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Substitution Effect on the Cylization/Fluorination Reaction of *N*-Dienes in Superacid

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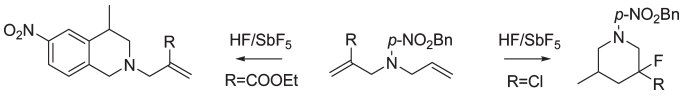

The novel cyclization/fluorination reaction of *N*-dienes in superacid was extended to substituted substrates. The influence of the substitution on superelectrophilic character of dicationic intermediates was shown and its dramatic effect on the synthesis of fluoropiperidines was studied. On the basis of new dicationic α-chloronium ammonium intermediates, starting from halogen-substituted dienes, high-valued fluorinated piperidines were synthesized.

Introduction

Fluorine can be highly advantageous in pharmaceutical and agrochemical compounds. Only one or just a few atoms in an organic molecule can dramatically alter its chemical and biological nature, including its stability, lipophilicity, and bioavailability,[1] this being mainly due to the properties of the fluorine atom.[2] Among fluorocompounds, heterocyclic nitrogen-containing compounds and especially fluorinated piperidines are currently largely used in SAR studies.[3] Despite the general relevance of fluorinated piperidines, few methods currently exist for their synthesis. Fluoropiperidines are usually prepared by dehydroxyfluorination of hydroxylated amines by using (diethyl)aminosulfurtrifluoride (DAST) or derivatives.[4] However, this methodology suffers from the formation of rearranged and/or dehydrated products which greatly diminish the yields of fluoroanalogues.[5] The encountered rearrangement is usually due to the anchimeric assistance of an electron-rich group present at a vicinal position of the reacting alcohol. Starting from prolinol derivatives, this rearrangement has been recently elegantly applied to the synthesis of 3-fluoropiperidines.[6] Other methods, such as ring-opening of aziridines[7] or Prins cyclization of aldehydes with protected amines in ionic liquid hydrogen fluorine salts,[8] have also been employed to access *N*-protected fluoropiperidines. However, these methods

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(2) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319 and references cited therein.

(3) For a recent example please see: Shipe, W. D.; Barrow, J. C.; Yang, Z.-Q.; Lindsley, C. W.; Yang, F. V.; Schlegel, K. S.; Shu, Y.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Tang, Q.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Uebele, V. N.; Nuss, C. E.; Connolly, T. M.; Doran, S. M.; Fox, S. V.; Kraus, R. L.; Marino, M. J.; Kuzmick Graufelds, V.; Vargas, H. M.; Bunting, P. B.; Hasbun-Manning, M.; Evans, R. M.; Koblan. K. S.; Renger. J. J. *J. Med. Chem.* **2008**, *51* (13), 3692−3695.

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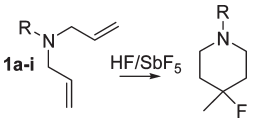
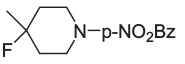
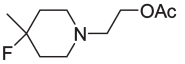
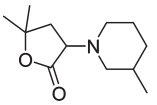
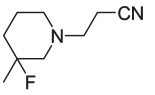
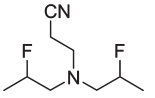
TABLE 1. N-Substituent Effect on Reaction in Superacid[a]



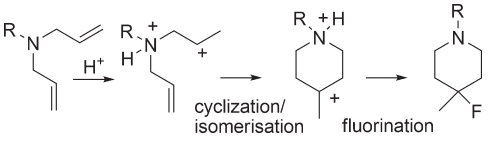
entry		R		product	Yield(%)
1	**1a**	Bz	/[b]		/[b]
2	**1b**	*p*-NO_2Bz	**2b**		55
3	**1c**	-CH_2-CH_2-OH	/[b]		/[b]
4	**1d**	-CH_2-CH_2-OMe	/[b]		/[b]
5	**1e**	-CH_2-CH_2-OAc	**2e**		50
6	**1f**	-CH_2-COOMe	/[b]		/[b]
7	**1g**	-CHMe-COOMe	/[b]		/[b]
8[c]	**1h**	-CH*iBu*-COOMe	**2h**		15[d]
9[c]	**1i**	-CH_2-CH_2-CN	**2i**		45
			2i'		7

[a]Standard conditions: HF/SbF_5 molar ratio 8/1, 5 min, −30 °C. [b]Complex mixture. [c]Reaction performed at −50 °C. [d]Side products formation.

require starting materials that are not readily available and lack generality and substrate scope. Carrying on our research work on the synthesis of fluorinated nitrogen-containing compounds in superacid HF/SbF_5,[9,10] we recently developed a new cyclization/fluorination reaction starting from nitrogen-containing dienes as a new route to 3- and 4-fluoropiperidines.[11] This reaction is based on the double protonation of a *N*-allylic group to form a superelectrophilic dicationic intermediate.[12] This superelectrophilic intermediate can undergo intramolecular nucleophilic attack by the double bond, leading to the formation of fluorinated piperidines after isomerization and fluorination (Scheme 1).

Considering the increased interest in fluorinated piperidine synthesis and the few methods existing to access such structural units, we set out to explore the scope and limitations of the cyclization/fluorination reaction in superacid HF/SbF_5. In this paper we describe the dramatic influence of substitution (nitrogen or double bond substitutions) on the reaction. In addition, the compatibility of halogen-substituted starting material with the reaction is demonstrated, making it an alternative method to synthesize *gem*-chlorofluoro or difluoropiperidines.

SCHEME 1. Cyclization/Fluorination Reaction in Superacid



Results and Discussion

***N*-Substitution Effect.** First, we investigated the ability to perform cyclization/fluorination starting from elaborated substrates such as amino alcohols, amino esters, or amino nitriles (Table 1).

In a previous study, we showed that the potential participation of an aromatic ring could influence the reaction course in superacid.[11] Whereas *N*-benzoyl diallylamine **1a** led to the formation of a complex mixture of compounds after reaction in standard conditions, deactivation of the

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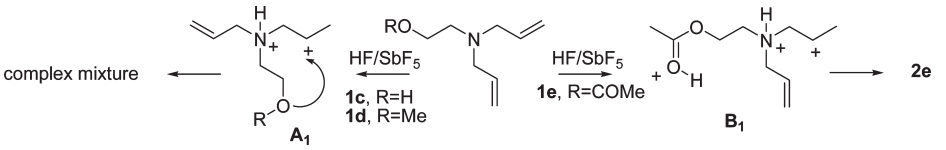
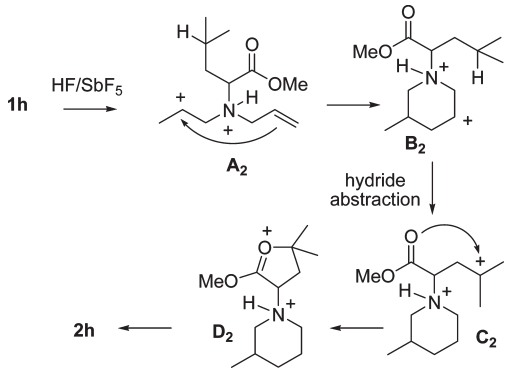
SCHEME 2. Reaction Mechanism for Substrates **1c**−**e**



aromatic ring by a nitro group (entry 2) allowed the formation of the desired fluoropiperidine **2b**. These results suggested that a side reaction occurred between the formed dication and the aromatic ring. In the same way, we also described the intramolecular trapping of dicationic species by neutral oxygen (alcohol,[13] carbonyl[14]) in superacid HF/SbF_5. To evaluate the influence of a potential chelating group on the reaction, amino alcohol (protected or not), amino esters, and amino nitriles were subjected to the reaction. Substrate **1c** gave a complex mixture of compounds whatever conditions were used. On the basis of the hypothesis of a participation of nonprotonated alcohol to the stabilization of the dicationic intermediate, alcohol was protected. Whereas ether protection was not successful to prevent oxygen participation (entry 4), it was better to add ester function, as shown by the formation of desired fluorinated piperidine **2e** in 50% yield starting from substrate **1e** (entry 5). During his famous work on protonation studies in superacid, Olah observed an equilibrium between diprotonated (protonation of acid and amine functions) and monoprotonated (protonation of nitrogen atom) amino acids in superacid.[15] On the basis of this observation and postulating a similar behavior of the amino esters, we propose the potential formation of a tricationic intermediate starting from substrate **1e** (Scheme 2).

For amino alcohol **1c** and amino ether **1d**, the proximal distance between functions disallowed the protonation of oxygen, and dicationic species $\mathbf{A_1}$ should be the intermediate of the reaction. The potential formation of a six-membered ammonium−oxonium dication by intramolecular quenching, leading to a less electrophilic dication, prevents substrates from undergoing the cyclization/fluorination process. This intra- or intermolecular participation could explain the absence of selectivity starting from these substrates. For substrate **1e**, the distance between the nitrogen atom and the carbonyl group of the ester function as well as the conjugation in the protonated ester group should allow protonation on both sites, followed by double bond protonation to give the intermediate $\mathbf{B_1}$. No chelating effect of the function can occur and the cyclization/fluorination process can take place. To access valuable fluorinated building blocks, we focused our work on the reactivity of *N*-diallylic amino esters. Unfortunately it appeared that the amino ester function was not compatible with the reaction (entries 6 and 7). The result obtained starting from substrate **1h** is in accordance with the postulated hypothesis (entry 8). Substrate **1h** led to the formation of the bicyclic product **2h** and this result encouraged us to postulate the following mechanism (Scheme 3).

