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Reaction Mechanisms

Elemental F_2 with Transannular Dienes: Regioselectivities and Mechanisms

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Abstract: Three reaction paths, namely, molecule-induced homolytic, free radical, and electrophilic, were modeled computationally at the MP2 level of ab initio theory and studied experimentally for the reaction of F_2 with the terminal dienes of bicyclo[3.3.1]nonane series. The addition of fluorine is accompanied by transannular cyclization to the adamantane derivatives in which strong evidence for the electrophilic mechanism both in nucleophilic (acetonitrile) and non-nucleophilic ($CFCl_3$, $CHCl_3$) solvents were found. The presence of KF in $CFCl_3$ and $CHCl_3$ facilitates the addition and substantially reduces the formation of tar products.

Introduction

The preparations of fluorine-containing organic compounds for medicinal,[1] polymer,[2] and material[3] applications usually utilize a large variety of fluorinating agents[4] rather than direct fluorinations with elementary F_2.[5] Exponentially growing attention to direct fluorinations of unsaturated systems is associated with the development of the new electronic materials based on fullerenes,[6] nanotubes,[7] and in particular, graphenes.[8] However, the addition of fluorine mechanistically is not well understood: The simplest prototypical $F_2 + H_2C{=}CH_2$ reaction still puzzles theoreticians due to substantial discrepancies between the computed and experimental (5.5 ± 0.5 kcal mol^{-1})[9] barriers. Already, earlier studies have ruled out both concerted[10] and nonconcerted[11] addition mechanisms due to the high computed barriers of 51 and 23 kcal mol^{-1}, respectively. The more realistic C_s symmetric (close to C_{2v}) transition structure (**TS1**, Figure 1) for the F_2 attack on the C=C bond was located at many levels. However, all DFT and high-level ab initio methods are not able to reproduce the experimental barrier (from $+1.8$ kcal mol^{-1} at B3LYP to $+6.3$ kcal mol^{-1} at BHH with aug-cc-pVTZ basis set),[12] and overestimate it by 1.6 and 2.5 kcal mol^{-1} at CASPT2[9] and CCSD(T),[13] respectively. The problem may arise from the fact that due to low dissociation energy of fluorine (37 kcal mol^{-1}) the $F_2 + H_2C{=}CH_2$ reaction proceeds through the molecule-induced homolysis, that is, with the formation[14] of two radical species ($F^{\bullet}$ and $^{\bullet}CH_2{-}CH_2F$) at the first reaction step (see below). This mechanism, which was confirmed[9] for the gas phase by crossed beam experiments, is difficult to validate computationally. Although, it was demonstrated that single-reference computational approaches such as CCSD, CCSD(T), and MP2 are trustworthy,[9,13] the open-shell states may develop on route to the F_2 attack and cause

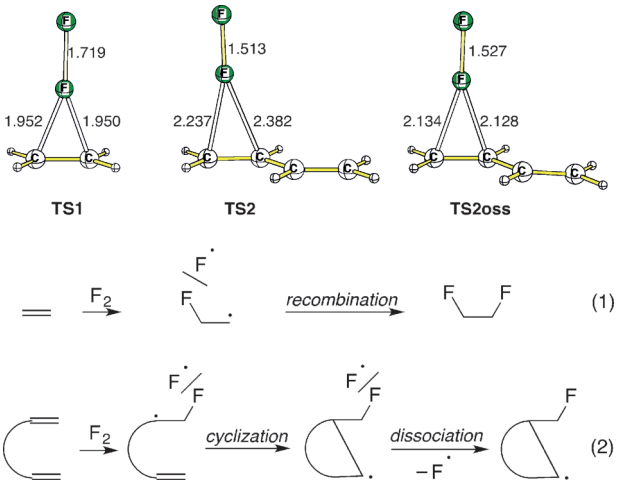

Figure 1. The MP2/aug-cc-pVTZ-optimized transition structures for the attack of molecular fluorine on ethylene (**TS1**) and 1,3-butadiene (**TS2**) as well as molecular-induced homolytic 1,2- [Eq. (1)] and transannular [Eq. (2)] additions of elemental fluorine to the unsaturated systems.

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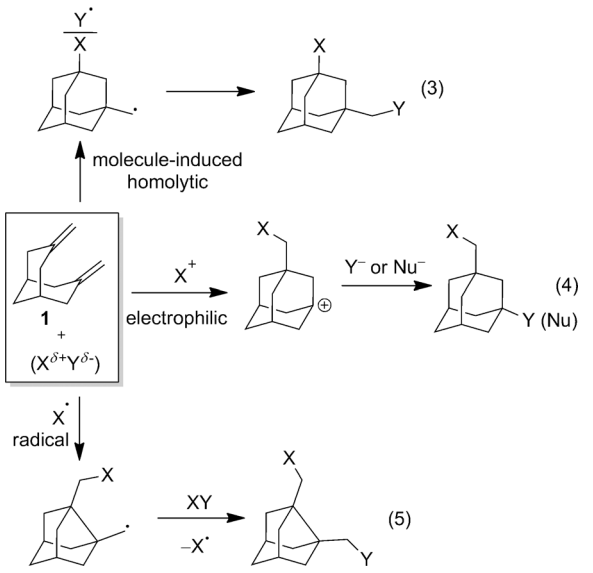
discrepancies between the experimental and theoretical data. Whereas the attack of F_2 on $H_2C{=}CH_2$ occurs on the singlet surface cleanly (our **TS1** reoptimized[15] as the open-shell singlet is identical geometrically and energetically to the closed-shell singlet structure), the situation with other olefins is clearly different. For instance, already for 1,3-butadiene the closed-shell singlet transition structure (**TS2**, Figure 1) is distinctly different from the one reoptimized as the open-shell singlet (**TS2oss**, Figure 1) due to much higher spin separations.

The experimental mechanistic studies of the homolytic reaction paths are also complicated because the F radical, which is released from the diradical intermediate, may cause parallel free-radical processes, resulting in the same $CH_2F{-}CH_2F$ product as expected from the molecular homolysis-rebound mechanism. Alkyl substituents increase the reactivity of the C=C double bond and create additional reaction channels associated with HF elimination.[16] As a consequence, the primary reaction channel is hard to determine experimentally for propylene, cyclohexene, and butadiene as they react spontaneously with F_2 even at 15 K.[17,18] Again, high-level ab initio computations overestimate the experimental reaction barriers systematically.[9]

In the condensed state the fluorination occurs under the strong influence of solvent in which the electrophilic addition of fluorine was postulated.[19] At low temperatures a very diluted stream of fluorine promotes this mechanism in polar solvents (C_2H_5OH and AcOH) resulting in *syn*-addition of F_2 to the double bonds. However, such stereochemistry also may be attributed to the homolytic mechanism due to difficulties in the diffusion of F atom.[11, 12] Such contradictions make the stereochemical results insufficient for the mechanistic studies.

