by low-temperature NMR spectroscopy, X-ray diffraction analysis and confirmed by DFT calculations. Its potential for the diastereoselective remote hydrofunctionalization of non-activated alkene is also explored.

Introduction

Highly reactive electrophilic carbocations^[1] are intermediates in classic textbook reactions, such as additions to alkene^[2] or S_N1 reactions.^[3] To control the facial selectivity of the nucleophile substitution on the carbenium ion intermediate, chemists have gone to great lengths through the use of catalysts.^[4] This strategy recently culminated with the use of strong and confined (super)organoacids that catalyze asymmetric intramolecular hydroarylation of unactivated olefins^[5] or exert enantiocontrol over simple and highly reactive carbocations.^[6] In superacid,^[7] reactions involving polycationic superelectrophiles^[8] can be exploited

to generate innovative molecules in bioactive series.^[9] However, these reactions are limited by the absence of stereoselective versions (Figure 1a).^[10] This is due to the inherent superelectrophilic short-lived character of the generated intermediates and the necessity to work in a non-nucleophilic highly acidic environment,^[11] obliterating any use of temporary ion-pair strategy in a catalytic way.^[12] Only rare examples of chiral benzylic dicationic superelectrophiles have been suggested and observed (Figure 1b).^[13] By taking advantage of the formation of stabilized long-lived α -chiral carbocations in superacid, when the substrate bears a stereogenic carbon center in the α -position to the electrophilic carbon atom, facial diastereoselective substitution can be high.^[13,14] In addition, while enantioselective synthesis of ammonium cations is highly challenging,^[15] their diastereoselective synthesis is successful when inversion of nitrogen's lone pair is prevented or when the stereochemical information is transferred from the carbon skeleton in a diastereoselective way.^[16] Capitalizing on the previously shown ability to diprotonate aminoacids in superacid solutions,^[17]

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[†] Prof. Dr. A. Kornath passed away in march 2024. It's an honour to have worked together over the years, a fantastic friend and chemist who leaves behind a legacy of innovation and camaraderie that we already miss.

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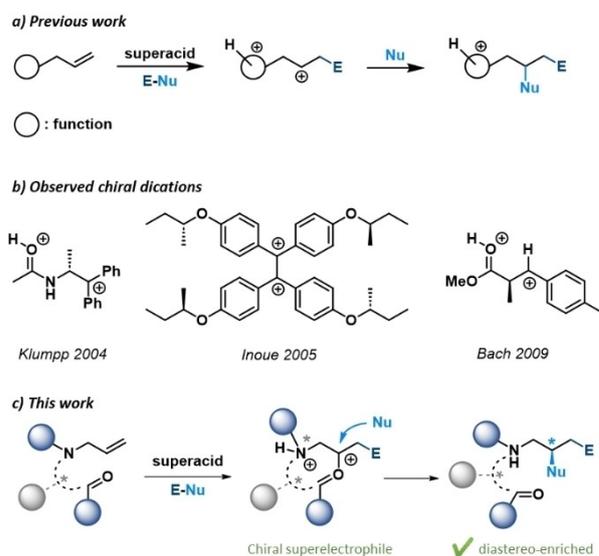


Figure 1. a) Superelectrophilic activation of non-activated alkenes is limited by the absence of a stereoselective version; b) Previously observed chiral dicationic superelectrophiles; c) This work: accumulation and full characterization of ammonium-carboxonium superelectrophiles and exploration of their synthetic potential.

here we show that chiral ammonium-carboxonium dications could be temporarily generated from *N*-allyl substituted aminoesters, allowing a tandem diastereoselective proton-transfer/intramolecular cyclization to accumulate chiral cyclic ammonium-carboxonium dications.^[18] Their diastereoselective trapping is also explored (Figure 1c).

Results and Discussion

The steric and electronic effects of substituents in close or remote positions of cyclic oxocarbenium ions are known to influence their conformational behavior and consequently their reactivity.^[19] This phenomenon also occurs in superacid environment, where glycosyl oxocarbenium ions generated in the medium are long lived. In these conditions, a preferential conformation depending on the nature of the substituents can be observed, resulting also in a selective reactivity with nucleophiles.^[20] To test the feasibility of this original approach, glycine methylester derivatives have been used as model substrates. First, the reactivity of *N,N*-dimethylglycine methylester in a solution of HF/SbF₅ (22 mol % SbF₅) was explored at -20 °C. In situ NMR spectra (¹H and ¹³C, see the SI) confirmed the formation and persistency of the corresponding ammonium carboxonium dication **A1** in these conditions (Figure 2a). Having confirmed that ammonium-carboxonium dication could be generated in superacid solution, the hypothesized tandem

proton transfer/intramolecular stabilization was next evaluated (Figure 2b). A solution of **1a** in HF/SbF₅ at 0 °C was scrutinized by NMR spectroscopy. After 3 h, a clean ¹³C NMR spectrum revealed the unique formation of one dicationic diastereomer **B1** (Figure 2c). The experimental chemical shift values perfectly match the theoretical NMR parameters deduced from calculations for the most stable postulated intermediate, exhibiting a conformation in solution with methyl groups pointing in equatorial position. (Figures 2c and 2d). This result was particularly encouraging as it demonstrated that the tandem process occurs in a diastereoselective way. Importantly, single crystals grown from this solution were analyzed by X-ray diffraction at low temperature, also confirming the structure of dication **B1** (Figure 2e).

