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Superelectrophilic Csp³-H bond fluorination of aliphatic amines in superacid: The striking role of ammonium-carbenium dications.

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The superacid-promoted electrophilic Csp³-H bond activation of aliphatic amines generates superelectrophilic species that can be subsequently fluorinated. Demonstrated by low-temperature *in situ* NMR experiments, the ammonium-carbenium dications, crucial for this reaction, can also react with C-H bonds opening future synthetic perspectives for this mode of activation.

Tuning of molecules properties through fluorine atom insertion¹ is a very popular strategy in many fields.² Its selective introduction in a bioactive molecule can modify its conformation, pK_a, biological potency, membrane permeability, metabolism and kinetic properties.³ As a consequence, the use of fluorine in drug design expands⁴ as rapidly as the understanding of the impact of its stereoelectronic properties.⁵ Fluorine is the second favourite heteroatom after nitrogen in life science-oriented research.⁶ Consequently, fluorinated amines are extremely popular in drug discovery⁷ and their synthesis is of upmost importance.⁸ C-H bond activation is now a mature field⁹ for the synthesis of complex molecules,¹⁰ and C-H bond fluorination is not an exception.¹¹ The most popular methods to fluorinate Csp³-H bond of nitrogen-containing compounds are based on organopalladium intermediates¹² and carbon-centered radicals,¹³ which elegantly supplement existing strategies employing elemental fluorine¹⁴ or electrochemical activation.¹⁵ Conversely, Csp³-H bond fluorination in the presence of a fluoride ion source is limited to the use of manganese-porphyrines catalytic activation.¹⁶ Superacid-promoted¹⁷ electrophilic activation of alkanes through the concept of σ -basicity¹⁸ has been initiated by Olah and Sommer¹⁹ and extended to functionalized substrates²⁰ in the presence of CCl₄²¹ as a source of superelectrophile.²² However, the difficulty to selectively fluorinate the generated dications, even in the presence of the fluorinating agent HF/pyridine, led somehow to abandon this strategy (Figures 1A & B). As suggested by

Klumpp,²³ we reasoned that the difficulty of a poor nucleophile to substitute these cations could be directly correlated to their insufficient electrophilic character. Reducing the distance between the generated charges should thus enhance their electrophilicity favouring their fluorination (Figure 1C).

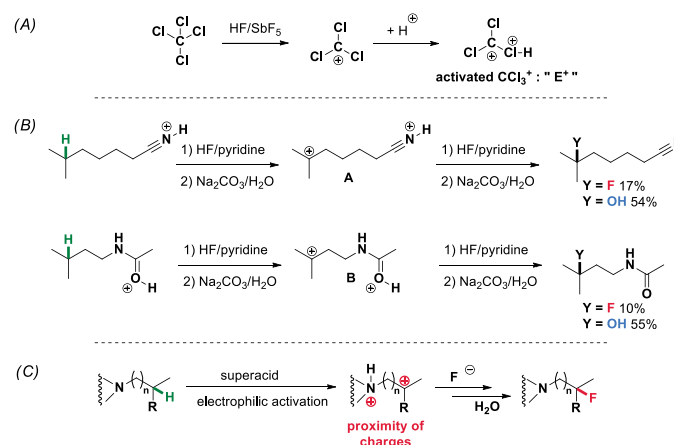


Figure 1. Superelectrophilic activation in superacid: (A) Activation of CCl₄⁺ to generate a superelectrophilic species, able to react with σ -bonds; (B) Nitrogen-containing dications **A** and **B** generated by Csp³-H bond electrophilic activation of nitrile and amide in HF/SbF₅/CCl₄ and their reactivity; (C) Proposed strategy for the synthesis of the targeted fluorinated amines.