Generally, for 1,2-addition it is rather difficult to identify the molecule-induced homolytic channel, because the biradical states, even if formed, are very tightly bound and may recombine rapidly ([Eq. (1)], Figure 1). One can expect that the situation with the transannular addition is distinctly different as the cyclization, which follows the fluorine attack, separates the radical centers spatially and may hamper the rebound ([Eq. (2)], Figure 1). The most pronounced effects may be expected for relatively rigid transannulated systems like unsaturated 3,7-derivatives of bicyclo[3.3.1]nonane.[20] With electron-deficient reagents, the bicyclo[3.3.1]nonane dienes usually undergo transannular cyclizations to adamantane or noradamantane derivatives depending on the reagent employed.[21] Herein, we present a combined experimental and computational study on the reaction of F_2 with dienes of bicyclo[3.3.1]nonane series that allows one to distinguish between the free radical, molecule-induced homolytic, and electrophilic addition modes already on the structures of products (Scheme 1). Distinctly different results are expected for the molecular-induced homolytic ([Eq. (3)], Scheme 1) and electrophilic ([Eq. (4)], Scheme 1) additions that give differently substituted adamantane derivatives. For the free-radical additions, the formation of noradamantane derivatives is characteristic ([Eq. (5)], Scheme 1).



Scheme 1. Products expected form the addition of the reagent XY to 3,7-dimethylenebicyclo[3.3.1]nonane (**1**).

Results and Discussion

Molecule-induced homolytic reaction of diene 1 + F_2

We first computed the reaction of 3,7-dimethylenebicyclo-[3.3.1]nonane (**1**) with elemental fluorine at the MP2/6-31+G* level of theory. We have chosen this method because of the size of the systems and the fact that the MP2 results parallel the most trusted CCSD(T) computations for the $F_2 + H_2C{=}CH_2$ reaction.[11] The DFT functionals were not considered because the discrepancies with the experiment for this reaction are too high.[12,22] At MP2/6-31+G* the reaction starts with the exothermic (18.7 kcal mol^{-1}) formation of the entrance complex **MIN1** (Figure 2). Further reaction may proceed either as 1,2-addition through **TS3**, or as a synchronous transannular cyclization though **TS4**. Despite the first reaction, which gives the 1,2-adduct **MIN2**, is highly exothermic (−103.9 kcal mol^{-1}) it is characterized by relatively high barrier of 14.2 kcal mol^{-1} and the cyclization through **TS4** ($\Delta H_{298}^{\neq} = 10.5$ kcal mol^{-1}) is about 4 kcal mol^{-1} more favorable than the 1,2-addition. This reaction path is accompanied by substantial spin/charge delocalizations within a number of carbon atoms of the cage and resulted in the formation of two radicals (**MIN3**). The fact that substantial spin separation occurs on route the cyclization, arises from the reoptimization of **TS4** as open-shell singlet that led, in contrast to **TS1** (see above), to the entirely different structure **TS4oss**. This structure features the molecule-induced homolytic path as the F–F bond is almost broken (2.549 Å). This open-shell singlet state is very close energetically and structurally to the triplet **TS4T**, indicating the possibility of almost complete spin separation already at the early stages of the cyclization to the adamantane structure. Although the open-shell states are about 5 kcal mol^{-1} higher in energy than the close shell **TS4**, the homolytic path may be followed in the condensed state, in which charge separations are favored: We found a substantial

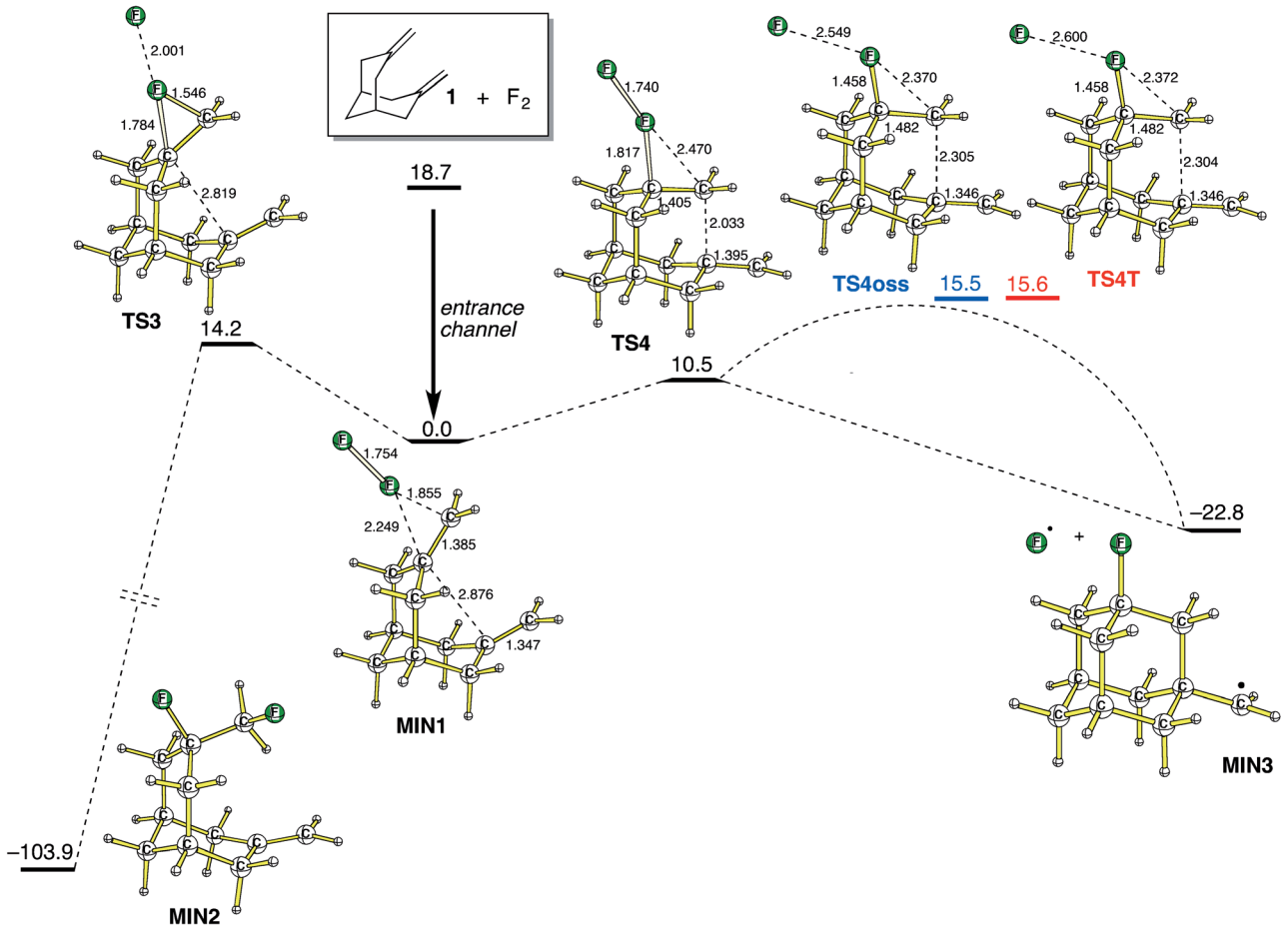


Figure 2. The MP2/6-31+G* stationary points for reaction of 3,7-dimethylenebicyclo[3.3.1]nonane (**1**) with F_2 (critical bond lengths [Å] and relative ΔH_{298} [kcal mol^{-1}]).

negative charge (0.55 e) accumulated on the "outer" fluorine in **TS4**.

Computations clearly show that the transannular cyclization is more favorable than the 1,2-addition of F_2 to **1** and may occur as a molecule-induced homolysis, in which, due to large spatial spin separations, the F radical may eliminate, causing side free-radical processes. Thus, we modeled the possible outcome of the reaction between **1** and the F radical.