To verify the synthetic opportunities offered by this strategy, we explored the reaction substrates **1** in superacidic conditions (Table 1). Aminoester **1a** did not react in neat HF but afforded the expected β -fluorinated amine **1b** after reaction in HF/SbF₅ (Table 1, entries 1–2). Increasing SbF₅ amount, temperature and reaction time favored the formation of lactone **1c**, at the expense of the fluorinated product (Table 1, entries 3–5). The formation of the lactone **1c** which must result from the hydrolysis of the suggested ammonium-oxocarbenium intermediate confirmed our initial hypothesis. The screening of other functions substantially prone to intramolecularly stabilize the cation was then conducted. Using ketones **2a** and **3a** led to the selective formation of the corresponding β -hydroxyamines **2d** and **3d** (Table 1, entries 6–7). The amide analogue **4a** and the acid **5a** afforded the lactone **4c** and **5c** in poor yields. The *tert*-butyl substituted ester **6a** led to 23 % of lactone **6c**, when this product could be formed in 65 % yield from its methyl-substituted analogue in the same conditions. Remarkably, by adjusting acidity and reaction conditions, lactone **1c** and

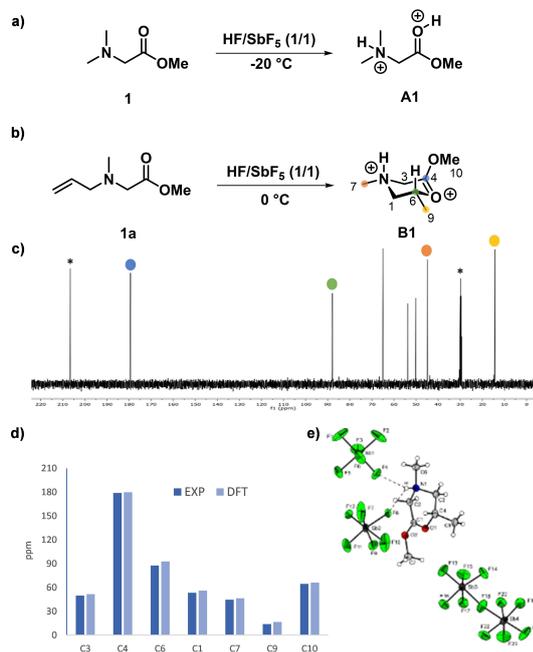


Figure 2. a) Dicationic ammonium-carboxonium species **A1**, generated from aminoester **A** in superacid HF/SbF₅ (22 mol % SbF₅) after 10 min reaction; b) Dicationic ammonium-carboxonium species **B1**, generated from aminoester **1a** in superacid HF/SbF₅ (22 mol % SbF₅); c) ¹³C NMR analysis of a cyclic ammonium-carboxonium dication **B1**; (*) (CD₃)₂CO used as external standard; d) ¹³C NMR chemical shifts of dication **B1**, comparing the DFT model to the experimental value (see SI for details); e) Crystal structure of dication **B1** in superacid HF/SbF₅.

Table 1: Superacid-promoted hydrofluorination and hydration of unsaturated amines **1a–6a**.

Entry	R	SbF ₅ [mol%] ^[a]	T [°C]	t [h]	(Conv) Yield [%] ^[b]			
					b	c	d	
1	1a OMe	0	-20	2	-	-	-	-
2	1a OMe	8	-20	10 min	1b (100)	65	-	-
3	1a OMe	22	-20	10 min	1b (66)	-	1c (8)	-
4	1a OMe	22	0	2	1b (14)	-	1c (86)	65
5	1a OMe	22	0	8	-	-	1c (100)	90
6	2a Ph	22	0	2	-	-	-	2d 58
7	3a Me	22	0	2	-	-	-	3d 15
8	4a NH ₂	22	0	2	-	-	4c (<5) ^[d]	-
9	5a OH	22	0	2	-	-	5c (100)	10
10	6a OtBu	22	0	2	-	-	6c (100)	23