Therefore, we embarked in screening the reactivity of substrate **1a**, exhibiting a tertiary C-H bond in γ position of the amine function (Table 1). No reaction occurred in the presence of CCl₄ in HF/SbF₅ at a 4 mol% SbF₅ concentration (Table 1, entry 1). When acidity was increased using 12 mol% SbF₅ concentration, C-H bond functionalization was observed leading to the partial conversion of the substrate to the fluorinated and hydroxylated products **2a** and **3a** respectively (Table 1, entry 2). Under the same conditions, decreasing the temperature allowed for the selective formation of the fluorinated product albeit with a poor conversion (Table 1, entry 3). To favour the activation process, acidity was further increased leading to the formation of the fluorinated amine **2a** as the main product with concomitant formation of alcohol **3a** (Table 1, entry 4). No reaction occurred without CCl₄ (Table 1, entry 5). To force the

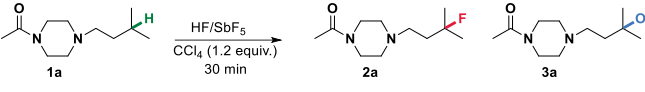
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† Footnotes relating to the title and/or authors should appear here.

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fluorination to completion, HF/pyridine was added (Table 1, entry 6) and the fluorinated product **2a** could be isolated in 69% yield under optimized conditions.

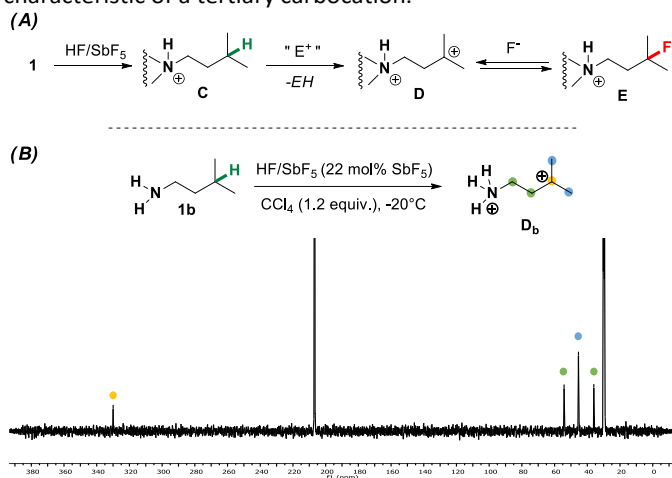
Table 1. Behaviour of aliphatic amine **1a** in HF/SbF₅



Entry	Acidity ^a	Temperature (°C)	Yields ^b (%)	
			2a	3a
1	4	-20	- ^c	- ^c
2	12	-20	<20 ^d	- ^e
3	12	-40	<20 ^d	-
4	22	-40	55	18
5 ^f	22	-40	- ^c	- ^c
6 ^g	22	-40	69%	-

^a mol% of SbF₅ in HF. ^b Isolated. ^c No reaction. ^d Only 25% conversion. ^e Traces. ^f Without CCl₄. ^g HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 30 min, -40 °C and HF/Pyridine, 1 h, -40 °C.

The formation of the fluorinated amine can be interpreted as follows: After protonation in superacid, amine **1** must generate ammonium ion **C** (Scheme 1A). Then, due to the σ -donor ability of a shared electron pair, *via* a two-electron three-centres bond formation,^{18,24} activated CCl₃⁺ (E⁺) insert into the C-H bond to generate a dicationic intermediate **D** after chloroform elimination. The superelectrophilic character of this ammonium-carbenium species allows its fluorination to generate ion **E** as a precursor of product **2a**. To demonstrate this mechanism, *in situ* NMR experiments at low temperature were conducted. First, CCl₄ was dissolved in HF/SbF₅ and studied by ¹³C NMR (See SI). The ¹³C NMR spectrum of the reaction mixture displayed only one single peak at 235.5 ppm, matching with literature data reported for CCl₃⁺,²¹ the dication CCl₃H²⁺ being not observed in these conditions at the NMR time scale.²⁵ Isopentylamine **1b** was also submitted to the same conditions (Scheme 1B). The good quality of the recorded NMR spectra enabled us to identify the dication **D_b** as the main species generated in these conditions. In the ¹H NMR spectrum, three signals were respectively observed at 4.59, 3.01 and 2.40 ppm, corresponding to ammonium, methylene and methyl protons.²⁵ In the ¹³C NMR and DEPT spectra, three signals at 53.5, 35.3 and 44.7 ppm were consistent with the formation of **D_b**. The observed singlet at 329.4 ppm is characteristic of a tertiary carbocation.



Scheme 1. Superelectrophilic activation in superacid: (A) Proposed mechanism for the C-H bond fluorination of generic amines **1**. (B) Generation of ammonium-carbenium superelectrophile **D_b** and recorded ¹³C NMR signals.