Homolytic reaction of 1 and the F radical

Fortunately, compound **1** allows us distinguish between the radical and non-radical addition modes because the reaction of **1** with radicals gives noradamantane derivatives predominantly,[20c,21b] in contrast to the reactions with electrophiles that lead to substituted adamantanes.[21a,23] We found that this is indeed true for treatment of **1** with the F radical (Figure 3). The F-radical attack on **1** is exothermic by 46.6 kcal mol^{-1} and gives the intermediate radical **MIN4**. Further exothermic cyclizations of this radical may give either substituted adamantyl (**MIN5**) or noradamantyl (**MIN6**) radicals through **TS5** and **TS6**, respectively. The cyclization to noradamantane **MIN6** is characterized by substantially lower barrier (9.8 kcal mol^{-1}) implying that if the F radical would participate in the side free-radical reactions with **1**, the formation of noradamantane derivatives is expected.

In contrast, the formation of adamantane derivatives would provide strong evidence against the participation of the F radical in the fluorinations with F_2.

Electrophilic addition of F_2 to 1

In accordance to the experimental data, the attack of the electrophilic reagent X^+ on **1** is always directed on the terminal carbon atoms resulting in the X-methyladamantyl derivatives (Scheme 1, [Eq. (4)]). The main driving force of this reaction is the formation of stable tertiary adamantyl cations. We computed the electrophilic transannular cyclization of **1** with the complex $F^+\cdots H_2O$ to model the transfer of hypothetical "F^+" from the solvent to the double bond of **1**. The reaction is highly exothermic and the transition structure for the "F^+" transfer (**TS7**) is located 86.3 kcal mol^{-1} below the reactants. The attack of fluorine is accompanied by the participation of both double bonds of **1** that is viewed from the changes in the C=C and non-valent sp^2C–sp^2C distances in **TS7** versus those in diene **1** (Figure 4). The transannular cyclization downhill from **TS7**

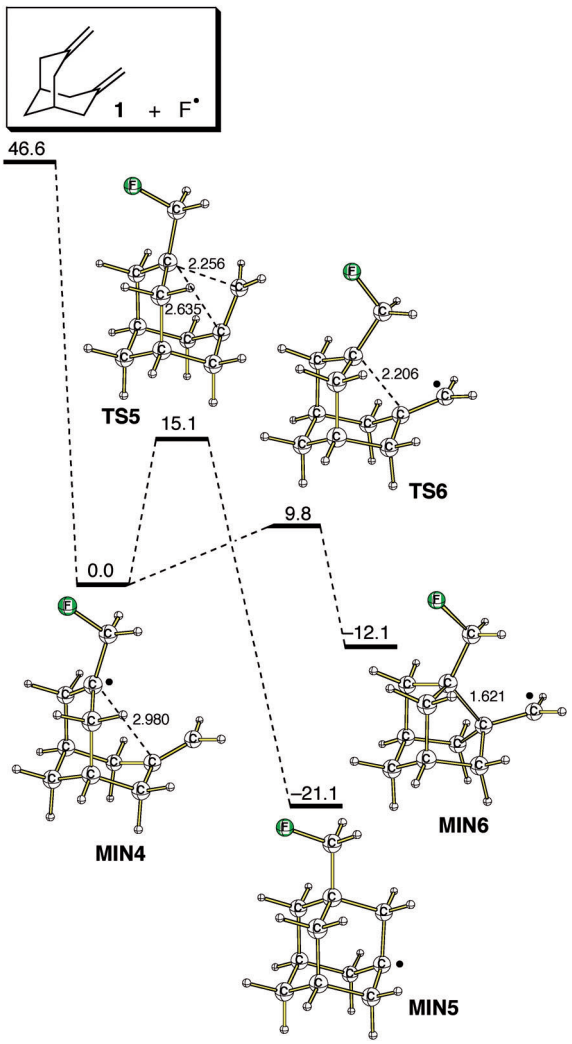


Figure 3. The MP2/6-31+G* stationary points for reaction of 3,7-dimethylenebicyclo[3.3.1]nonane (**1**) with the F radical (critical bond lengths [Å] and relative ΔH_{298} [kcal mol^{-1}]).

leads to the fluoromethyl-adamantyl cation **MIN7** complex with water additionally releasing about 95 kcal mol^{-1} of energy. Based on the high overall 181.4 kcal mol^{-1} exothermicity for the electrophilic addition to **1**, one should expect the formation of adamantane derivatives exclusively. Questioning the positional selectivities, we modeled this reaction for unsymmetrical diene **1a** (Figure 4) and found that the differences between the attack of fluorine onto the methylene (path ***A***) and ethylidene fragments (path ***B***) are negligible. This is in sharp contrast to the transannular cyclization of **1a** with uncharged electrophile {1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)} (F-TEDA-BF_4), in which the attack on the substituted double bond of **1a** is favored energetically and agrees nicely with the experimentally observed selectivity.[20a] Thus, any pronounced regioselectivities for the fluorinations of **1a** through the electrophilic Scheme are not expected.

Experimental fluorinations of the dienes of bicyclo-[3.3.1]nonane series

The reaction of **1** with elemental fluorine highly diluted with nitrogen was studied at −78 °C in the solution of $CFCl_3$ or its 1:1 mixture with $CHCl_3$. The fluorination in pure $CFCl_3$ gave difluoro- (**2**) and monofluoro (**3**) adamantane derivatives in low yields and was accompanied by the formation of tar products complicating the mechanistic findings. When $CHCl_3$ is present in the reaction mixture, the difluoride **2** and the monofluoride **3** were isolated in high preparative yield (Scheme 1), which is attributed to the fluorination with HF formed from the reaction of $CHCl_3$ with F_2.[24] The formation of difluoride **2** may be in accord with electrophilic reaction path (Scheme 1, [Eq. (4)], X = Y = F), in which the intermediate 1-fluoromethyl-adamant-3-yl cation is trapped with HF. As the side nucleophiles may trap the cationic intermediates (if formed) more efficiently, we have first tested the influence of KF on the fluorination in the $CFCl_3$/$CHCl_3$ system and indeed found that the relative amount of the difluoride **2** increases (Scheme 2). Even higher selectivities were observed for the fluorination in nucleophilic acetonitrile in which the formation of acetamides **4**–**6** was observed (Scheme 2). The formation of **4** as main reaction product is attributed to electrophilic attack of solvated fluorine followed by the transannular cyclization to fluoromethyl-adamantyl cation of type **MIN7** (Figure 4) and its trapping with acetonitrile; further side CH_3 fluorinations of **4** gave fluorides **5** and **6**.

The participation of the F radical, which may be formed through homolysis, can be excluded because the noradamantane derivatives that result from the F-radical attack on **1** (see Figure 3) were not detected in the reaction mixture. The set of the products formed allows us to postulate the electrophilic addition Scheme for the fluorination of **1** in the condensed phase.

