Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Anti-Selective Aminofluorination of Alkenes with Amidines Mediated by Hypervalent Iodine(III) Reagents

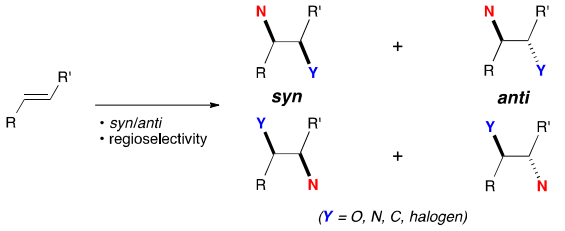
Hui Chen[a] Atsushi Kaga[a] and Shunsuke Chiba[a]*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

***Anti*-selective aminofluorination of alkenes with amidines were enabled by hypervalent iodine(III) reagents, affording 4-fluoroalkyl-2-imidazolines. Further reductive ring-opening of the 2-imidazoline moiety could deliver highly functionalized 3-fluoropropane-1,2-diamine derivatives.**

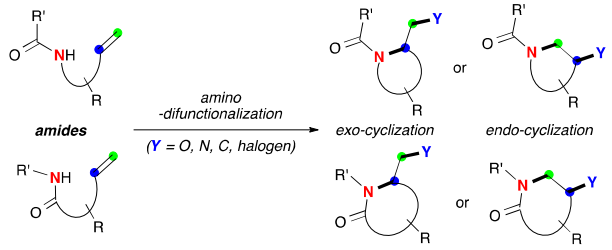
Difunctionalization of alkenes is one of the most powerful processes for chemical transformations in organic synthesis. A variety of synthetic methods enabling stereo- and chemoselective difunctionalization of alkenes, including the Sharpless dihydroxylation[1] and aminohydroxylation[2] as representative examples, have been exploited to generate diverse molecular complexity.[3] A major concern in the methodology development of hetero difunctionalization of alkenes such as amino-functionalization is regioselectivity and stereoselectivity (*anti*- or *syn*-) (Scheme 1).



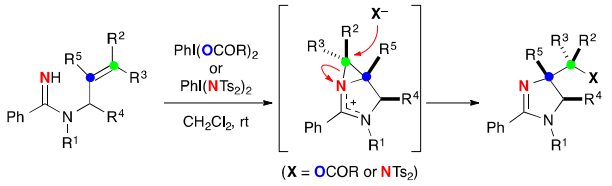
Scheme 1. Regio- and stereoselectivtiy in amino-difunctionalization of alkenes.

Among the known difunctionalization reactions, intramolecular amino-difunctionalization of alkenes[4] provides a convenient access to various nitrogen-containing heterocycles (azaheterocycles), which were prevalent scaffolds in potent pharmaceutical drugs.[5,6] Within this arena, a mainstream strategy is to use alkenyl amides/sulfonamides under various oxidative reaction conditions with/without transition metal catalysis (Scheme 2).

In comparison with these alkenyl amides, alkenyl amidines are expected to exhibit somewhat different reactivity trends in the oxidative amino-difunctionalization for synthesis of nitrogen-containing molecules, because (1) the electron-rich nature of amidines might provide a unique and unprecedented mode of reaction in alkene difunctionalization; (2) azaheterocyclic products, cyclic amidines such as 2-imidazolines, include 1,3-diamino functionality, and further reductive ring-opening of cyclic amidines enables construction of highly functionalized 1,2-diamines.[7] In this context, we have recently disclosed hypervalent iodine(III)-mediated (transition-metal free) diastereoselective *anti*-selective aminoacetoxylatio/formal-aminohydroxylation, and diamination of alkenes with amidines (Scheme 3).[8] The process likely involves concerted alkene-aziridination with a putative amidine-I(III) intermediate and subsequent nucleophilic ring-opening of the aziridine moiety caused by the corresponding counter O- or N-ions, which therefore results in *anti*-selective amino-functionalization of alkenes.