SCHEME 3. Reaction Mechanism for **2h** Formation



After protonation, carbocation $\mathbf{A_2}$ can be trapped by a double bond, leading to the formation of intermediate $\mathbf{B_2}$. Then, we postulate that such β-ammonium−carbenium dication can act as an hydride abstracting agent[14] to form tertiary carbocation $\mathbf{C_2}$. After intramolecular quenching with the carbonyl group in neutral form, the more stable cyclic carboxonium ion $\mathbf{D_2}$ is formed as precursor of product **2h**. We suppose that both formation of a more stable carbocation $\mathbf{C_2}$, and subsequent intramolecular quenching leading to a five- membered-ring carboxonium ion $\mathbf{D_2}$ probably act as driving forces for this process. It should also be mentioned that because of the low yield and side products formation, we cannot rule out a potential hydride abstraction in an intermolecular way and/or an intermolecular quenching of carbocation $\mathbf{C_2}$. To the best of our knowledge, such reaction involving an ammonium−carbenium dicationic intermediate as hydride abstracting agent has not been reported before. Besides the originality of the result, the formation of product **2h**, resulting from the hydrolysis of a probably less electrophilic ammonium−carboxonium dication, emphasizes the potential participation of the ester function on the stabilization of ammonium−carbenium dications starting from amino esters. To confirm this hypothesis, the reactivity of nitrile **1i** (more basic) was tested. After reaction in superacid HF/SbF_5 at −50 °C, amino nitrile **1i** led to 3-fluoropiperidine **2i** in 45% yield. Besides product **2i**, we could separate and identify a small amount of the linear difluorinated mixture of diastereoisomers **2i′** showing a limited undesired effect of nitrile in this case. The formation of a 3-fluoropiperidine at −50 °C was in accordance with already observed similar effects of temperature on reaction course.[11] At higher temperature, the reaction became less selective.

Double Bond Substitution Effect. To investigate the influence of the double bond substitution on the formation of a potential ammonium−carbenium superlectrophilic intermediate, and thus, on the cyclization/fluorination reaction, the reactivity of substrates **3a**−**i** was tested (Table 2).

We had previously showed[11] that the reaction of methyl-substituted (entries 1 and 2) or homoallylic substrates led to

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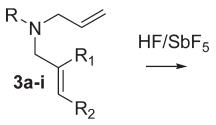
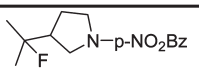
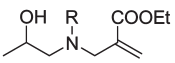
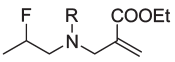
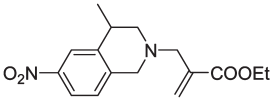
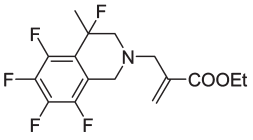
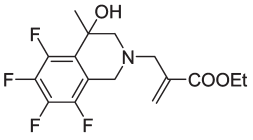
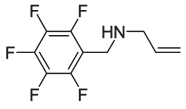
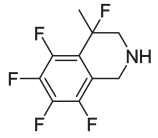
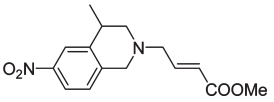
TABLE 2. Double Bond-Substituted *N*-Dienes Reaction in Superacid[a]



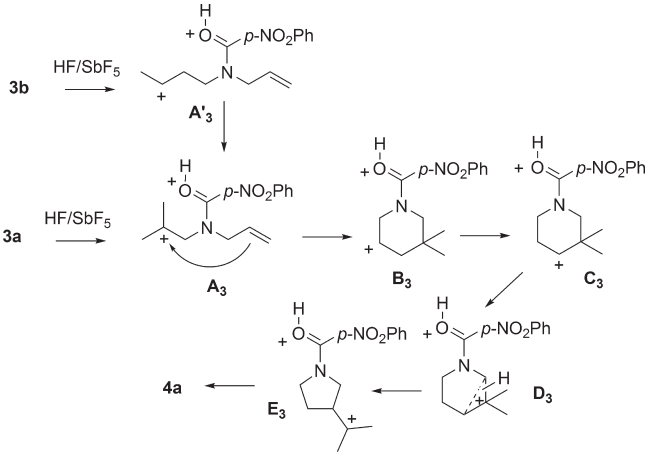
entry		R	R_1	R_2		product	Yield (%)
1	**3a**	*p*-NO_2Bz	Me	H	**4a**		86
2	**3b**	*p*-NO_2Bz	H	Me	**4a**		50
3	**3c**	*p*-NO_2Bz	Ph	H	/[b]		/[b]
4	**3d**	*p*-NO_2Bz	H	Ph	/[b]		/[b]
5	**3e**	*p*-NO_2Bz	COOEt	H	**4e**		41 (100)[c]
6	**3f**	Me	COOEt	H	**4f**		58
7	**3g**	*p*-NO_2Bn	COOEt	H	**4g**		46
8	**3h**	-CH_2-Ph-F_5	COOEt	H	**4h**		33
					4h'		20
9	**3h'**				**4h''**		44
10	**3i**	*p*-NO_2Bn	H	COOMe	**4i**		51

[a]Standard conditions: HF/SbF_5 molar ratio 8/1, 3 min, 0 °C. [b]Complex mixture. [c]Sole product detected by ^1H NMR of the crude mixture.

fluorinated pyrrolydine **4a**. After working on this alternative of the cyclization/fluorination process, and based on the amount of formed pyrrolidine depending on starting material, we propose the mechanism in Scheme 4.

After successive protonations, **3a** gives dication $\mathbf{A_3}$, which undergoes cylization to $\mathbf{B_3}$. After isomerization toward the more stable ion $\mathbf{C_3}$ (less repulsion of charges), the isomerization process through protonated cyclopropane could give the more stable dication $\mathbf{E_3}$ (less repulsion of charges and inductive donating effect), precursor of the fluorinated product. The formation of $\mathbf{A_3}$ requires two steps (protonation followed by isomerization) or one step, depending on the substrate. In addition, intermediate $\mathbf{A'_3}$ might be subjected to potential side reactions, which could explain the difference of selectivity (yield) depending on substrate. Phenyl substitution (entries 3 and 4) was not compatible with the cyclization/fluorination process. Starting from phenyl-substituted substrates, whatever reaction conditions used, a mixture of compounds was obtained. The absence of selectivity could be explained by a competition between the desired reaction and a potential intra- or intermolecular Friedel−Crafts-type reaction. Deactivation of the double bond by an electron-withdrawing group, like an ester function (on protonated or nonprotonated form in superacid), prevented the substrate from undergoing the desired reaction (entries 5−8, 10). Starting from **3e**, a monohydroxylated product **4e** was obtained in 41% yield after purification and no other compounds were detected in the crude. Modification of the substituent on the

SCHEME 4. Formation of Pyrrolidine 4a

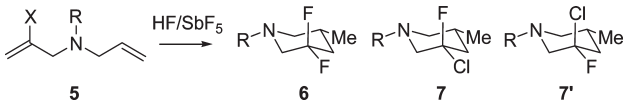


nitrogen atom allowed the formation of tetrahydroisoquinolines **4g**−**i** (entries 7−10) or fluorinated product **4f** (entry 6). The observed effect of the function on the reactivity of the substrate is in accordance with the influence of the distance between charges on the electrophilic character of the formed dicationic intermediate.[10] Starting from substrate **3h**, fluorinated and hydroxylated products **4h** and **4h′** were obtained in 33% and 20% yields, respectively. This original dehydrofluorination/fluorination process seems to come from the intramolecular Friedel−Crafts reaction, followed by dehydrofluorination (rearomatization)/fluorination. As Friedel Crafts alkylation of polyfluorobenzenes requires relatively harsh conditions,[16] to support our hypothesis, the reactivity of substrate **3h′** was tested. In similar conditions, the fluorinated isoquinoline **4h′′** was formed in 41% yield (entry 9). Interestingly, these results emphasize the superelectrophilic character of the ammonium−carbenium dication, as it can be trapped by a very poor nucleophile such as a polyfluorinated aromatic.

Halogen-Substituted Double Bond. In our ongoing work on the fluorination reaction in superacid, we recently showed a dramatic effect of halonium ions on difluorination.[17] Encouraged by these results, we studied the halogen-substitution influence on the cyclization/fluorination reaction (Table 3).

First, the reactivity of brominated substrates **5a**−**c** was tested. Unfortunately, whatever reaction conditions, the reaction was not selective and no products resulting from the cyclization/fluorination process could be identified. The formation of a cyclic bromonium ion after protonation of the double bond and the absence of regioselectivity for its opening by intra- or intermolecular nucleophilic attack could explain the formation of a mixture of compounds. Then, chlorinated substrates were submitted to reaction. Starting from chlorinated amines **5d**−**g**, except for *p*-NO_2-benzoyl protection (substrate **5d**), in all cases difluoropiperidines and/or chlorofluoroanalogues were obtained in good yields. Starting from amine **5e**, after reaction at 0 °C difluorinated piperidine **6e** was obtained selectively in 57% yield. The product observed experimentally was the

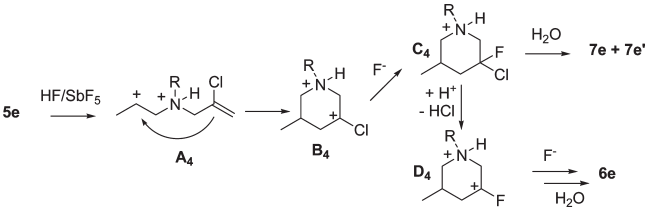
TABLE 3. Cyclization/Fluorination Reaction of Halogen-Substituted Substrates[a]



entry		R	X	temp (°C)	products (yield %[c])			6/7/7′ [d]
1	**5a**	*p*-NO_2Bz	Br	0	/[b]			
2	**5b**	*p*-NO_2Bn	Br	0	/[b]			
3	**5c**	Me	Br	0	/[b]			
4	**5d**	*p*-NO_2Bz	Cl	0	/[b]			
5	**5e**	*p*-NO_2Bn	Cl	0	**6e** (57)	**7e** (0)	**7′e** (0)	
6	**5e**	*p*-NO_2Bn	Cl	−50	**6e** (0)	**7e**/**7′e** (73)		0/90/10
7	**5f**	Me	Cl	0	**6f** (25)	**7f** (0)	**7′f** (0)	94/6/0
8	**5f**	Me	Cl	−30	**6f**	**7f**	**7′f**	51/40/9
9	**5f**	Me	Cl	−50	**6f** (0)	**7f** (26)	**7′f** (6)	14/71/15
10	**5f**	Me	Cl	−78	**6f**	**7f**	**7′f**	9/79/12
11	**5g**	*i*Pr	Cl	0	**6g** (33)	**7g** (0)	**7′g** (0)	97/3/0
12	**5g**	*i*Pr	Cl	−50	**6g** (0)	**7g** (29)	**7′g** (8)	27/60/12

[a]Standard conditions: HF/SbF_5 molar ratio 8/1, 3 min. [b]Complex mixture. [c]Yield of isolated product. [d]Relative abundances were determined by ^1H, ^{19}F NMR and confirmed by GC analysis of the crude reaction mixture (excepted for entry 6 by HPLC analysis).