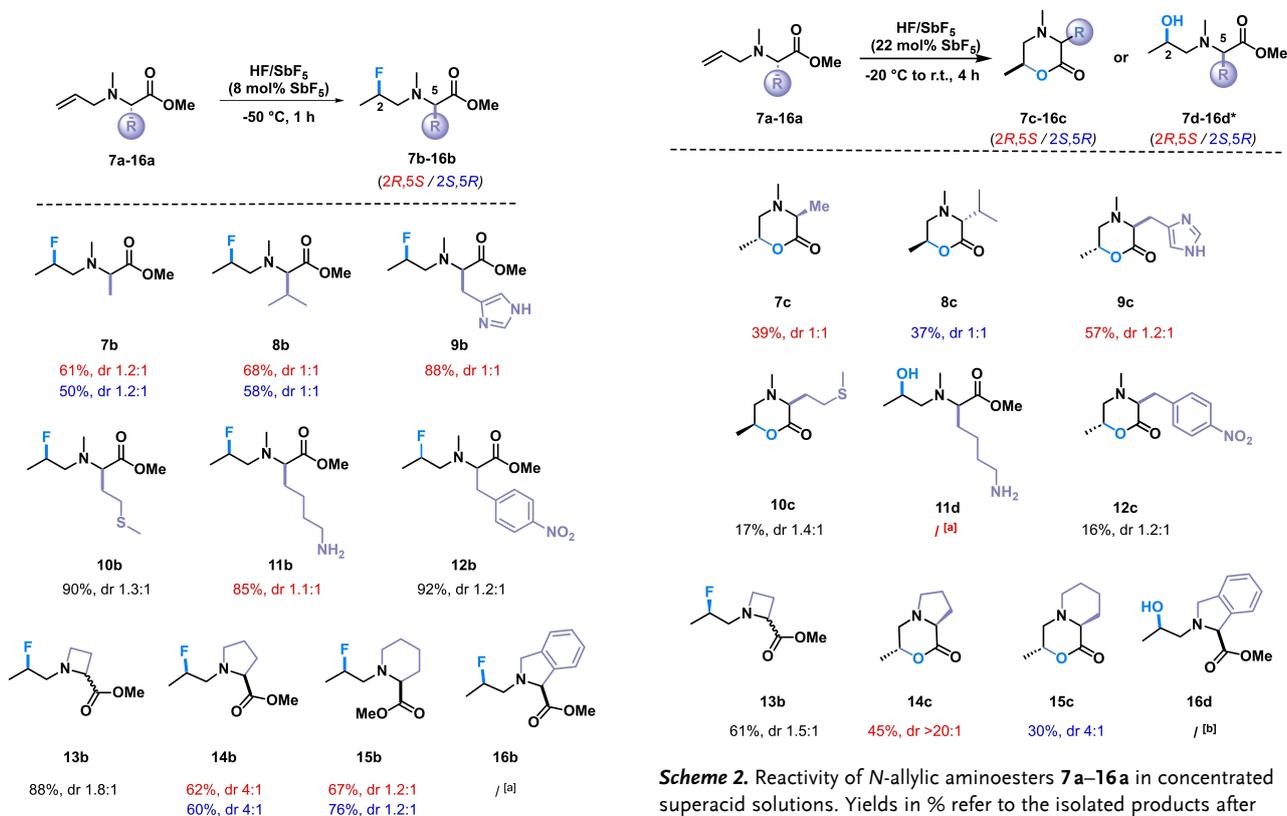
[a] mol % of SbF₅ in HF solution; [b] (conversion determined by crude mixture NMR analysis)/yield after flash-chromatography purification; [c] No reaction; [d] Only traces of lactone **4c** were observed from the complex mixture.

β -fluorinated **1b** were selectively obtained from aminoester **1a** (Table 1, entries 2 and 5).

These first results on glycine derivatives encouraged us to pursue this exploration using chiral substrates. A series of linear and cyclic *N*-allylic chiral aminoesters were synthesized and submitted to superacid (Scheme 1). Considering the exponential interest for fluorinated compounds^[21,22] and the known impact of fluorine atom(s) on conformation^[23,24] and pKa of molecules, especially in the nitrogen-containing compounds series,^[25,26] we first focused our attention on the hydrofluorination reaction.^[27] Besides compound **16a** which led to a complex mixture, fluorinated products **7b–15b** were selectively synthesized in reasonable yields after reaction in optimized conditions (SbF₅=8 mol %, –50 °C, 1 h). As expected, the reaction proved to be diastereoselective in most cases. The best results were observed for the proline analogue **14b**, which showed a d.r. of 4:1. The configuration of the newly created stereogenic center was also confirmed by X-ray crystal analysis of the corresponding amide (compound **14b-NH₂** analogue (see SI, Figure S8)).