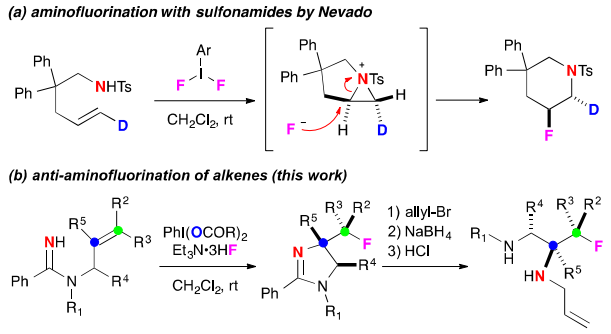
Scheme 2. Intramolecular amino-difunctionalization of alkenyl amides for azaheterocycle synthesis**.**



Scheme 3. Metal-free diastereoselective amino-difinctionalization of alkenes with amidines by hypervalent I(III) reagents.

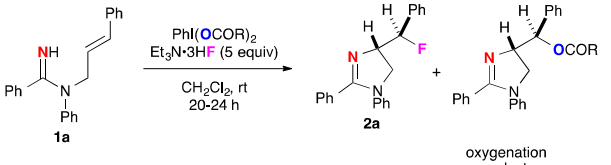
To explore further potential of this hypervalent iodine(III) reagents-mediated transition-metal free strategy for alkene amino-functionalization with amidines,[9] we wondered if the transient aziridinium ions could be attacked by external fluoride nucleophiles for aminofluorination of alkenes.[10] Aminofluorination of alkenyl sulfonamides were recently reported independently by Nevado[10f] and Meng/Li[10i] using difluoroiodoarenes ($ArIF_2$) and a $PhI(OPiv)_2$-HF•pyridine system, respectively (Scheme 4-a for Nevado's work). However, both of these reactions resulted in the formation of *endo*-selective aminofluorination products, and substrates amenable to these methods were limited to terminal alkenes. We describe herein

anti-selective aminofluorination of *N*-allylamidines by the combined use of iodobenzene dicarboxylates and Et_3N•3HF for construction of diastereochemically pure 4-fluoroalkyl-2-imidazolines divergently from internal *E*- and *Z*-alkenes (Scheme 4-b).[11] Furthermore, facile reductive ring-opening of the 4-fluoroalkyl-2-imidazoline moiety has also been executed to synthesize highly functionalized 3-fluoropropane-1,2-diamine derivatives.[12,13]



Scheme 4. Aminofluorination mediated by hypervalent iodine(III) reagents.

The initial study commenced with the reactions of *N*-allylamidine **1a** (Scheme 5). It is known that the reactions of iodobenzene dicarboxylates with fluoride salts generate the corresponding difluoroiodanes,[14] which might be used for aminofluorination with amidine **1a**. As expected, the reaction of amidine **1a** with 1.3 equiv of $PhI(OAc)_2$ and 5 equiv of Et_3N•3HF in CH_2Cl_2 delivered 4-fluoromethyl-2-imidazoline **2a** in 59% yield along with aminoacetoxylation product **3a** in 18% yield (Scheme 5). To improve the yield of **2a** with reduction of the amount of undesired aminocarboxylation product, more bulky carboxylates on hypervalent iodine reagents were examined. Use of iodobenzene dipivalate [$PhI(OPiv)_2$] slightly improved the yield of **2a** to 69% yield, and the yield of the corresponding aminopivalation product **4a** was 13%. Use of 2-isopropyl-2,3-dimethylbutanoate counter ion could enhance the yield of **2a** to 73% yield with 8% yield of carboxylation product **5a**.