Additional information about the fluorination mechanism was obtained utilizing methyl (**1a**) and phenyl (**1b**) bicyclo-[3.3.1]nonane derivatives (Scheme 3). Fluorination in a $CFCl_3$/$CHCl_3$ mixture gave two types of difluoro derivatives (**2a,b** and **2a′,b′**) resulting from the attack of F_2 on both unsubstituted and substituted double bonds of **1a,b**. The difluorides **2a,a′** and **2b,b′** were formed in trace amounts and their ratio was determined from the NMR spectra of the reaction mixtures. The main products (**3a** and **3b**) resulted from the reaction with HF formed due to a F_2+$CHCl_3$ side reaction. This is typical for the reaction of dienes of bicyclo[3.3.1]nonane series with proton acids in which only the unsubstituted double bond is attacked.[25] Electrophilic halogenations are always less selective.[21a,26]

Transannular cyclization of **1a,b** with F_2 in acetonitrile is effective due to trapping of the intermediates with the nucleophilic solvent. We were able to isolate and characterize two types of 3-fluoromethyladamantyl derivatives **4a,b** and **4a′,b′**, as well as products of their consecutive fluorination (**5a,b**, **5a′,b′**, and **6b,b′**). The product **4a** was synthesized by treatment of **1a** with F-TEDA-BF_4 in CH_3CN with addition of 3 equiv of water. The same reaction of **1a** in dry acetonitrile following with addition of water leads to the formation of a byproduct

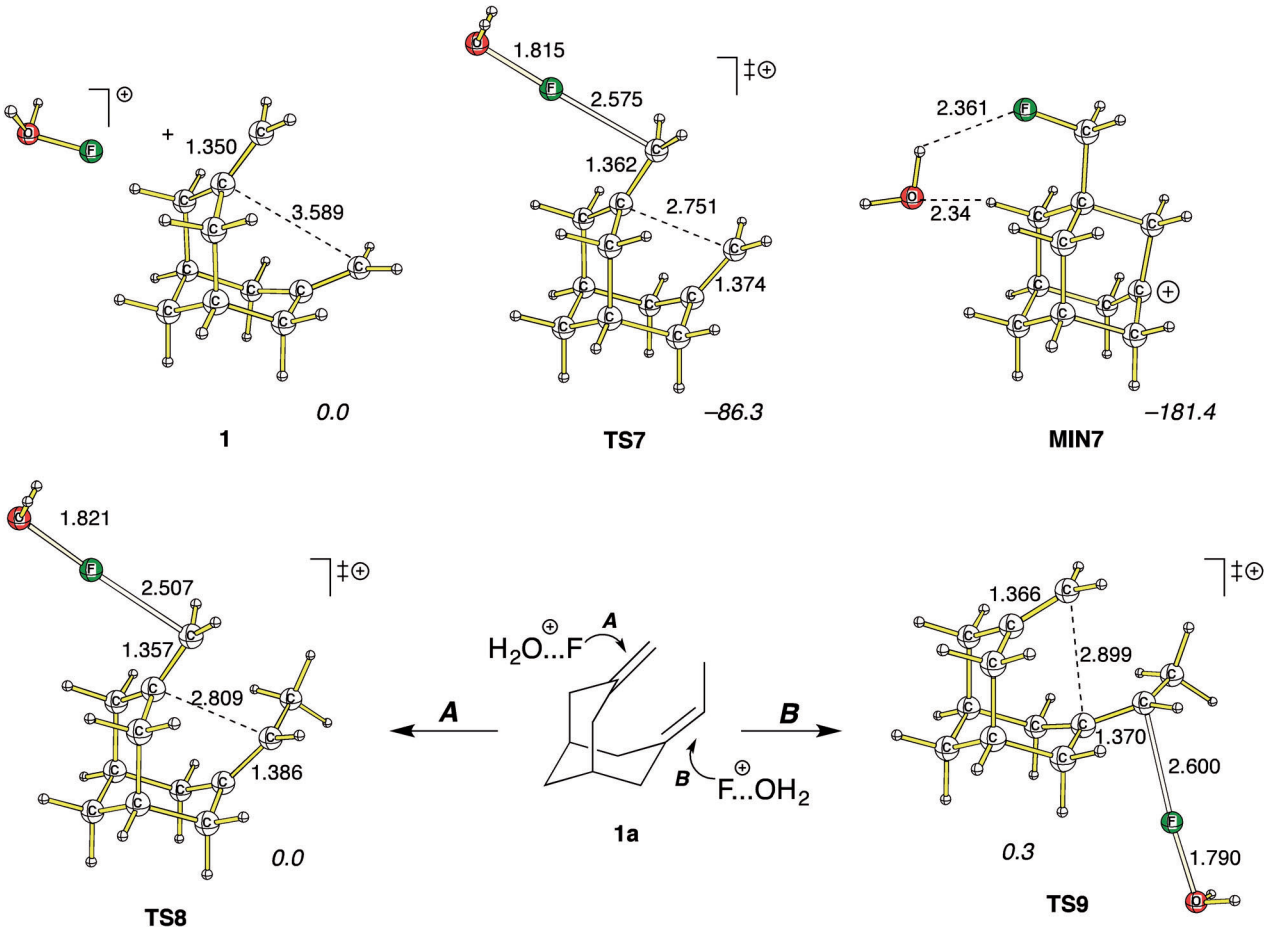


Figure 4. The MP2/6-31+G* stationary points (critical bond lengths [Å] and relative ΔH_{298} [kcal mol^{-1}]) for reaction of 3,7-dimethylenebicyclo[3.3.1]nonane (**1**) with the F···OH_2^+ complex (**TS7** and **MIN7**) and relative energies (in italics) of the transition structures (**TS8** and **TS9**) for the electrophilic fluorination of unsymmetrical 3-methylene-7-ethylidenebicyclo[3.3.1]nonane (**1a**).

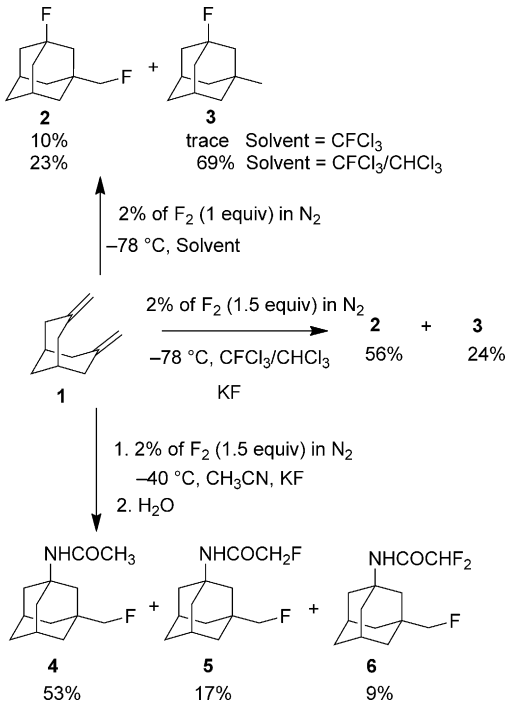
2a in 14% yield. Such a set of products unequivocally evidences for the electrophilic addition mechanism as differently substituted double bonds are not discriminated. Such selectivities are in sharp contrast with those observed for the reactions of **1a** and **1b** with perfluoroalkyl radicals[20c] or neutral electrophiles[20a] and are in accord with computed model reaction of **1a** with the F^+···H_2O complex (Figure 4).