Although modest, the observed diastereoselectivity is encouraging when considering that this reaction occurs in remote position from the stereocenter. Despite the distance between the remote chiral center and the generated cation, a spatial proximity of the chiral center with the reactive electrodeficient center can thus be postulated, in accordance with the formation of a transient chiral dication of type **B**. In the superacid promoted hydrofluorination reaction, the known equilibrium between the β -fluorinated product and

its cationic precursor must be detrimental to the diastereoselectivity of the whole process.^[28] When submitting the diastereopure fluorinated proline **14b** in the same conditions, a mixture of the two fluorinated diastereomers in 4:1 ratio was indeed observed (see SI, Figure S25). Accumulating any chiral ammonium-carboxonium dication of type **B** would thus be needed to envisage a fully diastereocontrolled reaction with an external nucleophile. The nucleophilicity of the fluoride ion source is likely to decrease when the concentration of SbF₅ increases.^[29] The transient cation would thus be accumulated in stronger acidic conditions, with the exclusive formation of **1c** from **1a** (Table 1, entry 5). To test this strategy, *N*-allylic aminoesters **7a–16a** were submitted to concentrated superacid conditions and gratifyingly the corresponding lactones and/or alcohols could be generated in these conditions (Scheme 2). In many cases, the products were obtained with a small diastereomeric excess. In the case of the azetidine analogue, the fluorinated product **13b** was obtained. This was most likely due to the high instability of the fused 4/6 rings system generated as reaction intermediate, prone to be opened by fluoride ion in situ. Decomposition was observed for the isoindoline derivative **16d**. However, and gratifyingly, it is also important to highlight that in the case of L-proline methyl ester **14a**, only one diastereoisomer was formed. The configuration of the newly created stereogenic center within compound **14c** was confirmed by X-ray crystal analysis of

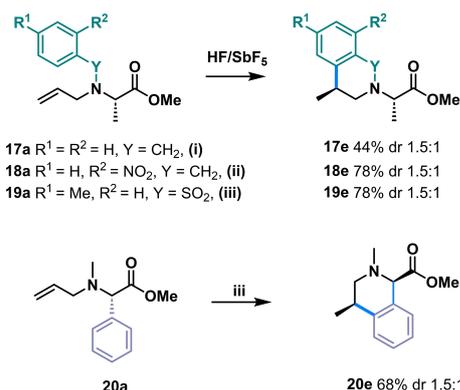


Scheme 1. Hydrofluorination of allylic aminoester **7a–16a** in superacid; [a] degradation. Yields in % refer to the isolated products.

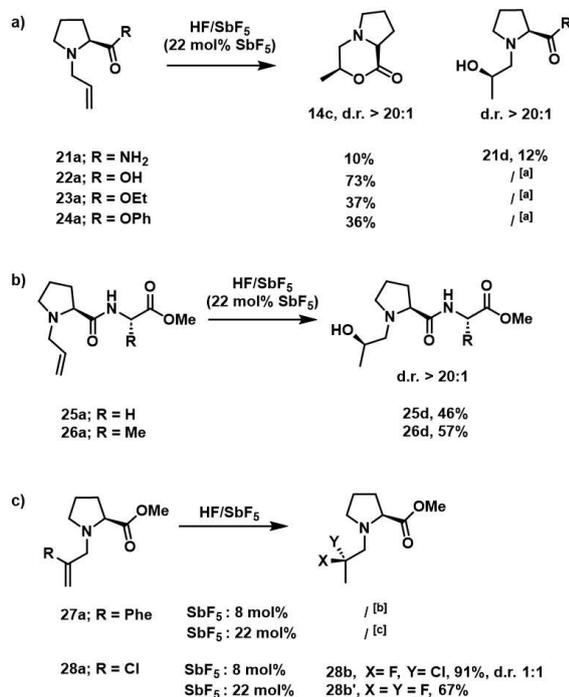
Scheme 2. Reactivity of *N*-allylic aminoesters **7a–16a** in concentrated superacid solutions. Yields in % refer to the isolated products after purification; d.r. values refer to the ester compound “d” when observed in the crude; [a] complex mixture; [b] degradation. * ¹H NMR ratios and yields for compounds **7d–16d** can be found in the SI.

the corresponding hydrolyzed acidic form **14c-OH** (see SI, Figure S9).

To further explore synthetic applications for this strategy, the intramolecular trapping of the reactive intermediate by carbon nucleophile was also tested (Scheme 3). *N*-Benzylamine substrate **17a** allowed to generate the chiral tetrahydroisoquinoline **17e** in 44% yield. Interestingly, its nitro-substituted analogue **18e** could also be directly synthesized starting from allylic substrate **18a**, confirming the superelectrophilic character of the transient intermediate. Chiral sultams could also be synthesized using this strategy, as exemplified by the formation of product **19e**. Direct access to constrained chiral α -aminoacids scaffolds was also



Scheme 3. Exploitation of internal nucleophile to generate chiral cyclic compounds. (i) HF/SbF₅ (8 mol% SbF₅), -20 °C, 10 min; (ii) HF/SbF₅ (22 mol% SbF₅), 0 °C, 30 min; (iii) HF/SbF₅ (22 mol% SbF₅), 0 °C, 2 h.