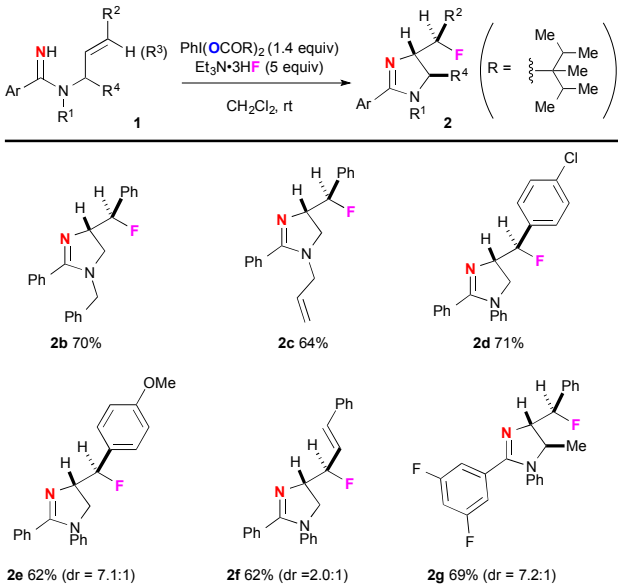


$PhI(OCOR)_2$	**2a**	oxygenation products
R = Me (1.3 equiv)	59%	**3a** 18%
R = *t*-Bu (1.3 equiv)	69%[a]	**4a** 13%
R = Me, Me, Me (1.4 equiv), Me, Me, Me	73%	**5a** 8%

Scheme 5. Aminofluorination of **1a** using Et_3N•3HF salt. [a] Isolated as an inseparable mixture with **4a**.

With the reaction conditions using $PhI[OCOC(i\text{-}Pr)_2Me]_2$ (1.4 equiv) and Et_3N•3HF (5 equiv), we examined substrate scope for aminofluorination of disubstituted *E*-alkenes (where R^3 = H) (Table 1). As for R^1 on the nitrogen, a benzyl (for **1b**) group was well tolerated and provided **2b** in 70% yield. The reaction of amidine **1c** having an allyl functionality as R^1 selectively afforded 2-imidazolines **2c** in 64% yield, demonstrating unique chemoselectivity of the present aminofluorination of alkenes that prefers internal alkenes. By varying substituents R^2 on the *E*-alkene part, it was shown that 4-chloro- (for **1d**) and 4-methoxyphenyl (for **1e**) groups were well tolerated, providing **2d** and **3e** in good yields. Aminofluorination of the dienyl moiety also worked efficiently to give 2-imidazoline **2f** in 62% yield, while the reaction resulted in moderate diastereoselectivity (2:1). The reaction of amidine **1g** with a methyl group as R^4 afforded 2-imidazoline **2g** bearing three successive stereogenic centers in good diastereoselectivity. In this process, the N–C bond could be constructed from the opposite side to the methyl group.

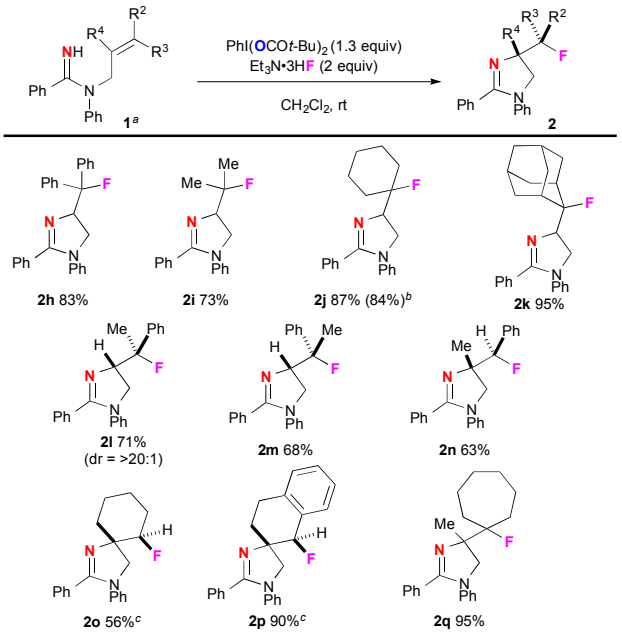
Table 1. Substrate scope on aminofluorination of disubstituted alkenes using Et_3N•3HF[a,b]



[a] The reactions were carried out using 0.3 mmol of amidines **1**. Unless otherwise noted, the reactions provided diastereomerically pure products **2**. [b] Aminocarboxylation compounds **5** were formed as a minor product in 8-21% yields. See the Electronic Supplementary Information (ESI) for more details.