SCHEME 5. Reaction of Substrate **5e**

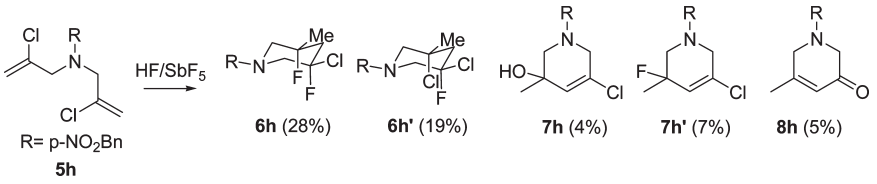


conformer with both methyl group and *N*-substituent in equatorial positions, the structure was determined by NMR experiments and confirmed by X-ray crystallography.[18] Under milder conditions (−50 °C, entry 6) substrate **5e** led to the formation of *gem*-chlorofluoroderivatives **7e** and **7′e** in good overall yield. As observed for the difluoroproduct **6e**, the more stable conformations present both the methyl group and the *N*-substituent in equatorial positions. Interestingly chlorofluoroderivatives **7e** and **7′e** were obtained as a mixture of diastereoisomers with a 9/1 ratio in favor of an axial fluorine mixture of enantiomers (**7e**). This ratio was determined by ^1H, ^{19}F NMR experiments and confirmed by HPLC analysis of the crude. A proposed mechanism to explain the reaction of chlorinated dienes is depicted in Scheme 5.

After successive protonations, superelectrophile $\mathbf{A_4}$ is formed and undergoes intramolecular cyclization to give α-chloronium ion $\mathbf{B_4}$.[19] Dication $\mathbf{B_4}$ is then fluorinated to give ammonium $\mathbf{C_4}$ precursor of chlorofluoro products. Elimination of HCl after protonation leads to the formation of α-fluoronium ion $\mathbf{D_4}$,[19] precursor of the difluorinated product.

(16) Beckert, W. F.; Lowe, J. U., Jr. *J. Org. Chem.* **1967**, *32*, 582–584.
(17) Zunino, F.; Liu, F.; Berrier, C.; Martin-Mingot, A.; Thibaudeau, S.; Jouannetaud, M. P.; Jacquesy, J. C.; Bachmann, C. *J. Fluorine Chem.* **2008**, *129*, 775–780.
(18) See Supporting Information, section I.
(19) 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*, 481−487 and references cited therein.

SCHEME 6. Reaction of Dichlorinated Substrate **5h**



This hypothesis, based on the formation of chlorofluoroderivative as intermediate, was confirmed by submitting a mixture of compounds **7e**/**7′e** to superacid at 0 °C. Starting from chlorofluoroderivatives, difluoroproduct **6e** was formed quantitatively. To know if the reaction could be influenced by the substituent on the nitrogen atom, we evaluated *N*-methyl substrate **5f** (entries 7−10) and *N*-isopropyl amine **5g** behaviors (entries 11 and 12). Analogously to substrate **5e**, difluorinated piperidines were formed at 0 °C (entries 7 and 11) and chlorofluoro analogues at −50 °C (entries 9 and 12). The obtained low yields could be the fact of the high volatility of the products as no other compounds were detected in the crude mixture. As shown by GC analysis of the crude mixtures, no notable influence of nitrogen atom substituent on diastereoisomers ratio was shown. For all substrates, the mixture of enantiomers with fluorine atom in the axial position was predominant. The relative stereochemistry of *gem*-chlorofluoroproducts was assigned by NMR experiments and confirmed by X-ray crystallography.[18] In summary, at low temperature chlorofluoroderivatives were formed with a diastereoselective excess in favor of axial fluorine atom diastereoisomers and at higher temperature (0 °C) difluorinated analogues could be obtained. On the basis of the postulated mechanism, the remarkable diastereoselectivity of the fluorination step prompted us to carry out theoretical studies to determine whether the fluorination was under kinetic or thermodynamic control.[20] For example, the products **7f** and **7′f** obtained experimentally are the more stable, but the relative energies between their more stable conformation are within 0.5 kcal mol^{-1} of each other and do not explain the observed diastereoselectivity. In addition, product ratios do not change over time under reaction conditions. To evaluate the thermodynamic control hypothesis, we also submitted a mixture of minor enantiomers (product **7′g**) to superacid at 0 °C. Difluorinated product **6g** was obtained besides the remaining **7′g**, a mixture of enantiomers **7g** was not observed in crude mixture. These results seemed to indicate that the fluorination step was under kinetic control. To confirm this hypothesis, we carried out theoretical calculations on α-chloronium−ammonium dication $\mathbf{B_4}$.[20] The calculations showed that the structure with the N^+−H bond in the axial position and the methyl in the equatorial position is the most stable conformer. It is likely to evaluate the approach of fluoride ion source (probably SbF_6^- or $Sb_2F_{11}^-$ in our conditions)[21] to the cationic center in this conformation. Two hypotheses can be considered. Fluorination could occur on the less hindered face of the pseudochair conformation (axial face). On the basis of the absence of considerable steric hindrance we propose a second hypothesis based on recent observations formulated on fluorinated cyclic ammonium ions.[22] On β-fluorinated piperidinium ions, intramolecular β-fluorine−ammonium interaction has been shown to be similar to that of a good hydrogen bond. Analogously, we postulate similar intermolecular ammonium−fluorine interaction between the axial N^+−H bond of the ammonium ion and one of the fluorine atoms of the antimony hexafluoride ion. Such interaction could explain a favorable approach of fluorinating agent by the upper face of the chloronium ion (N^+−H bond face of the ammonium ion). Further experimental and theoretical works are currently underway to confirm this hypothesis.

To evaluate the scope of this novel alternative of the cyclization/fluorination process, dichloro substrate **5h** was submitted to superacid (Scheme 6). After reaction at −50 °C, **5h** led to a mixture of compounds. After purification, five compounds were separated and identified as products coming from a cyclization process in superacid. Two major products were piperidines containing three halogen atoms (compounds **6h** and **6h′**). Besides, three minor products, probably coming from further elimination in the media, were obtained. The equatorial position of methyl and axial positions of fluorine atoms in **6h** and **6h′** were assigned by NMR experiments and confirmed by X-ray crystallography.[18] These preliminary results confirm a potent diastereoselective fluorination step as mentioned before. This recent result shows that cyclization/fluorination reaction could be applied to disubstituted (halogenated) nitrogen-containing dienes and further extends the scope of this reaction to high-valued polyhalogenated piperidines.

In conclusion, we have studied the scope and limitations of the recent cyclization/fluorination reaction of *N*-dienes in superacid. After showing a potential chelating effect of nitrogen substituent on the reaction, a dramatic double bond substitution effect on dicationic ammonium−carbenium intermediates reactivity has been showed. We have also studied the ability to use this reaction starting from halogenated substrates. On the basis of the formation of superlectrophilic novel dicationic α-chloronium ammonium intermediates in the media, this work has allowed the formation of high-valued *gem*-chlorofluoro- and difluoropiperidines in one step starting from easily accessible starting materials. In addition, stereoselective fluorination in superacid has been shown, which opens future innovative development for this particular chemistry.

Experimental Section

The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen

(20) See the Supporting Information, section H.

(21) (a) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley Interscience: New York, 1985. (b) Culmann, J. C.; Fauconet, M.; Jost, R.; Sommer, J. *New J. Chem.* **1999**, *23*, 863–867.

(22) (a) Sun, A.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. *Chem.—Eur. J.* **2005**, *11*, 1579–1591. (b) Gooseman, N. E. J.; O'Hagan, D.; Slawin, A. M. Z.; Teale, A. M.; Tozer, D. J.; Young, R. J. *Chem. Commun.* **2006**, 3190–3192.

fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Optimized Procedure in Superacidic Media. To a mixture of HF/SbF_5 (3 mL, 8/1 molar ratio) maintained at the indicated temperature was added nitrogen derivative (1 mmol). The mixture was magnetically stirred at the same temperature for the reaction time. The reaction mixture was then neutralized with water−ice−Na_2CO_3 and 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 2b: 4-fluoro-4-methyl-1-(4-nitrobenzoyl)piperidine: The optimized procedure (−30 °C, 5 min reaction time) was followed, starting from 500 mg of **1b** (2.03 mmol). Purification by flash column chromatography (70/30: petroleum ether/ethyl acetate) afforded 296 mg of the title compound as a colorless powder (55%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.43 (d, $^3J_{H-F}$ = 21.4 Hz, 3H, H-6); 1.79 (m, 4H, H-3); 3.19 (m, 1H) and 4.55 (m, 1H, H-2); 3.36 (m, 2H, H-2); 7.58 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, H-2′); 8.28 (d, $^3J_{H-H}$ = 6.8 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 27.0 (d, $^2J_{C-F}$ = 24 Hz, CH_3, C-6); 35.9 (d, $^2J_{C-F}$ = 22 Hz, CH_2) and 36.8 (d, $^2J_{C-F}$ = 23,3 Hz, CH_2, C-3); 38.8 and 43.6 (2 CH_2, C-2); 92.0 (d, $^1J_{C-F}$ = 168 Hz, C-4); 123.9 (2 CH, C-3′); 127.9 (2 CH, C-2′); 142.5 (C-1′) ; 148.3 (C-4′); 170.0 (C-5). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm) ppm) −154.72. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 266 (6), 247 (28), 150 (100), 104 (78), 83 (80). HRMS (ESI) calcd for $C_{13}H_{14}N_2O_3F$ 265.09885, found 265.0987. Mp 145 °C.