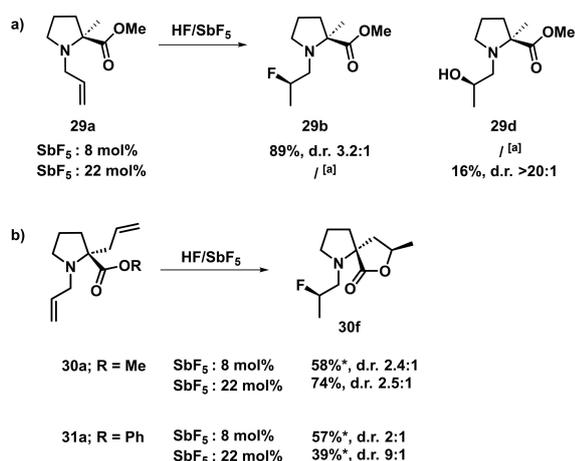


Scheme 4. Superacid-promoted functionalization of proline derivatives **21 a–28 a**. Yields in % refer to the isolated products. [a] product not detected; [b] starting material recovered; [c] complex mixture.

demonstrated when product **20e** was cleanly generated after reaction of phenyl glycine derivative **20a**.

Although very encouraging, these results confirmed the specificity of proline-based systems in stereoselective reactions.^[30] Therefore, we decided to further explore L-proline derivatives reactivity (Scheme 4). Insertion of different substituents on the carbonyl group was first evaluated (Scheme 4a). These modifications did not alter the diastereoselectivity of the reaction, with the formation of the expected lactone **14c** in good diastereomeric excess using HF/SbF₅ solution (22 mol% SbF₅). The variation of yields, depending on the R group might also reflect the ability of the function to stabilize the cation in this case. Interestingly, the possibility to perform the diastereoselective functionalization in amide containing systems, also in modest yield with compound **21a**, offered synthetic perspectives to generate peptidic analogues. In particular, Pro-Gly **25a** and Pro-Ala **26a** protected dipeptides were successively tested, furnishing the corresponding diastereopure hydroxylated dipeptides **25d** and **26d** (Scheme 4b). This confirms the feasibility of this strategy to generate diastereoenriched β -functionalized peptides. The impact of the substitution of the alkene chain with groups that must play different electronic effects on the reactive intermediate was also explored (Scheme 4c). Unfortunately, starting from the phenyl substituted derivative **27a**, whatever the conditions tested, either complex mixture was obtained or starting material recovered. Interestingly, the reaction occurs selectively with the chlorinated analogue **28a**, furnishing the difluorinated product **28b'** in good yield. Here, this result also highlight that the reactivity of the cationic intermediate is strongly influenced by the presence of the chlorine atom.^[31] In less acidic conditions (8 mol% SbF₅), the chlorine/fluorine exchange does not occur and the gem chloro fluorinated analogue was obtained, with no diastereomeric excess observed (product **28b**). This could be either directly related to a non-diastereoselective process on the hypothetical cyclization due to the presence of the chlorine atom, or from the erosion of selectivity due to the different stability of the α chloronium cation, compared to the standard carbocation.^[32]

In order to evaluate the impact of a substituent located on the proline stereogenic center, derivatives bearing reactive (allyl) and non-reactive (methyl) substituents were synthesized and submitted to superacid reactions (Scheme 5). Insertion of a methyl group in α position revealed to have no impact, furnishing the fluorinated product **29b** in 89% yield (d.r. 3.2:1) in fluorination conditions. The excellent diastereoselectivity for the hydration reaction (compound **29d**, d.r. >20:1) confirms in this case the robustness of the process (Scheme 5a). Very gratifyingly, the exotic proline derivative adorned with two allylic groups (substrate **30a**) led to the corresponding β -fluorinated spirocyclic lactone **30f** as a mixture of diastereoisomers (Scheme 5b). The spirocyclization looks fully diastereoselective, suggesting that this strategy can be synthetically employed to accessing chiral spiroderivatives. Interestingly, the diastereomeric ratio for the fluorination reaction leads to consider that the spirocyclic lactone also acts as stabilizing



Scheme 5. Superacid-promoted functionalization of proline derivatives **29a–31a**. Yields in % refer to the isolated products. * yields refer to the major diastereomer isolated after purification; [a] product not detected.