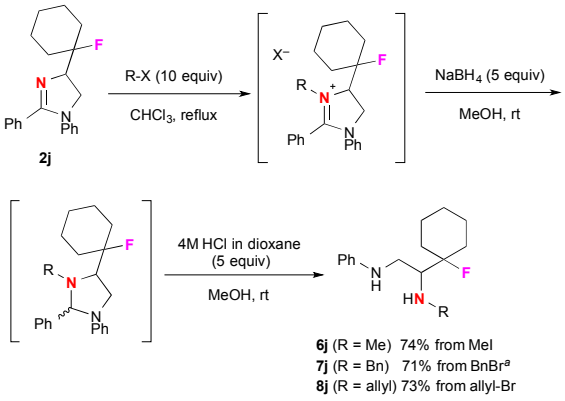
We next investigated the reactions of 3,3-disubstituted allyl amidines **1h-k** (Table 2). It was found that use of $PhI(OPiv)_2$ was optimal for aminofluorination of these *tri*-substituted alkenes, undergoing aminofluorination selectively to give 2-imidazolines **2h-k** in good yields. Similarly with the previous aminoacetoxylation and diamination,[8] diastereo-divergency could be observed for the aminofluorination of amidine **1l** with *E*-alkene and **1m** with *Z*-alkene, giving **2l** and **2m**, respectively, in good yields.[15] The process also enabled *anti*-selective aminofluorination of 2,3-disubstituted allylamidines **1n-1p** as well as aminofluorination of *tetra*-substituted alkene **1q** exclusively in *exo*-selective cyclization mode, giving the corresponding 2-imidazolines **2n-q** as the sole products..

Table 2. Substrate scope on aminofluorination of *tri*- and *tetra*-substituted alkenes using $Et_3N•3HF$[a]



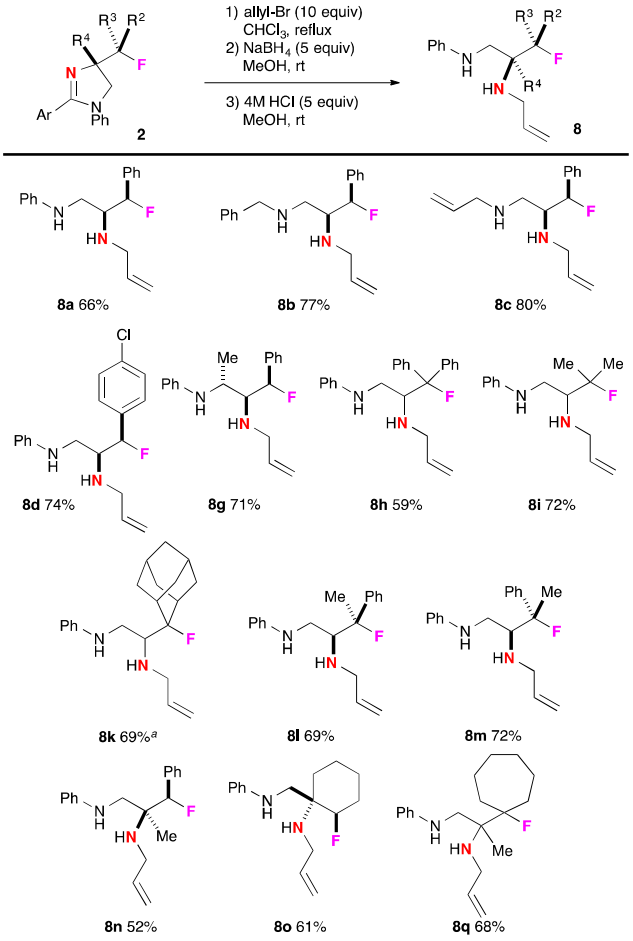
[a]Unless otherwise noted, the reactions were carried out using 0.3 mmol of amidines **1** and afforded diastereomerically pure products **2**. [b]The yield of **1j** in the reaction using 4 mmol of **1j**. [c]The reaction was carried out using 1.4 equiv of $PhI[OCO(i\text{-}Pr)_2Me]_2$ and 5 equiv of $Et_3N•3HF$ salt. Aminocarboxylation compounds **5o** and **5p** were formed as a minor product in 3% and 7% yields, respectively. See the ESI for more details.