Compound 2e: 2-(4-fluoro-4-methylpiperidine-1-yl)ethyl acetate: The optimized procedure (−30 °C, 5 min reaction time) was followed, starting from 310 mg of **1e**. Purification by column chromatography (dichloromethane/methanol/NH_3(aq) 98/1/1) afforded 173 mg of the title compound (50%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.33 (d, $^3J_{H-F}$ = 21.4 Hz, 3H, H-5′); 1.75 (m, 4H, H-3′); 2.06 (s, 3H, H-2″); 2.38 (m, 2H, H-2′$_{ax}$); 2.66 (m, 4H, H-2′$_{eq}$ and H-2); 4.19 (t, $^3J_{H-H}$ = 6.0 Hz, 2H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 21.4 (CH_3, C-2″); 27.3 (d, $^2J_{C-F}$ = 24 Hz, CH_3, C-5′); 36.8 (d, $^2J_{C-F}$ = 21 Hz, 2 CH_2, C-3′); 50.0 (2 CH_2, C-2′); 57.0 (CH_2, C-2); 62.4 (CH_2, C-1); 92.3 (d, $^1J_{C-F}$ = 167 Hz, C-4′); 171.4 (C-1″). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −151.71.MS (EI, 70 eV) *m*/*z* (rel intensity, %) 203 (4), 143 (5), 130 (100), 110 (23), 70 (7), 43 (11). HRMS (ESI) calcd for $C_{10}H_{18}NO_2F$ 203.13216, found 203.1331.

Compound 2h: dihydro-5,5-dimethyl-3-(3-methylpiperidin-1-yl)furan-2(3*H*)-one: The optimized procedure (−50 °C, 10 min reaction time) was followed, starting from 250 mg of **1h**. Purification by column chromatography (petroleum ether/ethyl acetate 95/5) afforded 32 mg of the title compound (15%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.83 (m, 1H, H-4′); 0.84 (d, $^3J_{H-H}$ = 6.4 Hz, 3H, H-7′); 1.35 (s, 3H, H-6); 1.44 (s, 3H, H-6); 1.63 (m, 4H, H-3′, H-4′ and H-5′); 1.85 (t, $^3J_{H-H}$ = 10.4 Hz, 1H, H-2′$_{ax}$); 2.10 (m, 3H, H-5′ and H-4); 2.48 (dt, $^2J_{H-H}$ = 10.9 Hz, $^3J_{H-H}$ = 3.3 Hz, 1H, H-6′$_{ax}$); 2.68 (m, 1H, H-6′$_{eq}$); 2.93 (m, 1H, H-2′$_{eq}$); 3.75 (dd, $^3J_{H-H}$ = 11.2 Hz, $^3J_{H-H}$ = 9.0 Hz, 1H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 19.5 (CH_3, C-7); 25.4 and 25.6 (CH_2, C-4′); 27.4 (CH_3, C-6); 29.0 (CH_3, C-6); 31.1 and 31.3 (CH, C-3′); 32.7 (CH_2, C-5′ or C-4); 35.6 and 35.8 (CH_2, C-5′ or C-4); 49.8 and 50.2 (CH_2, C-6′); 57.5 and 57.9 (CH_2, C-2′); 64.4 (CH, C-3); 79.8 (C-5); 174.5 (C-2). MS (EI, 70 eV) *m*/*z* (rel intensity, %) 211 (11); 168 (23); 152 (89); 124 (100); 98 (29). HRMS (ESI) calcd for $C_{12}H_{21}NO_2$ 211.5723, found 211.580. Mp 50 °C.

Compounds 2i and 2i′. The optimized procedure (−50 °C, 60 min reaction time) was followed, starting from 400 mg of **1i**. Purification by column chromatography (dichloromethane/methanol 99/1) afforded 34 mg of compound **2i′** (7%).

Compound 2i′: 3-(bis(2-fluoropropyl)amino)propanenitrile: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.32 (dd, $^3J_{H-F}$ = 23.6 Hz, $^3J_{H-H}$ = 6.3 Hz, 3H, H-1′ and H-1″); 2.48 (m, 2H, H-3); 2.62 (m, 4H, H-3′ and H-3″); 2.90 (m, 2H, H-2); 4.79 (dm, $^2J_{H-F}$ = 49.3 Hz, 2H, H-2′ and H-2″). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 17.5 (CH_2, C-2); 19.0 (d, $^2J_{C-F}$ = 24 Hz, 2 CH_3, C-1′ and C-1″); 52.2 and 52.3 (2s, CH_2, C-3); 60.1 and 60.9 (2d, $^2J_{C-F}$ = 21 Hz, CH_2, C-3′ and C-3″); 90.5 and 90.9 (2d, $^1J_{C-F}$ = 167 Hz, 2 CH, C-2′ and C-2″); 119.3 (C-1). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −175,95 and −176,07. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 190 (5), 150 (18), 143 (100), 102 (7), 90 (10), 43 (25). HRMS (ESI) calcd for $C_9H_{16}N_2F_2$ 190.12816, found 190.1293.

Then, dichloromethane/methanol/NH_3(aq) 98/1/1 afforded 205 mg of compound **2i** (45%).

Compound 2i: 3-(3-fluoro-3-methylpiperidine-1-yl)propanenitrile: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.35 (d, $^3J_{H-F}$ = 21.6 Hz, 3H, H-1″); 1.55 (m, 2H, H-5′); 1.81 (m, 2H, H-4′); 2.30 (m, 2H, H-2′ and H-6′); 2.50 (t, $^3J_{H-H}$ = 7.2 Hz, 2H, H-3); 2.67 (m, 2H, H-2′ and H-6′); 2.77 (t, $^3J_{H-H}$ = 7.2 Hz, 2H, H-2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 15.9 (CH_2, C-2); 22.1 (d, $^3J_{C-F}$ = 4 Hz, CH_2, C-5′); 25.3 (d, $^2J_{C-F}$ = 24 Hz, CH_3, C-1″); 35.1 (d, $^2J_{C-F}$ = 23 Hz, CH_2, C-4′); 52.6 (CH_2, C-6′); 53.6 (CH_2, C-3); 61.9 (d, $^2J_{C-F}$ = 23 Hz, CH_2, C-2′); 92.5 (d, $^1J_{C-F}$ = 171 Hz, C-3′); 119.1 (C-1). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −147,58. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 170 (4), 130 (46), 110 (8), 97 (4), 70 (5), 59 (18), 43 (32), 32 (25), 28 (100), 18 (25). HRMS (ESI) calcd for $C_9H_{15}N_2F$ 170.12193, found 170.1210.

Compound 4a: (3-(2-fluoropropan-2-yl)pyrrolidin-1-yl)(4-nitrophenyl)methanone: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 300 mg of **3a**. Purification by column chromatography (dichloromethane/methanol 99/1) afforded 240 mg of the title compound (86%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.28, 1.35, 1.40, and 1.41 (4d, $^3J_{H-F}$ = 20.8, 21.0, 21.4, and 21.3 Hz), 6H, H-1′; 1.96 (m, 2H, H-4); 2.39 (m, 1H, H-3); 3.47 (m, 3H, H-5 and H-2); 3.82 (m, 1H, H-2); 7.65 (d, $^3J_{H-H}$ = 8.8 Hz) and 7.67 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, H-2″); 8.25 (d, $^3J_{H-H}$ = 8.8 Hz) and 8.27 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, H-3″). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 25.3 and 27.2 (d, CH_2, $^3J_{C-F}$ = 4 Hz, C-4); 25.6 (d, CH_3, $^2J_{C-F}$ = 24.6 Hz) and 25.8 (d, CH_3, $^2J_{C-F}$ = 24.7 Hz) and 26.3 (d, CH_3, $^2J_{C-F}$ = 26.2 Hz) and 26.7 (d, CH_3, $^2J_{C-F}$ = 24.8 Hz), C-1′; 46.7 and 49.8 (CH_2, C-5); 47.2 (d, CH, $^2J_{C-F}$ = 22.7 Hz) and 49.0 (d, CH, $^2J_{C-F}$ = 22.2 Hz, C-3); 47.3 and 49.9 (d, 2 CH_2, $^3J_{C-F}$ = 4.8 Hz, C-2); 94.0 (d, $^1J_{C-F}$ = 168.9 Hz) and 94.2 (d, $^1J_{C-F}$ = 168.3 Hz), C-2′; 123.6 and 123.7 (2 CH, C-3″); 128.1 (2 CH, C-2″); 142.5 and 142.7 (C-1″); 148.4 (C-4″); 167.3 and 167.4 (C═O). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −151.41 and −151.31. MS (EI, 70 eV) *m*/*z* (rel intensity %) 168 (35), 150 (61), 73 (88), 59 (100). HRMS (ESI) calcd for $C_{14}H_{17}N_2O_3F$ 280.12232, found 280.1220. Mp 69 °C.

Compound 4e: ethyl 2-((*N*-(2-hydroxypropyl)-4-nitrobenzamido)methyl)acrylate: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 200 mg of **3e**. Purification by column chromatography (petroleum ether/ethylacetate 60/40) afforded 86 mg of the title compound (41%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.26 (t, $^3J_{H-H}$ = 5.4 Hz, 3H, H-7); 1.39 (d, $^3J_{H-H}$ = 6.3 Hz, 3H, H-4′); 2.85 (m, 2H, H-2′); 3.50 (s, 2H, H-2); 4.19 (q, $^3J_{H-H}$ = 7.2 Hz, 2H, H-6); 5.29 (m, 1H, H-3′); 5.72 (s, 1H, H-4); 6.24 (s, 1H, H-4); 8.20 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, H-2″); 8.29 (d, $^3J_{H-H}$ = 6.8 Hz, 2H, H-3″). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 14.5 (CH_3, C-7); 18.4 (CH_3, C-4′); 50.8 (CH_2, C-2); 53.4 (CH_2, C-2′); 61.1 (CH_2, C-6); 72.7 (CH, C-3′); 123.8 (CH, C-3″); 126.5 (CH_2, C-4); 131.0 (CH, C-2″); 136.3 (C-3 or C-1″ or C-4″); 138.7 (C-3 or C-1″ or C-4″); 150.8 (C-3 or C-1″ or C-4″); 164.6 (C-5 or C-8); 166.9 (C-5 or C-8). MS

and HRMS analyses were not performed on this compound due to its high instability.