Conclusion

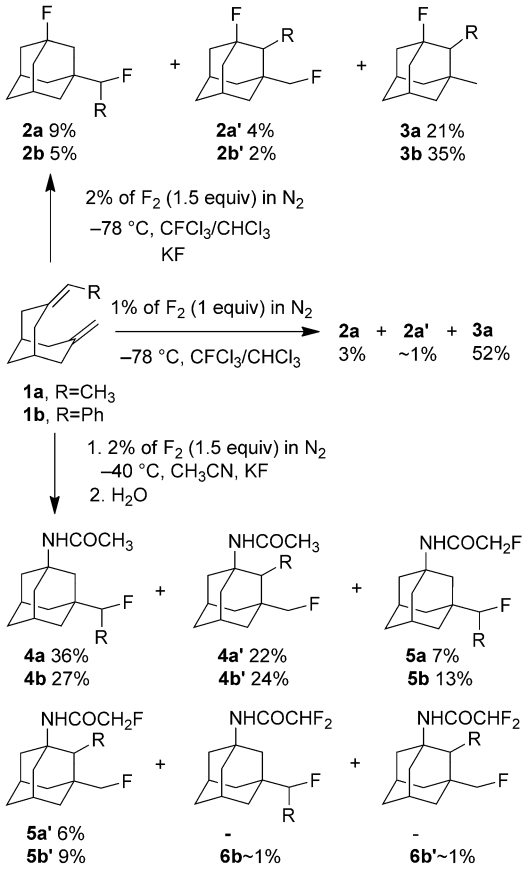
The unsaturated derivatives of bicyclo[3.3.1]nonane undergo selective transannular cyclization with elemental fluorine and serve as suitable mechanistic probes for the olefin fluorinations in solution. The molecular-induced homolytic mechanism, which is characteristic for the gas phase, in which the interaction of two closed-shell molecules (F_2 and olefin) leads to formation of the biradical states with further dissociation into two radical species, may be ruled out in solution ($CFCl_3$) even for transannulated dienes. There is also no evidence for the participation of the F radical in the reaction because the noradamantane derivatives were not found even in trace amounts. The main driving force of the reaction is the formation of stable *tert*-adamantyl cationic intermediates that are trapped efficiently by nucleophiles. We have found strong evidence for the electrophilic addition of elementary fluorine both in nucleophilic (acetonitrile) and non-nucleophilic ($CFCl_3$/$CHCl_3$) solvents. In the latter case, the presence of KF facilitates the electrophilic addition and substantially reduces the formation of tar products.

Experimental Section

$CHCl_3$ and CH_3CN were dried, and trace amounts of water (<5–6 ppm) were controlled by a Karl Fischer titration. Reactions were carried out in traps made from FEP tubes (i.d. = 25 mm). Fluorine gas (Solvay) was passed through a layer of KF to absorb traces of HF and its flow was adjusted to 2 mL min^{-1} by means of a mass flow controller (MKS type 1479 A). Parallel flow of nitrogen was adjusted to 98 mL min^{-1} by a second mass flow controller (MKS type 1179 A) and both gases were mixed in stainless steel tube (i.d. = 4 mm). The gas mixture was forced through a FEP tube (i.d. = 0.7 mm) and finally bubbled through the reaction mixtures while stirring with a magnetic stirring bar. ^{1}H- (399.78 MHz), ^{13}C- (100.53 MHz), and ^{19}F (376.17) NMR spectra were recorded using TMS or CCl_3F as internal standard. Column chromatography was performed on Kieselgel Merck 60 (230–400 mesh).



Scheme 2. Preparative yields for the transannular cyclization of 3,7-dimethylenebicyclo[3.3.1]nonane (**1**) with F_2 in different solvents.



Scheme 3. Transannular cyclizations of 3-methylen-7-ethylinedenebicyclo-[3.3.1]nonane (**1a**) and 1-methylen-7-benzylidenebicyclo[3.3.1]nonane (**1b**) with F_2 in different media.

General fluorination procedure $CHCl_3/CFCl_3$

F_2 gas (0.116 g, 3.04 mmol, 2% in N_2) was bubbled through a mixture of **1** (0.30 g, 2.03 mmol) and spray-dried KF (0.14 g, 2.41 mmol) in a $CHCl_3/CFCl_3$-mixture (60 mL, 1:1) at −78 °C. Then, N_2 gas was passed through the reaction mixture for 30 min, and the solvents were removed under reduced pressure. The residue was dissolved with CH_2Cl_2 (30 mL), and the mixture was washed with $NaHCO_3$ (aq., 2×5 mL), water (2×5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude reaction mixture was separated by column chromatography on SiO_2 (*n*-hexane). The spectral data of products **2** (211 mg, 56%), **2a**,**b** (**a**: 33 mg, 9%; **b**: 17 mg, 5%), and **2a′**,**b′** (**a′**: 15 mg, 4%; **b′**: 6 mg, 2%) are identical to described previously.[20a,27]

1-Fluoro-3-methyladamantane (**3**): Colorless oil (81 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (m, 2H), 1.88–1.72 (m, 4H), 1.59 (d, J = 6.0 Hz, 2H), 1.54–1.46 (m, 2H), 1.37 (m, 4H), 0.88 ppm (s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 93.3 (d, J = 183.0 Hz, C-1), 49.4 (d, J = 16.3 Hz), 43.1 (d, J = 2.0 Hz), 42.1 (d, J = 17.2 Hz), 35.2 (d, J = 2.2 Hz), 34.7 (d, J = 9.6 Hz, C-3), 31.6 (d, J = 9.7 Hz, C-5, C-7), 30.1 ppm (d, J = 1.3 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −131.0 ppm (s); elemental analysis calcd (%) for $C_{11}H_{17}F$: C 78.52; H 10.18; found: C 78.43; H 10.14.

1-Fluoro-2,3-dimethyladamantane (**3a**): Colorless oil (71 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22–2.11 (m, 2H), 2.02–1.94 (m, 1H), 1.92–1.37 (m, 9H), 1.14–1.06 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H, 2-CH_3), 0.80 ppm (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 94.8 (d, J = 185.9 Hz, C-1), 48.4 (d, J = 15.7 Hz, C-2), 45.7 (d, J = 2.0 Hz), 44.1 (d, J = 17.9 Hz), 36.6 (d, J = 1.6 Hz), 36.4 (d, J = 6.8 Hz, C-3), 36.1 (d, J = 2.0 Hz), 35.8 (d, J = 17.7 Hz), 31.4 (d, J = 10.4 Hz, C-5 or C-7), 31.0 (d, J = 10.1 Hz, C-5 or C-7), 27.3 (d, J = 2.4 Hz, CH_3), 8.6 ppm (d, J = 4.4 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −139.0 ppm (s); elemental analysis calcd (%) for $C_{12}H_{19}F$: C 79.07; H 10.51; found: C 78.85; H 10.47.

1-Fluoro-3-(fluoromethyl)-2-methyladamantane (**2a′**):[20a] Pale-yellow oil (14 mg, 4%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.13 (ABX, $^2J_{AB}$ = 9.0 Hz, $^2J_{AF}$ = 48.0 Hz, 1H, CH_2F), 4.02 (ABX, $^2J_{BA}$ = 9.1 Hz, $^2J_{BF}$ = 48.0 Hz, $^4J_{BH}$ = 1.6 Hz, 1H, CH_2F), 2.26 (m, 2H), 2.10–1.38 (m, 11H), 0.98 ppm (d, J = 6.9 Hz, 3H, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −140.7 (s, 1F, F-1), −232.4 ppm (t, J = 47.7 Hz, 1F, CH_2F); elemental analysis calcd (%) for $C_{12}H_{18}F_2$: C 71.97; H 9.06; found: C 71.70; H 10.43.