group to generate a hypothetical tricyclic chiral ammonium-oxocarbenium dication in solution. This seems confirmed by the enhanced diastereoselectivity observed when reacting the phenyl ester analogue **31a** to get the fluorinated compound **30f** (d.r. 9:1). While these data open interesting synthetic perspectives by exploiting this strategy,^[33] they also awaken our curiosity at the mechanistic level. In order to get more insights behind the enhanced diastereoselectivity observed for proline aminoesters when compared to other aminoacids (i.e. alanine, d.r. 1:1), analysis of the protonation of the chiral dications generated in superacid was first conducted through in situ NMR experiments. When the *N*-methyl-*N*-propylalanine methylester **7** was submitted to superacid, the in situ NMR analysis showed the formation of **A7** as a 1:1 mixture of diastereomers (two sets of signals in the ¹³C NMR spectrum (see SI, Figure S14)). The same experiment with *N*-methyl-proline methylester **14** in HF/SbF₅ (22 mol % SbF₅) clearly revealed the unique formation of one diastereomer **A14** at the NMR time scale (Figure 3). In the ¹H NMR spectrum, the ammonium proton appears as a broad singlet at 5.73 ppm and the protonated methyl ester as a singlet at 12.74 ppm. NOE experiments revealed the anti-relationship of the CH of the chiral carbon atom and the NH of the ammonium ion. The formation of a unique diastereomer was also confirmed with a unique set of carbon signals in the ¹³C NMR spectrum (Figure 3).

The diastereoselective protonation observed for proline seems therefore crucial for the diastereoselectivity of the subsequent intramolecular trapping/cyclization. Same results were also obtained when testing the same *N*-methyl proline derivative at lower acidity (see SI, Figure S17). Then, the behavior of the *N*-allyl substituted derivative **14a** was analyzed by in situ NMR in HF/SbF₅ solution (8 mol % SbF₅). Two fluorinated ammonium oxocarbenium diastereoisomers **C14** were observed in 4:1 ratio (see SI, Figure S20), in agreement with the fluorinated products obtained after reaction in these conditions (Scheme 1). These fluorinated ammonium ions were found stable in superacid solution up to 24 h, with no

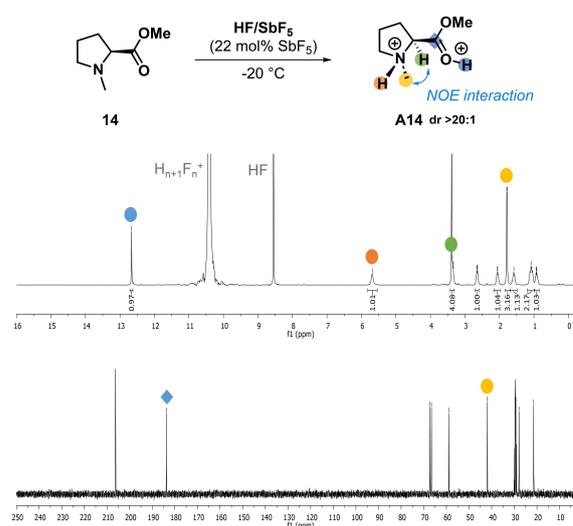


Figure 3. ¹H and ¹³C NMR spectra of a solution of **14** in HF/SbF₅. Observation of the unique formation of a chiral dication **A14**.

changing in the d.r. over time (see SI, Figure S21). To our delight, the analysis of the reactivity of **14a** in stronger acidic conditions (22 mol % SbF₅) after 4 h reaction showed the clean formation of a unique diastereomer **B14** in solution (Figure 4).^[34]

The structure of this dication is characterized by a broad singlet at 5.53 ppm in the ¹H NMR spectrum (ammonium group). The ammonium-dioxocarbenium dication **B14** adopts a preferred conformation in solution where N–H and C–H bond point in axial direction, as shown by NOE interactions (Figure 4). In the carbon NMR spectrum, the signal of the oxocarbenium carbon appears at 181.1 ppm.

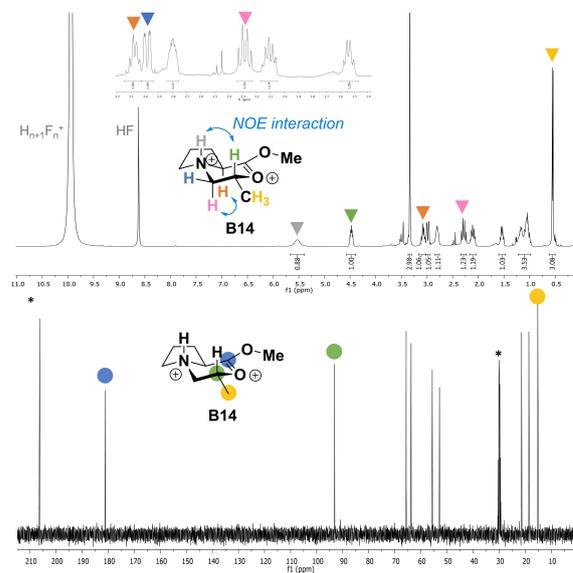


Figure 4. ¹H and ¹³C NMR of a solution of **14a** in HF/SbF₅ and observation of the unique formation of a chiral dication **B14** adopting a privileged conformation in solution, as confirmed by observed NOE interactions. (CD₃)₂CO used as external standard (*).