Compound 4f: ethyl 2-((*N*-(methyl)(2-fluoropropyl))methyl)-acrylate: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 90 mg of **3f**. Purification by column chromatography (dichloromethane/NH_3(aq) 99/1) afforded 58 mg of the title compound (58%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.28 (dd, $^3J_{H-F}$ = 23.5 Hz, $^3J_{H-H}$ = 6.3 Hz, 3H, H-4′); 1.28 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, H-7); 2.28 (s, 3H, H-8); 2.55 (m, 2H, H-2′); 3.25 (s, 2H, H-2); 4.19 (q, $^3J_{H-H}$ = 7.1 Hz, 2H, H-6); 4.81 (dm, $^2J_{H-F}$ = 49.4 Hz, 1H, H-3′); 5.74 (s, 1H, H-4); 6.23 (s, 1H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 14.5 (CH_3, C-7); 19.6 (d, $^2J_{C-F}$ = 22 Hz, CH_3, C-4′); 43.2 (CH_3, C-8); 58.7 (CH_2, C-2); 61.0 (CH_2, C-6); 62.8 (d, $^2J_{C-F}$ = 22 Hz, CH_2, C-2′); 89.6 (d, $^1J_{C-F}$ = 167 Hz, CH, C-3′); 126.8 (CH_2, C-4); 138.2 (C-3); 167.2 (C-5). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −175,36. MS (EI, 70 eV) *m*/*z* (rel intensity, %) 203 (11), 156 (100), 128 (23), 104 (57), 85 (25). HRMS (ESI) calcd for $C_{10}H_{18}NO_2F$ 203.13216, found 203.1342.

Compound 4g: ethyl 2-((3,4-dihydro-4-methyl-6-nitroisoquinolin-2(1*H*)-yl)methyl)acrylate: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 300 mg of **3g**. Purification by column chromatography (dichloromethane) afforded 139 mg of the title compound (46%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.29 (t, $^3J_{H-H}$ = 7.3 Hz, 3H, H-7); 1.33 (d, $^3J_{H-H}$ = 7.0 Hz, 3H, H-4′); 2.49 (dd, $^2J_{H-H}$ = 11.5 Hz, $^3J_{H-H}$ = 6.0 Hz, 1H, H-2′); 2.81 (dd, $^2J_{H-H}$ = 11.5 Hz, $^3J_{H-H}$ = 4.8 Hz, 1H, H-2′); 3.07 (m, 1H, H-3′); 3.37 (s, 2H, H-8); 3.66 (d, $^2J_{H-H}$ = 16.1 Hz, 1H, H-2); 3.75 (d, $^2J_{H-H}$ = 16.1 Hz, 1H, H-2); 4.21 (q, $^3J_{H-H}$ = 7.1 Hz, 2H, H-6); 5.82 (d, $^2J_{H-H}$ = 0.8 Hz, 1H, H-4); 6.29 (d, $^2J_{H-H}$ = 0.7 Hz, 1H, H-4); 7.13 (d, $^3J_{H-H}$ = 8.5 Hz, 1H, H-2″); 7.94 (dd, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-H}$ = 2.2 Hz, 1H, H-3″); 8.06 (d, $^4J_{H-H}$ = 1.9 Hz, 1H, H-5″). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 14.5 (CH_3, C-7); 21.5 (CH_3, C-4′); 33.7 (CH, C-3′); 56.6 (CH_2, C-8); 57.5 (CH_2, C-2′); 58.3 (CH_2, C-2); 61.0 (CH_2, C-6); 120.9 (CH, C-3″); 123.2 (CH, C-5″); 126.7 (CH_2, C-4); 127.6 (CH, C-2″); 137.5, 141.9, 142.6, and 146.9 (C-3, C-1″, C-6″, and C-4″); 167.1 (C-5). MS and HRMS analyses were not performed on this compound due to its high instability.

Compounds 4h and 4h′. The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 100 mg of **3h**. Purification by column chromatography (petroleum ether/ethyl acetate 98/2) afforded 37 mg of compound **4h** (33%).

Compound 4h: ethyl 2-((4,5,6,7,8-pentafluoro-3,4-dihydro-4-methylisoquinolin-2(1*H*)-yl)methyl)acrylate: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.29 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, H-6′); 1.78 (dd, $^3J_{H-F}$ = 20.6 Hz, $^5J_{H-F}$ = 1.1 Hz, 3H, H-11); 2.85 (d, $^3J_{H-F}$ = 11.9 Hz, 2H, H-3); 3.44 (s, 2H, H-1′); 3.54 (d, $^2J_{H-H}$ = 15.7 Hz, 1H, H-1); 3.73 (d, $^2J_{H-H}$ = 16.6 Hz, 1H, H-1); 4.21 (q, $^3J_{H-H}$ = 7.1 Hz, 2H, H-5′); 5.81 (s, 1H, H-3′); 6.32 (s, 1H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 14.5 (CH_3, C-6′); 25.7 (dd, $^2J_{C-F}$ = 27 Hz, $^4J_{C-F}$ = 4 Hz, CH_3, C-11); 49.6 (CH_2, C-1); 57.7 (CH_2, C-1′); 61.3 (CH_2, C-5′); 61.5 (d, $^2J_{C-F}$ = 27 Hz, CH_2, C-3); 90.5 (d, $^1J_{C-F}$ = 173 Hz, C-4); 119.9 (m, C-9); 121.2 (m, C-10); 127.6 (CH_2, C-3′); 136.9 (C-2′); 138.5, 141.9, 145.2, and 148.5 (C-5, C-6, C-7 and C-8); 166.9 (C-4′). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −139.94 (m, 1F, F−C4); −140.55 (m, 1F, F-5); −145.37 (dd, $^3J_{F-F}$ = 19.8 Hz, $^4J_{F-F}$ = 11.3 Hz, 1F, F-8); −156.81 (t, $^3J_{F-F}$ = 19.8 Hz, 1F, F-6); −156.62 (t, $^3J_{F-F}$ = 18.3 Hz, 1F, F-7). MS and HRMS analyses were not performed on this compound due to its high instability.

Then, petroleum ether/ethyl acetate 95/5 afforded 22 mg of compound **4h′** (20%).

Compound 4h′: ethyl 2-((5,6,7,8-tetrafluoro-3,4-dihydro-4-hydroxy-4-methylisoquinolin-2(1*H*)-yl)methyl)acrylate: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.29 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, H-6′); 1.66 (s, 3H, H-11); 2.60 (d, $^2J_{H-H}$ = 11.7 Hz, 1H, H-3a); 2.77 (d, $^2J_{H-H}$ = 11.7 Hz, 1H, H-3b); 3.05 (s, 1H, OH); 3.42 (d, $^2J_{H-H}$ = 14.9 Hz, 1H, H-1a); 3.45 (s, 2H, H-1′); 3.78 (d, $^2J_{H-H}$ = 15.4 Hz, 1H, H-1b); 4.21 (q, $^3J_{H-H}$ = 7.1 Hz, 2H, H-5′); 5.79 (d, $^2J_{H-H}$ = 1.,3 Hz, 1H, H-3′a); 6.33 (d, $^2J_{H-H}$ = 1.2 Hz, 1H, H-3′b). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 14.5 (CH_3, C-6′); 25.7 (d, $^4J_{C-F}$ = 6.7 Hz, CH_3, C-11); 49.8 (CH_2, C-1); 58.4 (CH_2, C-1′); 61.3 (CH_2, C-5′); 64.7 (CH_2, C-3); 69.2 (C-4); 119.2 (m, C-9); 125.0 (m, C-10); 128.1 (CH_2, C-3′); 136.8 (C-2′); 138.0, 141.7, 145.2, and 148.5 (C-5, C-6, C-7 and C-8); 166.8 (C-4′). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −140.91 (m, 1F, F-5); −145.51 (dd, $^3J_{F-F}$ = 22.6 Hz, $^4J_{F-F}$ = 14.1 Hz, 1F, F-8); −158.66 (t, $^3J_{F-F}$ = 20.8 Hz, 1F, F-6); −158.93 (t, $^3J_{F-F}$ = 20.3 Hz, 1F, F-7). MS and HRMS analyses were not performed on this compound due to its high instability.

Compound 4h″: 4,5,6,7,8-pentafluoro-1,2,3,4-tetrahydro-4-methylisoquinoline: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 250 mg of **3h′**. Purification by column chromatography (petroleum ether/ethyl acetate 70/30) afforded 111 mg of the title compound (44%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.77 (dd, $^3J_{H-F}$ = 20.1 Hz, $^5J_{H-F}$ = 1.6 Hz, 3H, H-11); 1.83 (br s, 1H, NH, H-2); 2.97 (dd, $^3J_{H-F}$ = 23.0 Hz, $^2J_{H-H}$ = 14.1 Hz, 1H, H-3); 3.30 (t, $^3J_{H-F}$ = 14.8 Hz, $^2J_{H-H}$ = 14.8 Hz, 1H, H-3); 3.80 (dd, $^2J_{H-H}$ = 17.2 Hz, $^4J_{H-F}$ = 4.2 Hz, 1H, H-1); 4.06 (d, $^3J_{H-H}$ = 17.2 Hz, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 24.3 (dd, $^2J_{C-F}$ = 27 Hz, $^4J_{C-F}$ = 7 Hz, CH_3, C-11); 42.3 (CH_2, C-1); 55.7 (d, $^2J_{H-F}$ = 25 Hz, CH_2, C-3); 87.1 (d, $^1J_{C-F}$ = 171 Hz, C-4); 120.5 (m, C-9); 121.6 (m, C-10); 141−149 (m, C-5, m, C-6, m, C-7 and m, C-8). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −134.60 (br s, 1F, F−C4); −139.05 (m, 1F, F-5); −145.70 (dd, $^3J_{F-F}$ = 22.0 Hz, $^5J_{F-F}$ = 13.0 Hz, 1F, F-8); −156.40 (tm, $^3J_{F-F}$ = 21.1 Hz, 1F, F-6); −158. 89 (t, $^3J_{F-F}$ = 20.3 Hz, 1F, F-7). MS (EI, 70 eV) *m*/*z* (rel intensity, %) 237 (44), 216 (40), 208 (100), 187 (40), 169 (22). HRMS (ESI) calcd for $C_{10}H_8NF_5$ 237.05769, found 237.0568.