It has already been reported that reductive ring-opening of 2-imidazoline derivatives could be mediated by AlH_3 to afford 1,2-diamines.[7] However, treatment of 4-fluoroalkyl-2-imidazolines **2** with AlH_3 gave a complex mixture of unidentified compounds instead of desired diamines. We thus sought an alternative milder ring-opening method using **2j** and found that a stepwise procedure including 1) formation of amidinium salts with alkyl halides (MeI, BnBr, and allyl-Br); 2) $NaBH_4$ reduction; 3) acidic solvolysis gave the corresponding ring-opened diamines **6j**-**8j** in good yields (Scheme 6). Using this 3-steps procedure with allyl bromide, a variety of 3-fluoropropane-1,2-diamines **8** were synthesized from the corresponding 2-imidazolines **2** as shown in Table 3.



Scheme 6. Reductive ring-opening of **2j**. [a]4 equiv of BnBr was used.

Table 3. Reductive ring-opening of **2**



[a]15 equiv allyl-Br was used.

In summary, we have developed methods for diastereoselective aminofluorination of *N*-allylamidines that utilize hypervalent iodine(III) reagents. The resulting 4-fluoroalkyl-2-imidazolines could be concisely converted into various 3-fluoropropane-1,2-diamine derivatives. We anticipate that this strategy is capable of supplying various fluoro-containing polyamine compounds useful for medicinal, materials, and catalysis applications.

This work was supported by funding from Nanyang Technological University (NTU) and Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2012-T2-1-014).

Notes and references

[a] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. Fax: +65-67911961; E-mail: shunsuke@ntu.edu.sg*

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of products, and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b000000x/

1 For leading reviews, see: (a) H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.* 1994, **94**, 2483. (b) A. B. Zaitsev and H. Adolfsson, *Synthesis* 2006, 1725. (c) C. Bolm, J. P. Hildebrand and

K. Muñiz, *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, 2000, p. 299.

2 For leading reviews, see: (a) K. Muñiz, *Chem. Soc. Rev*. 2004, **33**, 166. (b) T. J. Donohoe, C. K. A. Callens, A. Flores, A. R. Lacy and A. H. Rathi, *Chem. Eur. J.* 2011, **17**, 58. (c) K. Muñiz, *Comprehensive Chirality*, Vol. 5 (Eds.: E. M. Carreira, H. Yamamoto), Elsevier, Amsterdam, 2012, 9.183.

3 For reviews, see: (a) S. R. Chemler and M. T. Bovino, *ACS Catal*. 2013, **3**, 1076. (b) K. Muñiz and C. Martínez, *J. Org. Chem.* 2013, **78**, 2168. (c) W. Wu and H. Jiang, *Acc. Chem. Res.* 2012, **45**, 1736. (d) S. E. Denmark, W. E. Kuester and M. T. Burk, *Angew. Chem., Int. Ed*. 2012, **51**, 10938. (e) T. J. Donohoe, C. K. A. Callens, A. R. Lacy and C. Winter, *Eur. J. Org. Chem.* 2012, 655. (f) D. M. Schultz and J. P. Wolfe, *Synthesis* 2012, 351. (g) R. I. McDonald, G. Liu and S. S. Stahl, *Chem. Rev*. 2011, **111**, 2981. (h) J. P. Wolfe, *Synlett* 2008, 2913. (i) K. H. Jensen and M. S. Sigman, *Org. Biomol. Chem*. 2008, **6**, 4083. (j) S. R. Chemler and P. H. Fuller, *Chem. Soc. Rev.* 2007, **36**, 1153. (k) A. Minatti and K. Muñiz, *Chem. Soc. Rev*. 2007, **36**, 1142.