The scope of this approach was next evaluated by screening a series of amines. First, the impact of the distance between the targeted C-H bond and the amine function was evaluated (Figure 2). While C-H bond fluorination does not occur for C-H bond located at the vicinal position of C-N bond (substrate **1c**), this reaction is efficient to generate γ , δ and ϵ fluorinated amines (products **2a** and acetylated **2b**, **2e** and **2f**). Unfortunately, and probably due to a lower σ -donor ability, the absence of methyl group geminal to the targeted C-H bond annihilates the process (substrate **1d**). Then, the effect of amine structure/function was also investigated. Secondary amine **1g** led selectively to the γ fluorinated analogue **2g**. The fluorinated aniline, sulfonamide and pyridine **2h-j** were also synthesized through this method. We next hypothesized that C-H bond fluorination could occur in the geminal position of a fluorine atom.²⁶

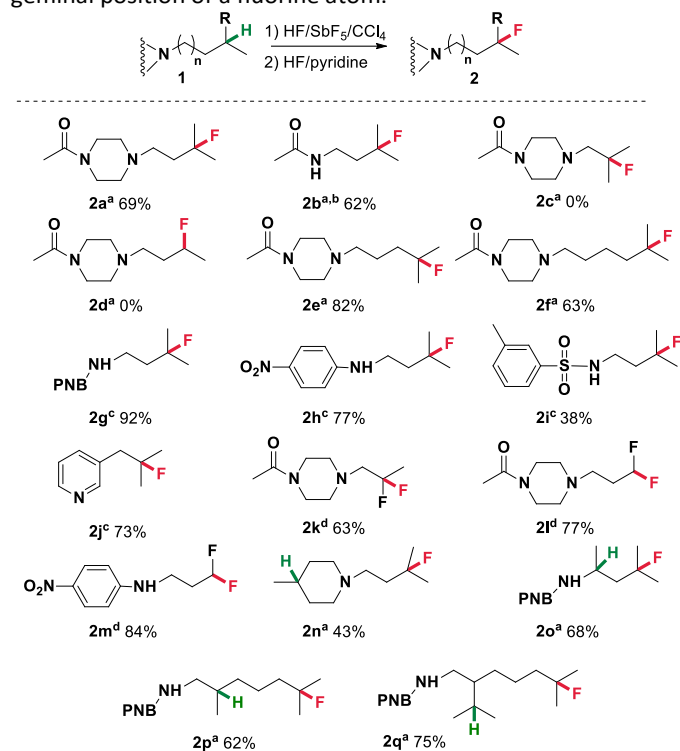


Figure 2. C-H bond fluorination of amines **1** in superacid HF/SbF₅ in the presence of CCl₄ under optimized conditions (Table 1, entry 6), PNB = para-nitro benzyl. [a] HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 30 min, -40 °C and HF/Pyridine, 1 h, -40 °C. [b] The crude mixture was acetylated (AcCl (excess), H₂O, overnight). [c] HF/SbF₅ (22 mol% SbF₅), CCl₄ (2.4 equiv.), 30 min, -40 °C and HF/Pyridine, 1 h, -40 °C. [d] HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 30 min, -20 °C and 24 h, RT.

Gratifyingly, the synthesis of the difluorinated products **2k-m** could be achieved starting from the corresponding monofluorinated analogues, even if longer reaction time was needed (See SI).²⁵ The formation of the difluorinated product **2k** also emphasizes the fact that the electrophilic activation/fluorination process can be applied for C-H bonds located in β position of the nitrogen atom in the case of fluorinated substrates. The exclusive formation of the monofluorinated product **2n** emphasizes the selectivity of the process for linear alkyl chains, as no fluorination occurred at the γ position on the piperidine ring. No competing C-H activation occurs to form an iminium ion after reaction of substrate **1o**, the product **2o** being obtained in a good 68% yield. Interestingly,

remote fluorination is strongly favoured as shown by the exclusive formation of products **2p** and **2q** in good yields, in accordance with the favoured activation of the richest electronic σ bond, far located from the protonated function.