Compound 4i: methyl 4-(3,4-dihydro-4-methyl-6-nitro-1-isoquinolin-2(1*H*)-yl)but-2-enoate: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 200 mg of **3i**. Purification by column chromatography (petroleum ether/ethyl acetate 90/10) afforded 102 mg of the title compound (51%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.33 (d, $^3J_{H-H}$ = 7.0 Hz, 3H, H-11); 2.42 (dd, $^2J_{H-H}$ = 11.5 Hz, $^3J_{H-H}$ = 6.5 Hz, 1H, H-3); 2.80 (dd, $^2J_{H-H}$ = 11.5 Hz, $^3J_{H-H}$ = 5.1 Hz, 1H, H-3); 3.09 (qd, $^3J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 6.5 Hz, 1H, H-4); 3.29 (d, $^3J_{H-H}$ = 6.0 Hz, 2H, H-1′); 3.67 (s, 2H, H-1); 3.72 (s, 3H, H-5′); 6.05 (dt, $^3J_{H-H\ trans}$ = 15.7 Hz, $^4J_{H-H}$ = 1.6 Hz, 1H, H-3′); 6.97 (dt, $^3J_{H-H\ trans}$ = 15.7 Hz, $^4J_{H-H}$ = 6.0 Hz, 1H, H-2′); 7.12 (d, $^3J_{H-H}$ = 8.5 Hz, 1H, H-8); 7,92 (dd, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-H}$ = 2.3 Hz, 1H, H-7); 8.06 (d, $^4J_{H-H}$ = 2.1 Hz, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 20.8 (CH_3, C-11); 33.5 (CH, C-4); 51.9 (CH_3, C-5′); 56.6 (CH_2, C-1); 57.8 (CH_2, C-3); 58.9 (CH_2, C-1′); 121.0 (CH, C-7); 123.1 (CH, C-7); 123.4 (CH, C-3′); 127.6 (CH, C-8); 141.6 (C-9 or C-10); 142.1 (C-9 or C-10); 145.1 (CH, C-2′); 147.0 (C-6); 166.8 (C-4′). MS (EI, 70 eV) *m*/*z* (rel intensity, %) 290 (16), 275 (26), 217 (28), 207 (32), 191 (53), 189 (28), 163 (38), 115 (100), 91 (37). HRMS (ESI) calcd for $C_{15}H_{18}N_2O_4$ 290.12666, found 290.1276.

Compound 6e: (5*S*)-1-(4-nitrobenzyl)-3,3-difluoro-5-methylpiperidine: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 100 mg of **5e**. Purification by column chromatography (petroleum ether/ethyl acetate 95/5) afforded 58 mg of the title compound (57%). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 0.93 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, CH_3); 1.35 (dtd, $^3J_{H\text{-}Fax}$ = 31.9 Hz, $^3J_{H-H5ax}$ and $^2J_{H-H}$ = 12.8 Hz, $^3J_{H\text{-}Feq}$ = 5.8 Hz, 1H, H-4ax); 1.79 (t, $^2J_{H-H}$ and $^3J_{H-H5ax}$ = 10.9 Hz, 1H, H-6ax); 2.03

(m, 1H, H-5); 2.16 (m, 1H, H-4eq); 2.27 (ddd, $^3J_{H\text{-}Fax}$ = 27.7 Hz, $^2J_{H-H}$ = 11.8 Hz, $^3J_{H\text{-}Feq}$ = 2.2 Hz, 1H, H-2ax); 2.77 (d, $^2J_{H-H}$ = 11.3 Hz, 1H, H-6eq); 2.99 (m, 1H, H-2eq); 3.64 (d, $^2J_{H-H}$ = 14.3 Hz, 1H, H-7); 3.70 (d, $^2J_{H-H}$ = 14.3 Hz, 1H, H-7); 7.52 (d, $^3J_{H-H}$ = 8.5 Hz, 2H, H-2′); 8.19 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 18.8 (CH_3); 28.5 (d, $^3J_{C-F}$ = 9.3 Hz, CH, C-5); 40.6 (dd, $^2J_{C-F}$ = 24.4 Hz, $^2J_{C-F}$ = 20.2 Hz, CH_2, C-4); 58.3 (dd, $^2J_{C-F}$ = 31.2 Hz, $^2J_{C-F}$ = 25.0 Hz, CH_2, C-2); 60.2 (CH_2, C-6); 61.3 (CH_2, C-7); 120.8 (dd, $^1J_{C-F}$ = 243.7 Hz, $^1J_{C-F}$ = 239.5 Hz, C-3); 124.0 (CH, C-3′); 129.6 (CH, C-2′); 146.0 (C-1′); 147.6 (C-4′). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −101.40 (d, $^2J_{F-F}$ = 241.3 Hz, Fax); −98.08 (d, $^2J_{F-F}$ = 241.3 Hz, Feq). MS (EI, 70 eV) *m*/*z* (rel intensity, %) 271 (94); 273 (18); 224 (28); 149 (100); 135 (98); 90 (38). HRMS (ESI) calcd for $C_{13}H_{16}N_2O_2F_2$ 270.11798, found 270.1183. Mp 74 °C.

Compounds 7e and 7e′. The optimized procedure (−50 °C, 3 min reaction time) was followed, starting from 400 mg of **5e**. Purification by column chromatography (petroleum ether/ethyl acetate 98/2) afforded 313 mg of the mixture **7e/7e′** (73%). A second purification of the mixture by preparative chromatography afforded pure compound **7e**.

Compound 7e: (3*R*,5*S*)-1-(4-nitrobenzyl)-3-chloro-3-fluoro-5-methylpiperidine: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.91 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, CH_3); 1.60 (ddd, $^3J_{H\text{-}Fax}$ = 26.3 Hz, $^2J_{H-H}$ or $^3J_{H-H}$ = 13.8 Hz and $^2J_{H-H}$ or $^3J_{H-H}$ = 12.5 Hz, 1H, H-4ax); 1.85 (t, $^2J_{H-H}$ and $^3J_{H-H}$ = 11.2 Hz, 1H, H-6ax); 2.12 (m, 1H, H-5); 2.49 (dd, $^3J_{H\text{-}Fax}$ = 30.0 Hz, $^2J_{H-H}$ = 12.4 Hz, 1H, H-2ax); 2.51 (m, 1H, H-4eq); 2.80 (dm, $^2J_{H-H}$ = 11.3 Hz, 1H, H-6eq); 3.28 (ddm, $^2J_{H-H}$ = 12.4 Hz, $^3J_{H\text{-}Fax}$ = 8.7 Hz, 1H, H-2eq); 3.66 (d, $^3J_{H-H}$ = 14.2 Hz, 1H, H-7); 3.72 (d, $^3J_{H-H}$ = 14.3 Hz, 1H, H-7); 7.52 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, H-2′); 8.10 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 18.7 (CH_3); 28.9 (CH, C-5); 47.3 (d, $^2J_{C-F}$ = 22.7 Hz, CH_2, C-4); 59.7 (CH_2, C-6); 60.9 (CH_2, C-7); 63.4 (d, $^2J_{C-F}$ = 21.5 Hz, CH_2, C-2); 110.4 (d, $^1J_{C-F}$ = 248.0 Hz, C-3); 124.0 (CH, C-2′); 129.5 (CH, C-3′); 146.0 (C-1′); 147.6 (C-4′). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −109.06.MS (EI, 70 eV) *m*/*z* (rel intensity, %) 289 (37), 287 (100). HRMS (ESI) calcd for $C_{13}H_{16}N_2O_2F^{35}Cl$ 286.08843, found 286.0877. Mp 71 °C.

Compound 6f: (5*S*)-3,3-difluoro-1,5-dimethylpiperidine: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 220 mg of **5f**. Purification by column chromatography (dichloromethane) afforded 57 mg of the title compound (25%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.95 (d, $^3J_{H-H}$ = 6.6 Hz, 3H, CH_3); 1.28 (dtd, $^3J_{H\text{-}Fax}$ = 32.8 Hz, $^3J_{H-H}$ and $^2J_{H-H}$ = 12.9 Hz, $^3J_{H\text{-}Feq}$ = 6.2 Hz, 1H, H-4ax); 1.63 (t, $^2J_{H-H}$ and $^3J_{H-H}$ = 11.0 Hz, 1H, H-6ax); 1.99 (m, 1H, H-5); 2.01 (m, 1H, H-4eq); 2.12 (ddd, $^3J_{H\text{-}Fax}$ = 27.8 Hz, $^2J_{H-H}$ = 11.8 Hz, $^3J_{H\text{-}Feq}$ = 3.1 Hz, 1H, H-2ax); 2.32 (s, 3H, N−CH_3); 2.79 (dm, $^2J_{H-H}$ = 11.0 Hz, 1H, H-6eq); 3.01 (tm, $^2J_{H-H}$ and $^3J_{H\text{-}Fax}$ = 11.4 Hz, 1H, H-2eq). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 18.9 (CH_3); 28.7 (d, $^3J_{C-F}$ = 9.5 Hz, CH, C-5); 40.2 (dd, $^2J_{C-F}$ = 24.6 Hz, $^2J_{C-F}$ = 20.1 Hz, CH_2, C-4); 45.9 (N−CH_3); 60.5 (dd, $^2J_{C-F}$ = 30.3 Hz, $^2J_{C-F}$ = 24.5 Hz, CH_2, C-2); 62.5 (CH_2, C-6); 120.9 (dd, $^1J_{C-F}$ = 242.9 Hz, $^1J_{C-F}$ = 239.3 Hz, C-3). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −104.41 (d, $^2J_{F-F}$ = 242.0 Hz, Fax); −98.65 (d, $^2J_{F-F}$ = 242.1 Hz, Feq). MS and HRMS analyses were not performed on this compound due to its high volatility.

Compounds 7f and 7f′. The optimized procedure (−50 °C, 3 min reaction time) was followed, starting from 200 mg of **5f**. Purification by column chromatography (dichloromethane) afforded 13 mg of compound **7f′** (6%).