4 For reviews on amino-functionalization of alkenes, see: (a) Y. A. Cheng, W. Z. Yu and Y.-Y. Yeung, *Org. Biomol. Chem.* 2014, **12**, 2333. (b) S. De Jong, D. G. Nosal and D. J. Wardrop, *Tetrahedron* 2012, **68**, 4067. (c) G. Li, S. R. S. S. Kotti and C. Timmons, *Eur. J. Org. Chem.* 2007, 2745.

5 For general reviews, see: (a) L. D. Quin and J. Tyrell, Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals; John Wiley & Sons Inc.: New York, 2010. (b) Comprehensive Heterocyclic Chemistry III; A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Eds.; Pergamon: Oxford, 2008. (c) Comprehensive Heterocyclic Chemistry II; A. R. Katritzky, E. F. V. Scriven and C. W. Rees, Eds.; Pergamon: Oxford, 1996. (d) Comprehensive Heterocyclic Chemistry; A. R. Katritzky and C. W. Rees, Eds.; Pergamon: Oxford, 1984. (e) T. Eicher and S. Hauptmann, The Chemistry of Heterocycles; Wiley-VCH: Weinheim, 2003.

6 For selected reviews on azaheterocycle synthesis, see: (a) C.-M. T. Vo and J. W. Bode, *J. Org. Chem*. 2014, **79**, 2809. (b) G. L. Thomas and C. W. Johannes, *Curr. Opin. Chem. Biol*. 2011, **15**, 516. (c) R. Tohme, N. Darwiche and H. Gali-Muhtasib, *Molecules*, 2011, **16**, 9665. (d) S. Dandapani and L. A. Marcaurelle, *Curr. Opin. Chem. Biol*. 2010, **14**, 362. (e) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol*. 2010, **14**, 347. (f) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem*. 2006, **4**, 2337.

7 For our reports on Cu-catalyzed oxidative molecular transformation of alkenyl amidines, see: (a) Y.-F. Wang, X. Zhu and S. Chiba, *J. Am. Chem. Soc*. 2012, **134**, 3679. (b) S. Sanjaya and S. Chiba, *Org. Lett*. 2012, **14**, 5342.

8 H. Chen, A. Kaga and S. Chiba, *Org. Lett*. 2014, **16**, 6136.

9 For reviews on application of hypervalent iodine reagents in organic synthesis, see: (a) J. Charpentier, N. Früh and A. Togni, *Chem. Rev*. 2015, **115**, 650. (b) R. Samanta, K. Matcha and A. P. Antonchick, *Eur. J. Org. Chem*. 2013, 5769. (c) V. V. Zhdankin, *J. Org. Chem*. 2011, **76**, 1185. (d) H. Liang and M. A. Ciufolini, *Angew. Chem., Int. Ed*. 2011, **50**, 11849. (e) A. Duschek and S. F. Kirsh, *Angew. Chem., Int. Ed*. 2011, **50**, 1524. (f) M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *Arkivoc* 2011, **i**, 370. (g) S. Quideau and T. Wirth, *Tetrahedron* 2010, **66**, 5727. (h) L. Pouységu and D. Deffieux, S. Quideau, *Tetrahedron* 2010, **66**, 2235. (i) E. A. Merritt and B. Olofsson, *Angew. Chem., Int. Ed*. 2009, **48**, 9052. (j) M. Uyanik and K. Ishihara, *Chem. Commun*. 2009, 2086. (k) T. Dohi and Y. Kita, *Chem. Commun*. 2009, 2073. (l) V. V. Zhdankin and P. J. Stang, *Chem. Rev*. 2008, **108**, 5299. (m) M. Ochiai and K. Miyamoto, *Eur. J. Org. Chem*. 2008, 4229. (n) N. R. Deprez and M. S. Sanford, *Inorg. Chem*. 2007, **46**, 1924. (o) M. Ochiai, *Chem. Rec*. 2007, **7**, 12. (p) T. Wirth, *Angew. Chem., Int. Ed*. 2005, **44**, 3656.