We recently demonstrated that a carbocation generated under HF/SbF₅ conditions can be stabilized by intramolecular participation of the carbonyl group of an ester or amide function, respectively generating dioxalenium or oxazolinium ions.²⁷ On this basis, we hypothesized that aliphatic amides could be regioselectively hydroxylated with this method. Starting from imide **1r** or amides **1s** and **1t**, the corresponding hydroxylated analogues **3r**, **3s** and the dihydro-1,3-oxazine **3t** were efficiently obtained (Figure 3A). As shown by the exclusive formation of alcohol **3u**, the method can also be extended to ester derivatives and complement existing strategies to hydroxylate C-H bond through directing effect.²⁸ Next, we explored the ability to trap the generated cationic intermediate by other nucleophiles (Figure 3B). In a context where deuterium is now a validated component of the medicinal chemistry repertory,²⁹ the direct transformation of amine **1a** to its deuterated analogue **4a** in the presence of cyclohexane-*d*₁₂ is of interest. Satisfyingly, the superelectrophilic dications can be substituted by poor nucleophiles such as benzene or trifluoromethyl benzene (formation of **5a** and **6a**). A similar reaction in its intramolecular version allowed to generate selectively the tetrahydroquinoline **4v**. A Ritter-type reaction was also achieved in the presence of acetonitrile to produce amide **7a** in 81% yield.

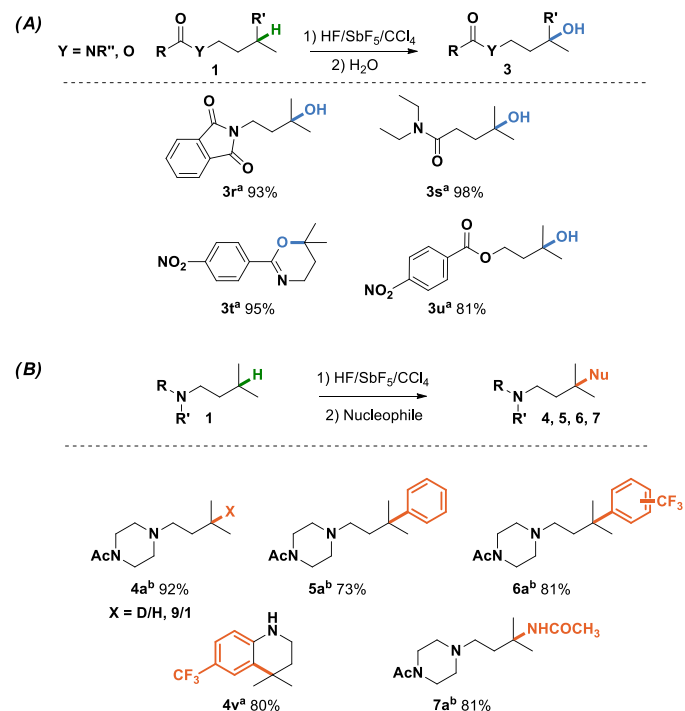


Figure 3. (A) Superacid guided C-H bond hydroxylation. (B) Functionalization of nitrogen-containing derivatives in superacid in the presence of cyclohexane-*d*₁₂ (2.0 equiv), aromatics (excess), from *N*-isopentyl-4-(trifluoromethyl)aniline and in the presence of acetonitrile (2.0 equiv). [a] HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 30 min, -40 °C. [b] HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 10 min, -20 °C and Nu, 10 min, 0 °C.

Considering their superelectrophilic character, we next explore the ability to use ammonium-carbenium dications to activate C-H bond. To this end, the reactivity of substrate **1a** in the presence of an excess of allylamine (which must furnish the

corresponding ammonium-carbenium dication) was evaluated in superacid HF/SbF₅ (Figure 4). Gratifyingly, in these conditions, the fluorinated product **2a** could be generated in 95% yield after reaction at -20 °C. No reaction occurred in the absence of allylamine. In HF/SbF₅, the substrate **1w** led to product **2w** in 40% yield. The fluorination of the aliphatic chain by the solvated fluoride ions of the superacid solution, concomitantly to the reduction of the allylic chain confirms the intramolecular variant of the process. To explore the potential of this alternative mode of activation, *versus* CCl₄, the behaviour of a protected aminoacid was tested. While substrate **1x** remained unreactive, even in the presence of CCl₄, *N*-allylic analogue **1y** was efficiently converted to the lactone **3y** confirming the efficiency of ammonium-carbenium dications to activate C-H bonds.