Compound 7f′: (3*S*,5*S*)-3-chloro-3-fluoro-1,5-dimethylpiperidine: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.96 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, CH_3); 1.50 (ddd, $^2J_{H-H}$ = 13.0 Hz, $^3J_{H-H}$ = 11.9 Hz, $^3J_{H\text{-}Feq}$ = 9.5 Hz, 1H, H-4ax); 1.67 (dd, $^2J_{H-H}$ = 12.2 Hz, $^3J_{H-H}$ = 9.8 Hz, 1H, H-6ax); 2.10 (m, 1H, H-5); 2.27 (dd, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H\text{-}Feq}$ = 5.3 Hz, 1H, H-2ax); 2.34 (m, 1H, H-4eq); 2.35 (s, 3H, N−CH_3); 2.82 (dm, $^2J_{H-H}$ = 11.4 Hz, 1H, H-6eq); 3.16 (dm, $^2J_{H-H}$ = 11.6 Hz, 1H, H-2eq). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 18.3 (CH_3); 28.9 (d, $^3J_{C-F}$ = 8.3 Hz, CH, C-5); 45.5 (N−CH_3); 46.0 (d, $^2J_{C-F}$ = 17.7 Hz, CH_2, C-4); 62.5 (CH_2, C-6); 65.5 (d, $^2J_{C-F}$ = 27.3 Hz, CH_2, C-2); 111.8 (d, $^1J_{C-F}$ = 241.5 Hz, C-3). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −99.80. MS and HRMS analyses were not performed on this compound due to its high volatility.

Then, dichloromethane afforded 26 mg of compound **7f** (26%).

Compound 7f: (3*R*,5*S*)-3-chloro-3-fluoro-1,5-dimethylpiperidine: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.90 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, CH_3); 1.49 (ddd, $^3J_{H\text{-}Fax}$ = 36.4 Hz, $^3J_{H-H}$ or $^2J_{H-H}$ = 13.8 Hz, $^3J_{H-H}$ or $^2J_{H-H}$ = 12.6 Hz, 1H, H-4ax); 1.61 (td, $^2J_{H-H}$ = 11.2 Hz$^3J_{H-H}$ = 11.2 Hz and $^4J_{H-H}$ = 1.5 Hz, 1H, H-6ax); 2.05 (m, 1H, H-5); 2.30 (s, 3H, N−CH_3); 2.30 (dd, $^3J_{H\text{-}Fax}$ = 30.0 Hz, $^2J_{H-H}$ = 12.4 Hz, 1H, H-2ax); 2.46 (m, 1H, H-4eq); 2.81 (dm, $^2J_{H-H}$ = 11.4 Hz, 1H, H-6eq); 3.28 (tm, $^3J_{H\text{-}Fax}$ and $^2J_{H-H}$ = 10.5 Hz, 1H, H-2eq). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 18.4 (CH_3); 29.8 (CH, C-5); 45.3 (N−CH_3); 46.5 (d, $^2J_{C-F}$ = 22.7 Hz, CH_2, C-4); 61.8 (CH_2, C-6); 65.3 (d, $^2J_{C-F}$ = 21.1 Hz, CH_2, C-2); 110.0 (d, $^1J_{C-F}$ = 247.1 Hz, C-3). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −108.80. MS and HRMS analyses were not performed on this compound due to its high volatility.

Compound 6g: (5*S*)-3,3-difluoro-1-isopropyl-5-methylpiperidine: The optimized procedure (0 °C, 3 min reaction time) was followed, starting from 120 mg of **5g**. Purification by column chromatography (petroleum ether/ethyl acetate 95/5) afforded 40 mg of the title compound (33%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.93 (d, $^3J_{H-H}$ = 6.4 Hz, 3H, H-9); 1.01 (d, $^3J_{H-H}$ = 6.6 Hz, 3H, H-8 or H-8′); 1.03 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, H-8 or H-8′); 1.28 (dtd, $^3J_{H\text{-}Fax}$ = 31.4 Hz, $^3J_{H-H}$ and $^2J_{H-H}$ = 12.8 Hz, $^3J_{H\text{-}Feq}$ = 5.9 Hz, 1H, H-4ax); 1.81 (td, $^2J_{H-H}$ and $^3J_{H-H}$ = 10.7 Hz, $^4J_{H-H}$ = 1.3 Hz, 1H, H-6ax); 1.91 (m, 1H, H-5); 2.11 (m, 1H, H-4eq); 2.28 (ddd, $^3J_{H\text{-}Fax}$ = 27.8 Hz, $^2J_{H-H}$ = 11.6 Hz, $^3J_{H\text{-}Feq}$ = 2.9 Hz, 1H, H-2ax); 2.76 (d, $^2J_{H-H}$ = 10.0 Hz, 1H, H-6eq); 2.81 (m, 1H, H-7); 2.99 (m, 1H, H-2eq). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 17.3 (CH_3, C-9); 18.4 (CH_3, C-8 or C-8′); 18.7 (CH_3, C-8 or C-8′); 28.6 (d, $^3J_{C-F}$ = 9.6 Hz, CH, C-5); 40.7 (dd, $^2J_{C-F}$ = 24.6 Hz, $^2J_{C-F}$ = 20.1 Hz, CH_2, C-4); 53.5 (dd, $^2J_{C-F}$ = 24.6 Hz, $^2J_{C-F}$ = 20.1 Hz, CH_2, C-2); 53.9 (CH, C-7); 56.0 (CH_2, C-6); 121.1 (dd, $^1J_{C-F}$ = 243.4 Hz, $^1J_{C-F}$ = 238.6 Hz, C-3). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −97.60 (d, $^2J_{F-F}$ = 238.1 Hz, Feq); −101.25 (d, $^2J_{F-F}$ = 238.1 Hz, Fax). MS (EI, 70 eV) *m*/*z* (rel intensity, %) 162 (2) M-CH_3; 128 (4); 99 (8); 28 (100). HRMS (ESI) calcd for $C_8H_{14}NF_2$ 162.10943, found 162.1105.

Compounds 7g and 7g′. The optimized procedure (−50 °C, 3 min reaction time) was followed, starting from 175 mg of **5g**. Purification by column chromatography (petroleum ether/ethyl acetate 99/1) afforded 15 mg of compound **7g′** (8%).

Compound 7g′: (3*S*,5*S*)-3-chloro-3-fluoro-1-isopropyl-5-methylpiperidine: ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 0.94 (d, $^3J_{H-H}$ = 6.5 Hz, 3H, CH_3); 0.99 (d, $^3J_{H-H}$ = 6.5 Hz, 3H, H-8 or H-8′); 1.06 (d, $^3J_{H-H}$ = 6.6 Hz, 3H, H-8 or H-8′); 1.52 (ddd, *J* = 13.0 Hz, *J* = 11.4 Hz, *J* = 9.9 Hz, 1H, H-4ax); 1.90 (t, $^3J_{H-H}$ and $^2J_{H-H}$ = 10.6 Hz, 1H, H-6ax); 2.02 (m, 1H, H-5); 2.35 (dm, $^2J_{H-H}$ = 13.1 Hz, 1H, H-4eq); 2.43 (dd, $^2J_{H-H}$ = 11.5 Hz, $^3J_{H\text{-}Feq}$ = 5.2 Hz, 1H, H-2ax); 2.76 (dm, $^2J_{H-H}$ = 10.8 Hz, 1H, H-6eq); 2.89 (m, 1H, H-7); 3.14 (dm, $^2J_{H-H}$ = 11.5 Hz, 1H, H-2eq). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 17.1 (CH_3, C-8 or C-8′); 18.8 (CH_3, C-9); 19.5 (CH_3, C-8 or C-8′); 29.5 (d,

$^3J_{C-F}$ = 8.3 Hz, CH, C-5); 47.4 (d, $^2J_{C-F}$ = 17.9 Hz, CH_2, C-4); 54.3 (CH, C-7); 57.2 (CH_2, C-6); 58.7 (d, $^2J_{C-F}$ = 27.8 Hz, CH_2, C-2); 113.2 (d, $^1J_{C-F}$ = 241.1 Hz, C-3). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −98.79. MS (EI, 70 eV) *m/z* (rel intensity, %) 180 (39); 178 (100); 158 (21); 69 (23). HRMS (ESI) calcd for $C_8H_{14}NF^{35}Cl$ 178.07988, found 178.0808.

Then, petroleum ether/ethyl acetate 98/2 afforded 57 mg of compound **7g** (29%).

Compound 7g: (3*R*,5*S*)-3-chloro-3-fluoro-1-isopropyl-5-methylpiperidine: ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 0.91 (d, $^3J_{H-H}$ = 6.6 Hz, 3H, CH_3); 1.02 (d, $^3J_{H-H}$ = 6.6 Hz, 3H, H-8 or H-8′); 1.05 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, H-8 or H-8′); 1.53 (ddd, $^3J_{H\text{-}Fax}$ = 36.4 Hz, $^3J_{H-H}$ or $^2J_{H-H}$ = 13.7 Hz, $^3J_{H-H}$ or $^2J_{H-H}$ = 12.5 Hz, 1H, H-4ax); 1.83 (td, $^2J_{H-H}$ and $^3J_{H-H}$ = 11.0 Hz, $^4J_{H-H}$ = 1.8 Hz, 1H, H-6ax); 2.01 (m, 1H, H-5); 2.48 (m, 1H, H-4eq); 2.51 (dd, $^3J_{H\text{-}Fax}$ = 29.4 Hz, $^2J_{H-H}$ = 12.2 Hz, 1H, H-2ax); 2.80 (m, 1H, H-6eq); 2.83 (m, 1H, H-7); 3.30 (m, 1H, H-2eq). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 17.5 (CH_3, C-9); 18.4 (CH_3, C-8 or C-8′); 18.6 (CH_3, C-8 or C-8′); 29.4 (CH, C-5); 47.7 (d, $^2J_{C-F}$ = 23.1 Hz, CH_2, C-4); 54.0 (CH, C-7); 55.7 (CH_2, C-6); 59.1 (d, $^2J_{C-F}$ = 20.9 Hz, CH_2, C-2); 111.0 (d, $^1J_{C-F}$ = 248.1 Hz, C-3). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −108.60. MS (EI, 70 eV) *m/z* (rel intensity, %) 180 (39); 178 (100); 158 (21); 69 (23). HRMS (ESI) calcd for $C_8H_{14}NF^{35}Cl$ 178.07988, found 178.0808.

Compounds 6h, 6h′, 7h, 7h′, and 8h. The optimized procedure (−50 °C, 3 min reaction time) was followed, starting from 200 mg of **5h**. Purification by column chromatography (petroleum ether/ethyl acetate 98/2) afforded 41 mg of compound **6h′** (19%).