1-Fluoro-3-methyl-2-phenyladamantane (**3b**): Colorless oil (114 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J = 7.6 Hz, 2H), 7.34–7.19 (m, 3H), 2.91 (s, 1H, H-2), 2.43 (m, 2H), 2.32 (m, 1H), 2.19 (d, J = 13.7 Hz, 1H), 2.11–1.95 (m, 2H), 1.76–1.60 (m, 4H), 1.52 (m, 1H), 1.31 (d, J = 13.8 Hz, 1H), 0.66 ppm (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.4 (d, J = 2.5 Hz), 130.8, 128.0, 126.6, 94.1 (d, J = 187.8 Hz, C-1), 62.4 (d, J = 16.4 Hz, C-2), 47.3 (d, J = 1.8 Hz), 45.6 (d, J = 17.9 Hz), 38.1 (d, J = 1.5 Hz), 38.0 (d, J = 5.9 Hz, C-3), 36.5 (d, J = 15.0 Hz), 36.4 (d, J = 1.1 Hz, C-6), 36.48 (d, J = 15.0 Hz), 36.38 (d, J = 1.1 Hz), 31.7 (d, J = 10.0 Hz, C-5 or C-7), 31.0 (d, J = 9.7 Hz, C-5 or C-7), 27.9 ppm (d, J = 2.3 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −136.4 ppm (s); elemental analysis calcd (%) for $C_{17}H_{21}F$: C 83.56; H 8.66; found: C 83.51; H 8.64.

1-Fluoro-3-(fluoromethyl)-2-phenyladamantane (**2b′**):[20a] Pale-yellow oil (6 mg, 2%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.06 (m, 5H), 3.85 (ABX, $^2J_{AB}$ = 9.0 Hz, $^2J_{AF}$ = 47.1 Hz, 1H, CH_2F), 3.81 (ABX, $^2J_{BA}$ = 9.0 Hz, $^2J_{BF}$ = 47.1 Hz, $^4J_{BH}$ = 1.6 Hz, 1H, CH_2F), 3.17 (s, 1H, H-2), 2.63–1.40 ppm (m, 12H); ^{19}F NMR (376 MHz, $CDCl_3$): δ = −138.1 (s,

1F, F-1), −231.9 ppm (d, J=46.8 Hz, 1F, CH_2F); elemental analysis calcd (%) for $C_{17}H_{20}F_2$: C 77.83; H 7.68; found: C 77.53; H 7.65.

General fluorination procedure in CH_3CN

F_2 gas (0.116 g, 3.04 mmol, 2% in N_2) was bubbled through a mixture of **1** (0.30 g, 2.03 mmol) and spray-dried KF (0.14 g, 2.41 mmol) in acetonitrile (60 mL) at −40 °C. The reaction mixture was warmed up to room temperature while passing N_2 gas through the reaction mixture for 30 min. The solvent was removed under reduced pressure. The residue was dissolved with CH_2Cl_2 (30 mL), and the mixture was washed with $NaHCO_3$ (aq., 2×5 mL), water (3×5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude reaction mixture was separated by column chromatography on SiO_2 (CH_2Cl_2/ether).

***N*-[3-(fluoromethyl)-1-adamantyl]acetamide** (**4**): White crystals. M.p. 97–98 °C (242 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.19 (brs, 1H, NH), 3.99 (d, $^2J_{HF}$=48.0 Hz, 2H), 2.17 (m, 2H), 1.94 (m, 4H), 1.89 (s, 3H, CH_3), 1.81 (s, 2H), 1.66 (m, $^2J_{AB}$=12.7 Hz, 1H), 1.58 (m, $^2J_{AB}$=12.5 Hz, 1H), 1.50 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=169.5, 91.9 (d, J=172.1 Hz), 52.1 (d, J=1.3 Hz), 42.0 (d, J=4.4 Hz), 41.1, 37.2 (d, J=4.2 Hz), 36.4 (d, J=17.7 Hz), 35.8, 29.0 (d, J=0.9 Hz), 24.7 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−230.1 (t, J=48.0 Hz); HRMS: *m/z* calcd for $C_{13}H_{20}FNNaO$: 248.1427 [M^+]; found: 248.1426.

2-Fluoro-*N*-[3-(fluoromethyl)-1-adamantyl]acetamide (**5**): Colorless oil (83 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.96 (brs, 1H, NH), 4.64 (d, $^2J_{HF}$=47.6 Hz, 2H, C(O)CH_2F), 4.01 (d, $^2J_{HF}$=47.9 Hz, 2H, AdCH_2F), 2.18 (m, 2H), 1.99 (m, 4H), 1.86 (s, 2H), 1.68 (m, $^2J_{AB}$= 12.7 Hz, 1H), 1.61 (m, $^2J_{AB}$=12.5 Hz, 1H), 1.52 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=166.6 (d, J=15.5 Hz), 91.7 (d, J= 172.5 Hz), 80.2 (d, J=187.9 Hz), 52.4 (d, J=1.4 Hz), 42.0 (d, J= 4.5 Hz), 41.1, 37.1 (d, J=4.3 Hz), 36.5 (d, J=17.7 Hz), 35.7, 29.0 ppm (d, J=0.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−220.1 (td, J=47.6, 4.2 Hz, 1F, C(O)CH_2F), −230.16 ppm (t, J=47.9 Hz, 1F, AdCH_2F); HRMS: *m/z* calcd for $C_{13}H_{19}F_2NNaO$: 266.1332 [M^+]; found: 266.1329.

2,2-Difluoro-*N*-[3-(fluoromethyl)-1-adamantyl]acetamide (**6**): Colorless oil (48 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.94 (brs, 1H, NH), 5.75 (t, $^2J_{HF}$=54.5 Hz, 1H, CF_2H), 4.01 (d, $^2J_{HF}$=47.9 Hz, 2H), 2.22 (m, 2H), 1.99 (m, 4H), 1.86 (s, 2H), 1.69 (m, $^2J_{AB}$=12.7 Hz, 1H), 1.62 (m, $^2J_{AB}$=12.5 Hz, 1H), 1.53 ppm (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=161.6 (t, J=23.4 Hz, C=O), 108.6 (t, J=254.0 Hz, CF_2H), 91.6 (d, J=172.5 Hz, CH_2F), 52.9, 41.7 (d, J=4.8 Hz), 40.7, 37.0 (d, J=3.8 Hz), 36.5 (d, J=17.3 Hz), 35.6, 29.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ=−125.1 (dd, J=54.7, 2.1 Hz, 2F), −230.2 ppm (t, J= 47.9 Hz, 1F); HRMS: *m/z* calcd for $C_{13}H_{18}F_3NNaO$: 284.1238 [M^+]; found: 284.1240.

***N*-[3-(Fluoromethyl)-2-methyl-1-adamantyl]acetamide** (**4a′**, from a mixture of **4a** and **4a′**): Colorless crystals. M.p.=46–51 °C, (256 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.02 (brs, 1H, NH), 4.09 (ABX, $^2J_{AB}$=9.0 Hz, $^2J_{AF}$=47.8 Hz, 1H, CH_2F), 4.02 (ABX, $^2J_{BA}$= 9.0 Hz, $^2J_{BF}$=47.8 Hz, 1H, CH_2F), 2.61 (m, 2H), 2.10 (m, 2H), 1.91 (s, 3H, C(O)CH_3), 1.86 (m, 1H), 1.80–1.46 (m, 8H), 0.86 ppm (d, $^3J_{HH}$= 7.0 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$): δ=169.2 (C=O), 90.4 (d, J=171.9 Hz, CH_2F), 55.0 (C-1), 41.8, 39.8 (d, J=3.6 Hz, C-2), 39.5 (d, J=4.0 Hz), 38.0 (d, J=17.1 Hz, C-3), 36.7, 36.6, 31.1, 31.0, 28.7, 24.5 (C(O)CH_3), 9.21 ppm (2-Ad-CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ= −231.2 ppm (t, J=47.9 Hz); elemental analysis calcd (%) for $C_{14}H_{22}FNO$: C 70.26; H 9.27; N 5.85; found (for the mixture of **4a** and **4a′**): C 70.01; H 9.25; N 5.84.