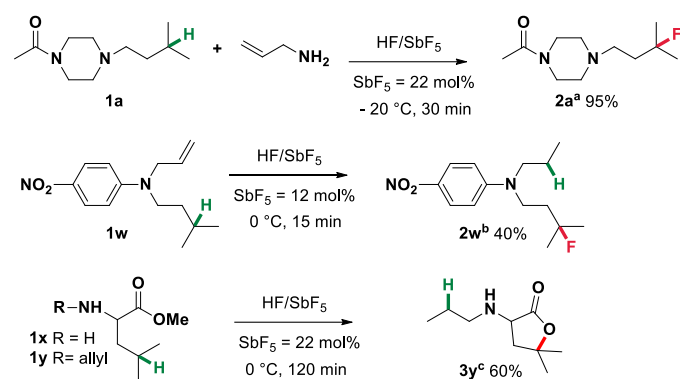


Figure 4. Exploitation of ammonium-carbenium dications to activate C-H. [a] HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 30 min, -20 °C. [b] HF/SbF₅ (12 mol% SbF₅), CCl₄ (1.2 equiv.), 15 min, 0 °C. [c] HF/SbF₅ (22 mol% SbF₅), CCl₄ (1.2 equiv.), 120 min, 0 °C.

In summary, exploiting the hydride abstraction capability of activated CCl₃⁺ species under HF/SbF₅ conditions, we have developed a direct method for the functionalization (fluorination, arylation, amination and deuteration) of unactivated Csp³-H bonds of aliphatic amines. Applied to amides and esters, the superacid-promoted electrophilic activation can be exploited to generate alcohols in a selective manner. The superelectrophilic character of the ammonium-carbenium dication, crucial to favour the fluorination, can also be exploited to activate inert C-H bonds, offering new opportunities for this original process.

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Notes and references

- 1 D. O'Hagan, *Chem. Soc. Rev.* 2008, **37**, 308.
- 2 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd ed, 2013, Wiley-VCH; I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, 2009, Wiley-Blackwell: Chichester; R. Littich, J. H. Scott, *Angew. Chem. Int. Ed.* 2012, **51**, 1106; S. Preshlock, M. Tredwell, V.