Compound 6h′: (3*S*,5*S*)-1-(4-nitrobenzyl)-3,5-dichloro-3-fluoro-5-methylpiperidine: ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.63 (s, 3H, H-8); 2.32 (dd, $^3J_{H\text{-}Fax}$ = 25.3 Hz, $^2J_{H-H}$ = 15.2 Hz, 1H, H-4ax); 2.46 (d, $^2J_{H-H}$ = 12.6 Hz, 1H, H-6ax); 2.78 (dd, $^3J_{H\text{-}Fax}$ = 28.5 Hz, $^2J_{H-H}$ = 13.8 Hz, 1H, H-2ax); 2.83 (t, $^2J_{H-H}$ = 12.5 Hz, $^3J_{H\text{-}Fax}$ = 12.5 Hz, 1H, H-4eq); 2.90 (d, $^2J_{H-H}$ = 12.2 Hz, 1H, H-6eq); 3.24 (t, $^2J_{H-H}$ = 11.0 Hz, $^3J_{H\text{-}Fax}$ = 10.8 Hz, 1H, H-2eq); 3.76 (d, $^2J_{H-H}$ = 14.7 Hz, 1H, H-7); 3.86 (d, $^2J_{H-H}$ = 14.6 Hz, 1H, H-7); 7.60 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, H-2′); 8.19 (d, $^3J_{H-H}$ = 8.7 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 30.9 (CH_3, C-8); 51.9 (d, $^2J_{C-F}$ = 21.4 Hz, CH_2, C-4); 59.9 (CH_2, C-7); 63.2 (d, $^2J_{C-F}$ = 23.6 Hz, CH_2, C-2); 64.2 (C-5); 64.5 (CH_2, C-6); 108.2 (d, $^1J_{C-F}$ = 251.7 Hz, C-3); 123.7 (CH, C-3′); 129.1 (CH, C-2′); 145.0 (C-1′); 147.4 (C-4′). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −103,33. MS (ESI, 70 eV) *m/z* (rel intensity, %) 343(14); 321 (52); 285 (100); 265 (19). HRMS (ESI) calcd for $C_{13}H_{16}N_2O_2F^{35}Cl_2$ 321.05729, found 321.0570. Mp 125 °C.

Then, petroleum ether/ethyl acetate 95/5 afforded 13 mg of compound **7h′** (7%).

Compound 7h′: (3*R*)-1-(4-nitrobenzyl)-5-chloro-3-fluoro-1,2,3,6-tetrahydro-3-methylpyridine. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 1.42 (d, $^3J_{H-F}$ = 20.5 Hz, 3H, H-8); 2.48 (dd, $^3J_{H-F}$ = 23.3 Hz, $^2J_{H-H}$ = 12.5 Hz, 1H, H-2); 2.91 (t, $^2J_{H-H}$ = 12.5 Hz and $^3J_{H-F}$ = 12.5 Hz, H-2); 3.10 (dd, $^2J_{H-H}$ = 16.3 Hz, $^4J_{H-H}$ = 9.7 Hz, 1H, H-6); 3.26 (dd, $^2J_{H-H}$ = 16.3 Hz, $^4J_{H-H}$ = 7.2 Hz, 1H, H-6): 3.75 (d, $^2J_{H-H}$ = 14.4 Hz, 1H, H-7); 3.83 (d, $^2J_{H-H}$ = 14.3 Hz, 1H, H-7); 5.93 (bs, 1H, H-4); 7.53 (d, $^3J_{H-H}$ = 8.4 Hz, 2H, H-2'); 8.18 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 24.9 (d, $^2J_{C-F}$ = 27.7 Hz, CH_3, C-8); 57.0 (d, $^4J_{C-F}$ = 2.6 Hz, CH_2, C-6); 58.9 (d, $^2J_{C-F}$ = 23.9 Hz, CH_2, C-2); 59.8 (CH_2, C-7); 90.5 (d, $^1J_{C-F}$ = 169.7 Hz, C-3); 123.7 (CH, C-3′); 125.4 (d, $^2J_{C-F}$ = 22.0 Hz, CH, C-4); 129.2 (CH, C-2'); 135.5 (d, $^3J_{C-F}$ = 12.6 Hz, C-5); 145.1 (C-1′); 147.4 (C-4′). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −139.45. MS (EI, 70 eV) *m/z* (rel intensity, %) 286 (13); 284 (25); 165 (22); 135 (33); 121 (42); 119 (100). HRMS (ESI)calcd for $C_{13}H_{14}N_2O_2F^{35}Cl$ 284.07278, found 284.0732.

Then, petroleum ether/ethyl acetate 90/10 afforded 57 mg of compound **6h** (28%).

Compound 6h: (3*S*,5*S*)-1-(4-nitrobenzyl)-3-chloro-3,5-difluoro-5-methylpiperidine: ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.35 (d, $^3J_{H\text{-}Fax}$ = 20.7 Hz, 3H, H-8); 2.10 (ddd, $^3J_{H\text{-}Fax}$ = 34.8 Hz, $^3J_{H\text{-}Fax}$ = 33.4 Hz, $^2J_{H-H}$ = 16.7 Hz, 1H, H-4ax); 2.37 (dd, $^3J_{H\text{-}Fax}$ = 31.9 Hz, $^2J_{H-H}$ = 13.1 Hz, 1H, H-6ax); 2.72 (dd, $^3J_{H\text{-}Fax}$ = 28.9 Hz, $^2J_{H-H}$ = 13.0 Hz, 1H, H-2ax); 2.83 (qm, $^2J_{H-H}$ = 13.2 Hz, $^3J_{H\text{-}Fax}$ = 13.2 Hz and $^3J_{H\text{-}Fax}$ = 13.2 Hz, 1H, H-4eq); 2.97 (bt, $^2J_{H-H}$ = 11.5 Hz, $^3J_{H\text{-}Fax}$ = 11.5 Hz, 1H, H-6eq); 3.34 (bt, $^2J_{H-H}$ = 11.1 Hz, $^3J_{H\text{-}Fax}$ = 11.1 Hz, 1H, H-2eq); 3.87 (s, 2H, H-7); 7.55 (d, $^3J_{H-H}$ = 8.5 Hz, H-2′); 8.18 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 25.0 (d, $^2J_{C-F}$ = 28.8 Hz, CH_3, C-8); 48.0 (t, $^2J_{C-F}$ = 22.3 Hz, CH_2, C-4); 59.6 (d, $^2J_{C-F}$ = 21.0 Hz, CH_2, C-6); 59.7 (CH_2, C-7); 62.1 (d, $^2J_{C-F}$ = 22.1 Hz, CH_2, C-2); 91.8 (d, $^1J_{C-F}$ = 177.6 Hz, C-5); 108.6 (d, $^1J_{C-F}$ = 252.0 Hz, C-3); 123.6 (CH, C-3′); 129.2 (CH C-2′); 145.2 (C-1′); 147.3 (C-4′). $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δ_F −162.90 ppm), ppm) −105.53 (F-CCl); −148.82 (F-CCH_3). HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2F_2^{35}Cl$ 304.07901, found 304.0777. Mp 123 °C.

Then, petroleum ether/ethyl acetate 80/20 afforded 7 mg of compound **7h** (4%).

Compound 7h: (3*R*)-1-(4-nitrobenzyl)-5-chloro-1,2,3,6-tetrahydro-3-methylpyridin-3-ol: ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.24 (s, 3H, H-8); 2.31 (d, $^2J_{H-H}$ = 11.3 Hz, 1H, H-2_{ax}); 2.61 (br s, 1H, OH); 2.69 (d, $^2J_{H-H}$ = 11.3 Hz, 1H, H-2_{eq}); 2.92 (d, $^2J_{H-H}$ = 16.1 Hz, 1H, H-6_{ax}); 3.24 (d, $^2J_{H-H}$ = 16.0 Hz, 1H, H-6_{eq}); 3.74 (s, 2H, H-7); 5.86 (s, 1H, H-4); 7.52 (d, $^3J_{H-H}$ = 8.4 Hz, 2H, H-2′); 8.20 (d, $^3J_{H-H}$ = 8.4 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 24.7 (CH_3, C-8); 57.6 (CH_2, C-6); 60.7 (CH_2, C-7); 62.3 (CH_2, C-2); 68.6 (C-3); 123.8 (CH, C-3′); 129.5 (CH, C-2′); 130.0 (CH, C-4); 131.5 (C-5); 144.9 (C-1′); 147.4 (C-4′). MS (EI, 70 eV) *m/z* (rel intensity, %) 282 (2); 161 (100); 133 (19); 118 (20); 116 (49); 103 (17); 101 (43). HRMS (ESI) calcd for $C_{13}H_{15}N_2O_3^{35}Cl$ 282.07712, found 282.0746.

Then, petroleum ether/ethyl acetate 50/50 afforded 8 mg of compound **8h** (5%).

Compound 8h: 1-(4-nitrobenzyl)-1,2-dihydro-5-methylpyridin-3(6*H*)-one (20%): ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.95 (s, 3H, H-8); 3.11 (s, 2H, H-2); 3.17 (s, 2H, H-6); 3.74 (s, 2H, H-7); 5.97 (q, $^4J_{H-H}$ = 1.4 Hz, 1H, H-4); 7.51 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, H-2′); 8.18 (d, $^3J_{H-H}$ = 8.8 Hz, 2H, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 21.7 (CH_3, C-8); 56.3 (CH_2, C-6); 60.2 (CH_2, C-2); 60.6 (CH_2, C-7); 123.6 (CH, C-3′); 125.0 (CH, C-4); 129.5 (CH, C-2′); 144.6 (C-1′); 147.4 (C-4′); 160.2 (C-3); 195.1 (C-5). MS (EI, 70 eV) *m/z* (rel intensity, %) 246 (10); 136 (11); 111 (19); 83 (89). HRMS (ESI) calcd for $C_{13}H_{14}N_2O_3$ 246.10044, found 246.0983.

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Supporting Information Available: Experimental details, spectral data, and copies of ^1H and ^{13}C NMR spectra for all new compounds and X-ray structure and crystal data for compounds **2b**, **6e**, **7e**, **6h** and **6h′**. This material is available free of charge via the Internet at http://pubs.acs.org.