2-Fluoro-*N*-[3-(1-fluoroethyl)-1-adamantyl]acetamide (**5a**) and **2-fluoro-*N*-[3-(fluoro-methyl)-2-methyl-1-adamantyl]acetamide** (**5a′**): Pale-yellow oil (62 mg, 13%). ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.96 (brs, 1H, NH, **5a**), 5.82 (brs, 1H, NH, **5a′**), 4.65 (d, $^2J_{HF}$= 47.7 Hz, 2H, C(O)CH_2F, **5a′**), 4.64 (d, $^2J_{HF}$=47.6 Hz, 2H, C(O)CH_2F, **5a**), 4.19 (dq, $^2J_{HF}$=47.1 Hz,$^3J_{HH}$=6.4 Hz, 1H, CHF, **5a**), 4.11 (ABX, $^2J_{AB}$=9.1 Hz, $^2J_{AF}$=47.8 Hz, 1H, CH_2F, **5a′**), 4.02 (ABX, $^2J_{BA}$=9.1 Hz, $^2J_{BF}$=47.8 Hz, 1H, CH_2F, **5a′**), 2.58 (qm, $^3J_{HH}$=7.0 Hz, 1H, H-2, **5a′**), 2.56–2.51 (m, 1H, **5a′**), 2.20 (m, 2H, **5a**), 2.14 (m, 2H, **5a′**), 2.03–1.40 (m, 12H **5a**, 10H **5a′**), 1.22 (dd, $^3J_{HF}$=25.2, $^3J_{HH}$=6.4 Hz, 3H, CH_3, **5a**), 0.88 ppm (d, $^3J_{HH}$=7.0 Hz, 3H, CH_3, **5a′**); ^{13}C NMR (101 MHz, $CDCl_3$): δ=166.6 (d, J=15.5 Hz, C=O), 166.3 (d, J= 15.4 Hz, C=O), 96.6 (d, J=170.5 Hz, CHF, **5a**), 90.2 (d, J=172.3 Hz, AdCH_2F, **5a′**), 80.3 (d, J=187.6 Hz, C(O)**C**H_2F), 80.2 (d, J=187.5 Hz, C(O)**C**H_2F), 55.3 (d, J=1.0 Hz, C-1, **5a′**), 52.6 (d, J=0.9 Hz, C-1, **5a**), 42.0, 41.5 (d, J=4.5 Hz), 41.2, 40.3 (d, J=3.5 Hz, C-2, **5a′**), 39.5 (d, J=3.9 Hz), 38.8 (d, J=18.9 Hz), 38.1 (d, J=17.1 Hz), 36.5, 36.3, 36.3 (d, J=4.3 Hz), 36.1 (d, J=4.2 Hz), 35.8, 30.9, 30.9, 29.1, 28.8, 28.7, 14.5 (d, J=24.0 Hz, CH_3, **5a**), 9.2 ppm (CH_3, **5a′**); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−185.1 (dq, $^2J_{FH}$=47.4 Hz, $^3J_{FH}$=25.2 Hz, 1F, CHF, **5a**), −219.8 (td, $^2J_{FH}$=47.7 Hz, J_{FH}=4.3 Hz, 1F, C(O)CH_2F, **5a′**), −220.1 (td, $^2J_{FH}$=47.6, J_{FH}=4.2 Hz, 1F, C(O)CH_2F, **5a**), −231.5 ppm (t, $^2J_{FH}$= 47.8 Hz, 1F, **5a′**); elemental analysis calcd (%) for $C_{14}H_{21}F_2NO$: C 65.35; H 8.23; N 5.44; found (for the mixture of **5a** and **5a′**): C 65.27; H 8.23; N 5.43.

***N*-{3-[Fluoro(phenyl)methyl]-1-adamantyl}acetamide** (**4b**) (109 mg, 27%): Colorless crystals. M.p. 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.39–7.27 (m, 3H), 7.20 (dm, J=7.9 Hz, 2H), 5.23 (brs, 1H, NH), 4.97 (d, $^2J_{HF}$=45.3 Hz, 1H, CH_2F), 2.14 (m, 2H), 2.00–1.79 (m, 5H), 1.88 (s, 3H, CH_3), 1.72 (dm, J=11.8 Hz, 1H), 1.65–1.54 (m, J=12.5 Hz, 3H), 1.50 (dm, J=12.5 Hz, 2H), 1.43 ppm (dm, J=12.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=169.5 (C=O), 136.6 (d, J=21.8 Hz), 128.1, 127.7, 127.1 (d, J=8.2 Hz), 100.8 (d, J= 176.6 Hz), 52.4, 41.6 (d, J=3.9 Hz), 41.0 (d, J=3.7 Hz), 39.5 (d, J= 21.8 Hz), 36.4 (d, J=10.9 Hz), 35.7, 29.1, 24.7 ppm (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−190.5 ppm (d, J=45.3 Hz); elemental analysis calcd (%) for $C_{19}H_{24}FNO$: C 75.71; H 8.03; N 4.65; found: C 75.65; H 8.02; N 4.64.

***N*-[3-(Fluoromethyl)-2-phenyl-1-adamantyl]acetamide** (**4b′**): colorless crystals (97 mg, 24%). M.p. 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.59 (d, J=7.5 Hz, 1H), 7.44–7.08 (m, 4H), 4.76 (brs, 1H, NH), 3.75 (ABX, $^2J_{AB}$=8.9 Hz, $^2J_{AF}$=47.5 Hz, 1H), 3.69 (ABX, $^2J_{BA}$= 8.9 Hz, $^2J_{AF}$=47.5 Hz, 1H), 3.58 (s, 1H), 2.72 (dm, ^2J=12.3 Hz, 1H), 2.34 (m, 1H), 2.24 (m, 1H), 2.19 (dm, ^2J=12.6, 1H), 2.09 (m, 2H), 1.98–1.85 (m, 2H), 1.77 (dm, ^2J=12.4 Hz, 1H), 1.69 (dm, ^2J= 12.4 Hz, 2H), 1.56 (s, 3H, CH_3), 1.45 ppm (dm, ^2J=13.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=169.6 (C=O), 139.1, 133.6, 128.6, 128.0, 127.5, 127.1, 90.2 (d, J=171.9 Hz), 55.1 (d, J=0.9 Hz, C_{Ad}-NH), 54.1 (d, J=3.4 Hz, CH-Ph), 42.8, 40.9 (d, J=3.6 Hz), 39.5 (d, J= 17.2 Hz), 37.0, 36.9, 31.9 (d, J=4.9 Hz), 29.1, 28.7 (d, J=1.3 Hz), 24.31 ppm (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−231.8 ppm (t, J= 47.7 Hz); elemental analysis calcd (%) for $C_{19}H_{24}FNO$: C 75.71; H 8.03; N 4.65; found: C 75.62; H 8.01; N 4.64.