- Gouverneur, *Chem. Rev.* 2016, **116**, 719; R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* 2011, **40**, 3496;
- 3 J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, 2008, Wiley: New Jersey.
 - 4 Y. Zhou, J. Wiang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* 2016, **116**, 422; E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* 2015, **58**, 8315; J. Wang, M. Sanchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.*, 2014, **114**, 2432.
 - 5 B. Linclau, Z. Wang, G. Compain, V. Paumelle, C. Q. Fontenelle, N. Wells, A. Weymouth-Wilson, *Angew. Chem. Int. Ed.* 2016, **55**, 674; J. Graton, Z. Wang, A.-M. Brossard, D. Gonçalves Monteiro, J.-Y. Le Questel, B. Linclau, *Angew. Chem. Int. Ed.*, 2012, **51**, 6176; N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philips, D. O'Hagan, *Nat. Chem.* 2015, **7**, 483; X.-G. Hu, D. S. Thomas, R. Griffith, L. Hunter, *Angew. Chem. Int. Ed.* 2014, **53**, 6176; L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* 2011, **50**, 11860.
 - 6 P. Jeschke, E. Baston, F. Leroux, *Mini-Reviews in Medicinal Chemistry*, 2007, **7**, 1027; I. Ojima, *J. Org. Chem.* 2013, **78**, 6358.
 - 7 B. Villemagne, M. Flipo, N. Blondiaux, C. Crauste, S. Malaquin, F. Leroux, C. Piveteau, V. Villeret, P. Brodin, B. O. Villoutreix, O. Sperandio, S. H. Soror, A. Wohlkönig, R. Wintjens, B. Deprez, A. R. Baulard, N. Willand, *J. Med. Chem.*, 2014, **57**, 4876; N. R. Curtis, S. H. Davies, M. Gray, S. G. Leach, R. A. McKie, L. E. Vernon, A. J. Walkington, *Org. Process Res. Dev.* 2015, **19**, 865; A. A. Pieper, S. L. McKnight, J. M. Ready, *Chem. Soc. Rev.* 2014, **43**, 6716.
 - 8 X. Yang, T. Wu, R. J. Phipps, F. Dean Toste, *Chem. Rev.*, 2015, **115**, 826; P. A. Champagne, J. Desroches, J.-D. Hamel, M. Vandamme, J.-F. Paquin, *Chem. Rev.* 2015, **115**, 9073.
 - 9 T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* 2016, **45**, 2900.
 - 10 J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* 2012, **51**, 8960.
 - 11 R. Szpera, D. F. J. Moseley, L. B. Smith, A. J. Sterling, V. Gouverneur, *Angew. Chem. Int. Ed.* 2019, **58**, 14824.
 - 12 J. M. Racowski, J. B. Gary, M. S. Sandford, *Angew. Chem. Int. Ed.* 2012, **51**, 3414; R.-Y. Zhu, K. Tanaka, G.-C. Li, J. He, H.-Y. Fu, S.-H. Li, J.-Q. Yu, *J. Am. Chem. Soc.* 2015, **137**, 7067; J. Piao, K. Yang, M. Kurek, H. Ge, *Org. Lett.* 2015, **17**, 3738; S. D. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton, *Angew. Chem. Int. Ed.* 2014, **53**, 4690; S. D. Halperin, D. Kwon, M. Holmes, E. L. Regalado, L.-C. Campeau, D. A. DiRocco, R. Britton, *Org. Lett.* 2015, **17**, 5200; K. Yamamoto, J. Li, J. A. O. Garber, J. D. Rolfes, G. B. Boursalian, J. C. Borghs, C. Genicot, J. Jacq, M. van Gastel, F. Neese, T. Ritter, *Nature* 2018, **554**, 511.
 - 13 E. N. Pinter, J. E. Bingham, D. I. AbusSalim, S. P. Cook, *Chem. Sci.* 2020, **11**, 1102; S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Letcka, *Angew. Chem. Int. Ed.* 2012, **51**, 10580; Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.*, 2013, **15**, 2160; X. Zhang, S. Guo, P. Tang, *Org. Chem. Front.* 2015, **2**, 806; Z. Yuan, M. B. Nodwell, H. Yang, N. Malik, H. Merckens, F. Bénard, R. E. Martin, P. Schaffer, R. Britton, *Angew. Chem. Int. Ed.* 2018, **57**, 12733; H. Egami, S. Masuda, Y. Kawato, *Org. Lett.* 2018, **20**, 1367; S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Letcka, *Angew. Chem. Int. Ed.*, 2012, **51**, 10580; C. R. Pitts, S. Bloom, R. Woltornist, D. J. Auvenshine, L. R. Ryzhkov, M. A. Siegler, T. Letcka, *J. Am. Chem. Soc.*, 2014, **136**, 9780.