Furthermore, the signal of the methyl carbon is shielded to 15.2 ppm, in accordance with the proximity of oxocarbenium ion.^[20] Noteworthy, this accumulated dication is highly stable in superacid solution, being observed at 20 °C for hours (see SI, Figure S23).

Single-crystals of the chiral dication **B14** grown from a solution of substrate **14a** in HF/SbF₅ solution could also be analyzed by X-ray crystallography, confirming its structure (Figure 5).

The C7–O1 bond length of 1.509(9) Å is determined to be longer than a CO single bond in a neutral lactone compound.^[35] The other two CO bond lengths of the lactone fragment C1–O1 [1.287(9) Å] and C1–O2 [1.251(9) Å] are in a range between a formal single and double bond. These values are in good agreement with cationic lactone species.^[36] The C5–N1 bond [1.520(1) Å] is significantly longer than the other two CN bonds [1.490(1) Å], in accordance with protonated tertiary amines.^[37] This ammonium ion is shown to be in a contact ion pair form with two Sb₂F₁₁[−] anions via moderate N–(H)⋯F donor–acceptor interactions. Moreover, a C⋯F contact with a donor–acceptor distance of 2.767(9) Å, which is below the sum of the van der Waals radii [3.17 Å],^[38] is observed.

To get more insight into the reaction mechanism leading to the diastereopure dication **B14**, we monitored its formation by in situ NMR analysis. The NMR spectrum of **14a** recorded after 25 min of reaction revealed the presence of the fluorinated **C14** in mixture with the cyclic dication **B14** in diastereopure form. After 4 hours, **B14** is the only species detected in solution (Scheme 6a, Figure S24). The dication **B14** is gradually formed in solution at the expense of the fluorinated species **C14**. This process was also explored by submitting the fluorinated diastereomers **14b** (4:1 ratio) in cyclization conditions (22 mol% SbF₅). After aqueous quenching, the diastereopure hydroxylated derivative **14d** and the lactone **14c** were observed as the major products (Scheme 6b, Figure S26). Hence, it is likely that the nucleophilic trapping to generate only one diastereomer of **B14** occurs from the open face of the ammonium oxocarbenium dication, in equilibrium with the fluorinated derivative in solution. The following reaction mechanism was thus postulated (Scheme 6c).

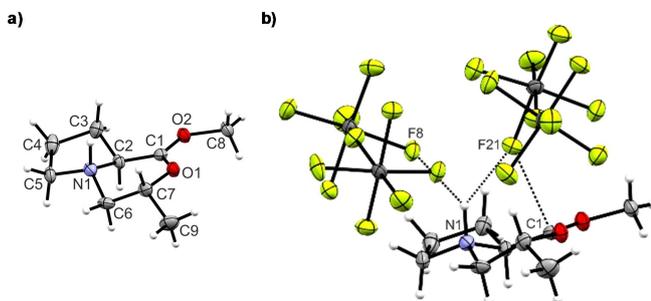
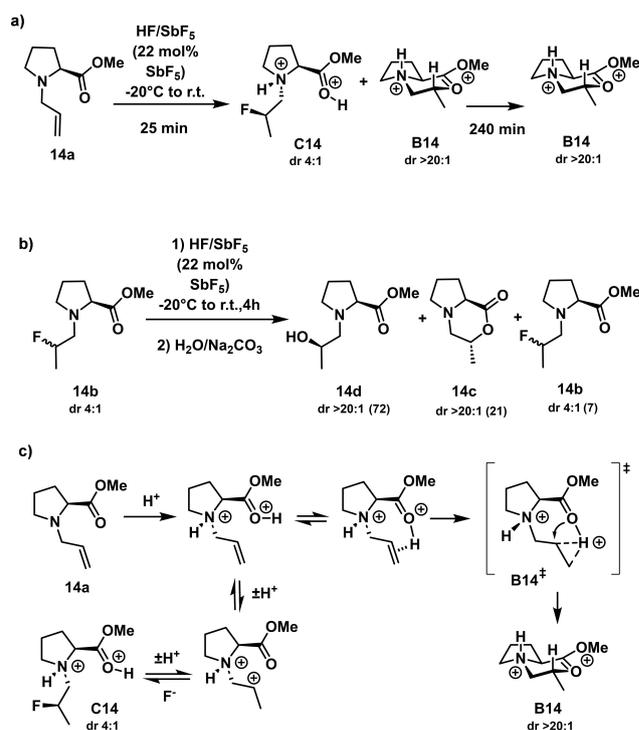


Figure 5. a) Crystallographic structure of dication **B14**. b) Projection of the interionic contacts (represented as dashed lines) between cation and anions (50% probability displacement ellipsoids).