10 For reports on azaheterocycle synthesis by aminofluorination of alkenyl amides, see: (a) D. Parmar and M. Rueping, *Chem. Commun.* 2014, **50**, 13928. (b) D.-F. Lu, G.-S. Liu, C.-L. Zhu, B. Yuan and H. Xu, *Org. Lett.* 2014, **16**, 2912. (c) J. Cui, Q. Jia, R.-Z. Feng, S.-S. Liu, T. He and C. Zhang, *Org. Lett.* 2014, **16**, 1442. (d) G.-Q. Liu and Y.-M. Li, *J. Org. Chem.* 2014, **79**, 10094. (e) S. Suzuki, T. Kamo, K. Fukushi, T. Hiramatsu, E. Tokunaga, T. Dohi, Y. Kita and N. Shibata, *Chem. Sci*. 2014, **5**, 2754. (f) W. Kong, P. Feige, T. de Haro and C. Nevado, *Angew. Chem., Int. Ed.* 2013, **52**, 2469. (g) Z. Li, L. Song and C. Li, *J. Am. Chem. Soc*. 2013, **135**, 4640. (h) T. Wu, J. Cheng, P. Chen and G. Liu, *Chem. Commun.* 2013, **49**, 8707. (i) Q. Wang, W. Zhong, X. Wei, M. Ning, X. Meng and Z. Li, *Org. Biomol. Chem.* 2012, **10**, 8566. (j) T. Xu, S. Qiu and G. Liu, *Chin. J. Chem.* 2011, **29**, 2785. (k) T. Wu, G. Yin and G. Liu, *J. Am. Chem. Soc.* 2009, **131**, 16354.

11 The present aminofluorination was not applicable to the substrates having terminal alkenes.

12 For recent reviews on fluorination reactions, see: (a) P. Chen and G. Liu, *Eur. J. Org. Chem*. 2015, 4295. (b) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed*. 2013, **52**, 8214. (c) G. Liu, *Org. Biomol. Chem*. 2012, **10**, 6243. (d) S. Stavber, *Molecules* 2011, **16**, 6432. (e) J. Baudoux and D. Cahard, *Org. React*. 2007, **69**, 347. (f) P. T. Nyffeler, S. G. Duron, M. D. Burkart, S. P. Vincent and C. H. Wong, *Angew. Chem. Int. Ed*. 2005, **44**, 192. (g) G. S. Lal, G. P. Pez and R. G. Syvret, *Chem. Rev*. 1996, **96**, 1737.

13 For general reviews on fluorine-containing molecules, see: (a) P. Kirsch, *Modern fluoroorganic chemistry: synthesis, reactivity, applications*, Wiley-VCH, Weinheim, 2013. (b) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, Chichester, 2009. (c) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Hoboken, 2008. (d) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev*. 2008, **37**, 320. (e) K. Müller, C. Faeh and F. Diederich, *Science* 2007, **317**, 1881.

14 (a) K. B. McMurtrey, J. M. Racowski and M. S. Sanford, *Org. Lett*. 2012, **14**, 4094. (b) H. Sun, B. Wang and S. G. DiMagno, *Org. Lett*. 2008, **10**, 4413.

15 The structure of compound **2l** was determined by X-ray crystallographic analysis. See the Electronic Supplementary Information for more details.