 - 14 S. Rozen, *Acc. Chem. Res.* 1988, **21**, 307; S. Rozen, G. Ben-Shushan, *J. Org. Chem.* 1986, **51**, 3522; S. Rozen, C. Gal, *J. Org. Chem.* 1987, **52**, 4928; R. D. Chambers, M. Parsons, G. Sandford, R. Bowden, *Chem. Commun.* 2000, 959; R. D. Chambers, A. M. Kenwright, M. Parsons, G. Sandford, J. S. Moilliet, *J. Chem. Soc. Perkin Trans I*, 2002, 2190; R. D. Chambers, M. Parsons, G. Sandford, E. Thomas, J. Trmcic, J. S. Moilliet, *Tetrahedron* 2006, **62**, 7162; G. Sandford, *J. Fluorine Chem.* 2007, **128**, 90. R. D. Chambers, T. Nakano, M. Parsons, G. Sandford, A. S. Batsanov, J. A. K. Howard, *J. Fluorine Chem.* 2008, **129**, 811; S. Stavber, M. Zupan, *J. Org. Chem.* 1991, **56**, 7347.
 - 15 E. Laurent, B. Marquet, R. Tardivel, *Tetrahedron*, 1989, **45**, 4431; T. Tajima, H. Ishii, T. Fuchigami, *Electrochemistry Communications*, 2002, **4**, 589.
 - 16 Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard III, J. T. Groves, *Science*, 2012, **337**, 1322; W. Liu, J. T. Groves, *Angew. Chem. Int. Ed.* 2013, **52**, 6024; X. Huang, W. Liu, H. Ren, R. Neelamegam, J. M. Hooker, J. T. Groves, *J. Am. Chem. Soc.* 2014, **136**, 6842; W. Liu, X. Huang, J. T. Groves, *Nat. Protoc.* 2013, **8**, 2348; W. Liu, X. Huang, M. S. Placzek, S. W. Krska, P. McQuade, J. M. Hooker, J. T. Groves, *Chem. Sci.* 2018, **9**, 1168.
 - 17 G. A. Olah, G. K. S. Prakash, A. Molnar, J. Sommer, *Superacids*, 2nd Ed, Wiley Intersciences, New York, 2009.
 - 18 For a review on the concept of σ basicity, see: G. A. Olah, *Angew. Chem. Int. Ed.* 1973, **12**, 173.
 - 19 For a seminal contribution in this field, see: G. A. Olah, J. Lukas, *J. Am. Chem. Soc.* 1967, **89**, 4739; For a review on superacid catalyzed electrophilic activation of alkanes, see: J. Sommer, J. Bukala, *Acc. Chem. Res.* 1993, **26**, 370.
 - 20 J. -C. Jacquesy, M. -P. Jouannetaud, A. Martin, *Bull. Soc. Chim. Fr.* 1997, **134**, 425; N. Yoneda, Y. Takahashi, A. Suzuki, *Chem. Lett.* 1978, **0**, 231; S. Thibaudeau, A. Martin-Mingot, M. -P. Jouannetaud, J. -C. Jacquesy, *Tetrahedron* 2002, **58**, 6643.
 - 21 G. A. Olah, G. Rasul, A. K. Yudin, A. B. urrichter, G. K. S. Prakash; A. L. Chistyakov, I. V. Stankevich, I. S. Akrem, N. P. Gambaryan, M. E. Vol'pin, *J. Am. Chem. Soc.*, 1996, **118**, 1446; G. A. Olah, G. Rasul, L. Heiliger, G. K. S. Prakash, *J. Am. Chem. Soc.* 1996, **118**, 3580.
 - 22 G. A. Olah, D. Klumpp, *Superelectrophiles and their chemistry*; John Wiley and Sons; New York, 2008.
 - 23 D. A. Klumpp, P. S. Beauchamp, G. V. Sanchez, S. L. Aguirre, S. Leon, *Tetrahedron Lett.* 2001, **42**, 5821; D. A. Klumpp, S. L. Aguirre, G. V. Sanchez, S. Leon, *Org. Lett.* 2001, **3**, 2781; Y. Zhang and D. A. Klumpp, *Tetrahedron Lett.* 2002, **43**, 6841; R. R. Naredla, D. A. Klumpp, *Chem. Rev.* 2013, **113**, 6905.
 - 24 For mechanistic investigation on superacid-promoted ionization of alkanes without carbonium ion formation, see: P. Dinér, *J. Phys. Chem. A* 2012, **116**, 9979.
 - 25 See supporting information.
 - 26 For a recent study on fluorocarbenium ions, see: G. A. Olah, G. K. S. Prakash, G. Rasul, *Proc. Nat. Acad. Sci.* 2013, **110**, 8427.
 - 27 A. Martin, A. Arda, J. Désiré, A. Martin-Mingot, N. Probst, P. Sinay, J. Jiménez-Barbero, S. Thibaudeau, Y. Blériot, *Nat. Chem.* 2016, **8**, 186.
 - 28 For recent examples, see: M. C. White, J. Zhao, *J. Am. Chem. Soc.* 2018, **140**, 13988; E. M. Simmons, J. F. Hartwig, *Nature* 2012, **483**, 70.
 - 29 T. G. Gant, *J. Med. Chem.*, 2014, **57**, 3595; R. D. Tung, *Future Med. Chem.* 2016, **8**, 491.
 - 30 For recent C-H bond arylation of amines, see: C. He, M. J. Gaunt, *Angew. Chem. Int. Ed.* 2015, **54**, 15840; O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902.