Scheme 6. a) In situ NMR monitoring of the formation of chiral dication **B14**; b) Reaction of **14b** as diastereomeric mixture (4:1) in HF/SbF₅ (22 mol% SbF₅) to give diastereopure hydroxylated compound **14d** as major product in the crude NMR (¹H NMR yields in parenthesis); c) Suggested mechanism to account for the transfer of chirality.

As suggested by DFT calculations (Figure 6), a concerted mechanism could account for the diastereoselective exclusive formation of dication **B14**, with the implication of a dication **B14[‡]** as a transition state.

In this mechanism, the ammonium-carboxonium dication first undergoes a proton transfer (from the carboxonium to the allyl moiety), immediately followed by trapping of the transient carbocation (concerted asynchronous mechanism). Four different transition state structures of the type **B14[‡]** could be isolated, depending on the absolute configuration of the ammonium ion and the protonated face of the alkene. The estimated activation energies suggest a kinetically controlled reaction favoring the subsequent formation of a privileged chiral dication **B14** in solution. The energy profile of this reaction step is indeed exoenergetic ($\Delta(E+ZPE) = -11.0$ to -15.7 kcal/mol) for all internal trappings and associated activation energies range between 14.7 to 18.0 kcal/mol, thus suggesting this reaction step to be irreversible. Using these relative energies of calculated TS to compute statistical distribution of products via the Maxwell-Boltzmann statistical model, we eventually obtain at 220 K a diastereoisomer ratio of 95:5, in reasonable agreement with experiment (Figure 6). Same calculations were performed also for alanine and piperidine methyl esters, and the diastereomeric excess obtained also matched with the experimental data (See SI). In HF/SbF₅ (22 mol% SbF₅), the long-lived dication **B14** leads to diastereopure

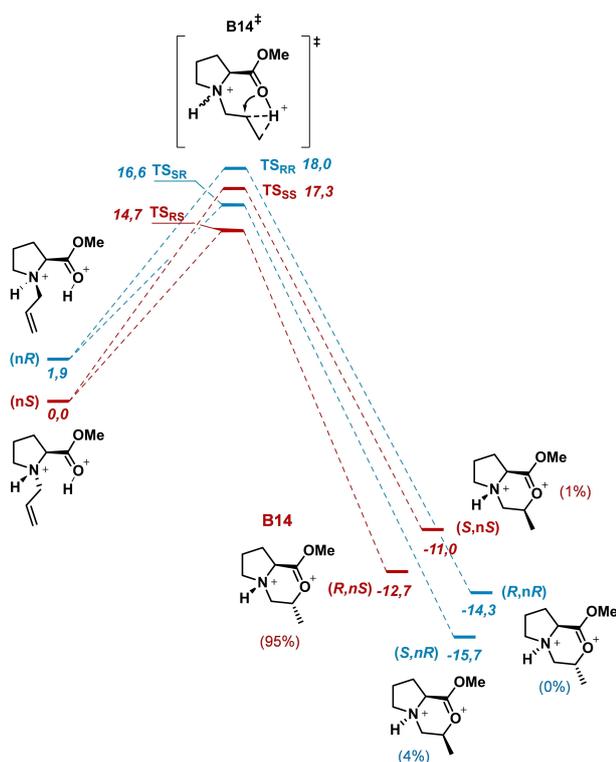


Figure 6. Relative energies ($E + \text{ZPE}$, in kcal/mol) for the geometries (reagents, transition states and products), with respect to the most stable reagent geometry. In parentheses, expected proportions of the cyclic dicationic products using Maxwell-Boltzmann approximation from the relative TS energies.

product after hydrolysis. In less acidic conditions, fluorination takes place to generate the β -fluorinated products. An equilibrium between these products and the open dicationic ammonium-carboxonium form partially explains the erosion of selectivity (Scheme 6c).

Conclusion

In conclusion, designed chiral superelectrophilic dicationic species have been accumulated and explored in superacid. Their structures have been evidenced by in situ NMR spectroscopy and collected crystals of these chiral dicationic species have been characterized by X-ray diffraction analysis. Confirmed by DFT calculations, the mechanism involves the diprotonation of unsaturated aminoesters followed by a concerted diastereoselective proton-transfer/cyclization with full diastereocontrolled formation of a chiral lactone from L-proline derived substrate. The persistency of the chiral dication opens future perspectives for the diastereoselective hydrofunctionalization of non-activated alkenes in superacid.

Supporting Information

The authors have cited additional references within the Supporting Information.^[39–61]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: cations • fluorine • mechanisms • reaction • superelectrophile

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