2-Fluoro-*N*-{3-[fluoro(phenyl)methyl]-1-adamantyl}acetamide (**5b**): Colorless crystals (55 mg, 13%). M.p. 54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.38–7.29 (m, 3H), 7.21 (dm, J=7.9 Hz, 2H), 5.93 (brs, 1H, NH), 5.00 (d, $^2J_{HF}$=45.2 Hz, 1H, CHFPh), 4.64 (d, $^2J_{HF}$=47.6 Hz, 2H, CH_2F), 2.18 (m, 2H), 1.95 (m, 5H), 1.78 (dt, J= 11.6, 2.0 Hz, 1H), 1.67–1.57 (m, 3H), 1.53 (dm, J=12.7 Hz, 2H), 1.46 ppm (d, J=12.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=166.6 (d, J=15.4 Hz, C=O), 136.5 (d, J=21.7 Hz), 128.2 (d, J=1.4 Hz), 127.8, 127.1 (d, J=8.0 Hz), 100.7 (d, J=177.0 Hz, CHF), 80.3 (d, J= 187.7 Hz, CH_2F), 52.6 (d, J=1.0 Hz, C-1), 41.6 (d, J=4.2 Hz), 41.0 (d, J=1.3 Hz), 39.6 (d, J=21.9 Hz, C-3), 36.3 (dd, J=16.9, 4.0 Hz, C-2), 35.5, 29.03 ppm (C-5,7); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−190.5 ppm

(d, J=45.3 Hz, 1F, CFH), −220.1 ppm (td, J=47.7, 4.1 Hz, 1F, CH_2F); elemental analysis calcd (%) for $C_{19}H_{23}F_2NO$: C 71.45; H 7.26; N 4.39; found: C 71.34; H 7.24; N 4.38.

2-Fluoro-*N*-[3-(fluoromethyl)-2-phenyl-1-adamantyl]acetamide (5b′): Colorless pale-yellow oil (38 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60 (d, J=7.7 Hz, 1H), 7.42–7.15 (m, 5H), 5.65 (brs, 1H, NH), 4.41 (ABX, $^2J_{AB}$=14.0 Hz, $^2J_{AF}$=47.7 Hz, 1H), 4.28 (ABX, $^2J_{BA}$=14.0 Hz, $^2J_{BF}$=47.7 Hz, 1H, C(O)CH_2F), 3.77 (ABX, $^2J_{AB}$=9.0 Hz, $^2J_{AF}$=47.5 Hz, 1H, AdCH_2F), 3.71 (ABX, $^2J_{BA}$=9.0 Hz, $^2J_{BF}$=47.5 Hz, 1H, AdCH_2F), 3.56 (s, 1H, CHPh), 2.63 (dm, J=7.4 Hz, 1H), 2.38 (m, 1H), 2.33–2.25 (m, 2H), 2.21 (dm, J=12.2 Hz, 1H), 2.10 (dm, J=13.5 Hz, 1H), 1.99 (m, Hz, 2H), 1.80 (dm, J=12.4 Hz, 1H), 1.71 (dm, J=12.5 Hz, 2H), 1.46 ppm (d, J=13.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=166.6 (d, J=15.6 Hz, C=O), 138.5, 133.4, 128.7, 128.2, 127.6, 127.4, 90.0 (d, J=172.0 Hz, AdCH_2F), 80.0 (d, J=187.7 Hz, C(O)CH_2F), 55.2 (d, J=0.9 Hz, C-1), 54.6 (d, J=3.7 Hz, C-2), 43.0, 40.9 (d, J=3.5 Hz), 39.6 (d, J=17.3 Hz, C-3), 36.9, 36.6, 31.7 (d, J=5.2 Hz), 29.2, 28.6 ppm (d, J=1.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−220.48 (td, J=47.6, 4.2 Hz), −232.03 ppm (t, J=47.6 Hz); elemental analysis calcd (%) for $C_{19}H_{23}F_2NO$: C 71.45; H 7.26; N 4.39; found: C 71.40; H 7.25; N 4.38.

2,2-Difluoro-*N*-{3-[fluoro(phenyl)methyl]-1-adamantyl}acetamide (6b) and 2,2-difluoro-*N*-[3-(fluoromethyl)-2-phenyl-1-adamantyl]acetamide (6b′): Pale-yellow oil (9 mg, 2%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60 (d, J=7.8 Hz, 1H, 6b′), 7.43–7.11 (m, 5H 6b, 4H 6b′), 5.90 (brs, 1H, NH, 6b), 5.74 (t, $^2J_{HF}$=54.7 Hz, 1H, CF_2H, 6b), 5.64 (brs, 1H, NH, 6b′), 5.46 (t, $^2J_{HF}$=54.6 Hz, 1H, CF_2H, 6b′), 4.99 (d, $^2J_{HF}$=45.4 Hz, 1H, CHFPh, 6b), 3.77 (ABX, $^2J_{AB}$=9.0 Hz, $^2J_{AF}$=47.7 Hz, 1H, CH_2F, 6b′), 3.72 (ABX, $^2J_{BA}$=9.0 Hz, $^2J_{BF}$=47.7 Hz, 1H, CH_2F, 6b′), 3.51 (s, 1H, CHPh, 6b′), 2.58 (dm, J=12.2 Hz, 1H, 6b′), 2.40 (m, 1H, 6b′), 2.35–1.40 ppm (m, 14H 6b, 10H 6b′); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−125.1 (dd, J=54.7, 2.0 Hz, 2F, CF_2H, 6b), −125.8 (dt, J=54.7, 2.5 Hz, 2F, CF_2H, 6b′), −190.6 (d, J=45.2 Hz, 1F, CH_2F, 6b), −232.1 ppm (t, J=47.5 Hz, CH_2F, 6b′); elemental analysis calcd (%) for $C_{19}H_{22}F_3NO$: C 67.64; H 6.57; N 4.15; found (for the mixture of **6b** and **6b′**): C 67.45; H 6.55; N 5.42.

Preparation of *N*-[3-(1-fluoroethyl)-1-adamantyl]acetamide (4a) using F-TEDA-BF_4

A solution of **1a** (0.693 g, 4.28 mmol) in acetonitrile (2 mL) was added to a mixture of F-TEDA-BF_4 (1.82 g, 5.14 mmol, 1.2 equiv) and water (0.23 mL, 3 equiv) in acetonitrile (8 mL). The reaction mixture was stirred for 2 h at ambient conditions. The solvent was removed under reduced pressure. The residue was dissolved with CH_2Cl_2 (50 mL), and the organic layer was washed with water (5× 5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The solvent was evaporated to obtain the crude product that was purified by crystallization from *n*-hexane giving 0.85 g (83% yields) of *N*-[3-(1-fluoroethyl)-1-adamantyl]acetamide (**4a**) as colorless crystals. M.p. 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.18 (brs, 1H, NH), 4.18 (dq, $^2J_{HF}$=47.3 Hz, $^3J_{HH}$=6.4 Hz, 1H, CHF), 2.16 (s, 2H, H-5, H-7), 1.93 (m, 4H), 1.89 (s, 3H, C(O)CH_3), 1.87 (m, 1H), 1.72 (dm, J=11.7 Hz, 1H), 1.65 (m, 1H), 1.61–1.51 (m, 3H), 1.37–1.49 (m, 2H), 1.21 ppm (dd, $^3J_{HF}$=25.2, $^3J_{HH}$ 6.4 Hz, 3H, $CFCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ=169.5 (C=O), 96.8 (d, J=170.1 Hz, CHF), 52.3 (C-1), 41.4 (d, J=4.4 Hz), 41.2 (d, J=2.8 Hz), 38.7 (d, J=18.9 Hz, C-3), 36.3 (d, J=4.2 Hz), 35.9, 29.1 (C-5, C-7), 24.7 (CH_3), 14.5 ppm (d, J=24.0 Hz, CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−185.0 ppm (dq, $^2J_{FH}$=47.8 Hz, $^3J_{FH}$=25.4 Hz); HRMS: *m/z* calcd for $C_{14}H_{23}FNO$: 284.1757 [M^+]; found: 240.1758.

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