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Fluorocyanation of Enamines

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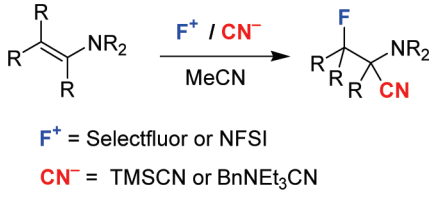
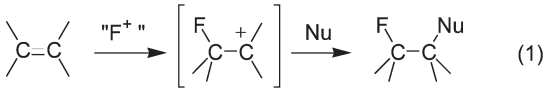
Received May 7, 2010



A method for the fluorocyanation of enamines has been described. The reaction involves fluorination of the electron rich double bond with N−F reagent (Selectfluor or NFSI) accompanied by trapping of β-fluoroiminium cationic intermediate with cyanide nucleophile.

Due to the unique properties of fluorinated compounds,[1] as well as their importance in pharmaceutical research,[2] methods for the direct introduction of a single fluorine atom into organic molecule have attracted considerable attention.[3] While processes involving introduction of nucleophilic fluoride have been studied for decades,[4,5] reactions in which the fluorine is introduced electrophilically have come to the fore only in recent times after the advent of convenient fluorinating reagents.[6−8] In particular, reagents with a N−F bond can be considered as equivalents of positive fluorine and can be employed in reactions with many organic and organometallic nucleophiles.[6−8] Typical N−F reagents such as Selectfluor, *N*-fluorobenzenesulfonimide (NFSI), and *N*-fluoropyridinium triflate are commercially available (Figure 1).

The interaction of alkenes with fluorinating reagent generates labile β-fluorocarbocations,[9] which are either trapped by oxygen or nitrogen nucleophile[10] (eq 1) or stabilized by elimination of an adjacent proton or silyl group.[11] Herein we report the first example of a process involving electrophilic fluorination accompanied by addition of a carbon nucleophile.



(1)

To realize this process in a three-component manner, a fluorinating reagent should react with alkene faster than with carbon nucleophile. At the same time, intermediate β-fluorocarbocation should react faster with nucleophile than with the starting alkene. To satisfy these criteria we selected enamines as electron rich alkenes readily susceptible to fluorination,[12,13] and trimethylsilyl cyanide (TMSCN) as terminating nucleophile.

(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319. (b) *Organofluorine Chemistry*; Uneyama, K., Ed.; Blackwell: Oxford, U.K., 2006. (c) *Fluorine in Organic Chemistry*; Chambers, R., Ed.; Blackwell: Oxford, U.K., 2004.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (c) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.

(3) (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321. (b) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803–819.

(4) (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561–2578. (b) Adams, D. J.; Clark, J. H. *Chem. Soc. Rev.* **1999**, *28*, 225–231. (c) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647–667. (d) Mascaretti, O. A. *Aldrichim. Acta* **1993**, *26*, 47−58. For recent works, see: (e) Lee, J. W.; Yan, H.; Jang, H. B.; Kim, H. K.; Park, S.-W.; Lee, S.; Chi, D. Y.; Song, C. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 7683–7686. (f) Sun, H.; DiMagno, S., G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720–2725. (g) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051. (h) Kim, K.-Y.; Kim, B. C.; Lee, H. B.; Shin, H. *J. Org. Chem.* **2008**, *73*, 8106–8108.

(5) For transition metal catalyzed nucleophilic fluorination, see: (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664. (b) Grushin, V. V. *Acc. Chem. Res.* **2009**, *43*, 160–171.

(6) (a) Baudoux, J.; Cahard, D. *Org. React. (N.Y.)* **2007**, *69*, 347–672. (b) Brunet, V., A.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1179–1182. (c) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737–1756. (d) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477.

(7) For reviews on Selectfluor, see: (a) Nyffeler, P. T.; Duryn, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192–212. (b) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2003**, *37*, 31–44. (c) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1–17.

(8) For transition metal catalyzed electrophilic fluorination, see: Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135. (b) Wang, X.; Mei, T.-S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520–7521. (c) Furuya, T.; Kaiser, H. M.; Ritter, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5993–5996.

(9) The mechanism of electrophilic fluorination is a matter of debate. Though one-step transfer of "F^{+}" is usually proposed, the ion-radical mechanisms have also been suggested. For discussion, see refs 6a, 6c, and 7a.

(10) (a) Lal, G. S. *J. Org. Chem.* **2002**, *58*, 2791–2796. (b) Stavber, S.; Sotler, T.; Zupan, M. *Tetrahedron Lett.* **1994**, *35*, 1105–1108. (c) Stavber, S.; Pecan, T. S.; Pape, M.; Zupan, M. *Chem. Commun.* **1996**, 2247–2248. (d) Vincent, S. P.; Burkart, M. D.; Tsai, C.-Y.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264–5279. (e) Zhou, C.; Li, J.; Lu, B.; Fu, C.; Ma, S. *Org. Lett.* **2008**, *10*, 581–583. (f) Wilkinson, S. C.; Lozano, O.; Schuler, M.; Pacheco, M. C.; Salmon, R.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 7083–7086.

(11) (a) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26–32. (b) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291–3294. (c) Gouverneur, V.; Greedy, B. *Chem.—Eur. J.* **2002**, *8*, 766–772. (d) Greedy, B.; Gouverneur, V. *Chem. Commun.* **2001**, 233–234.

(12) With N−F reagents: (a) Peng, W.; Shreeve, J. M. *J. Org. Chem.* **2005**, *70*, 5760–5763. (b) Stanton, M. G.; Hubbs, J.; Sloman, D.; Hamblett, C.; Andrade, P.; Angagaw, M.; Bi, G.; Black, R. M.; Crispino, J.; Cruz, J. C.; Fan, E.; Farris, G.; Hughes, B. L.; Kenific, C. M.; Middleton, R. E.; Nikov, G.; Sajonz, P.; Shah, S.; Shomer, N.; Szewczak, A. A.; Tanga, F.; Tudge, M. T.; Shearman, M.; Munoz, B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 755–758. (c) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595–596. (d) Poss, A. J.; Van der Puy, M.; Nalewajek, D.; Shia, G. A.; Wagner, W. J.; Frenette, R. L. *J. Org. Chem.* **1991**, *56*, 5962–5964. (e) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1992**, *112*, 8563–8575. (f) Purrington, S. T.; Jones, W. A. *J. Fluorine Chem.* **1984**, *26*, 43–46. (g) Alkhathlan, H. Z. *Tetrahedron* **2003**, *59*, 8163−8170. With O−F reagnets: (h) Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. *Chem. Commun.* **1968**, 804–806. (i) Njar, V. C. O.; Arunachalam, T.; Caspi, E. *J. Org. Chem.* **1983**, *48*, 1007–1011.

DOI: 10.1021/jo1008993 Published on Web 07/02/2010

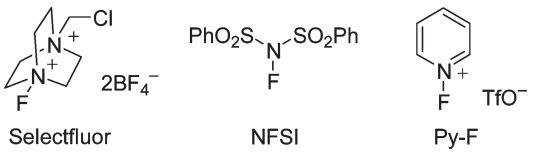
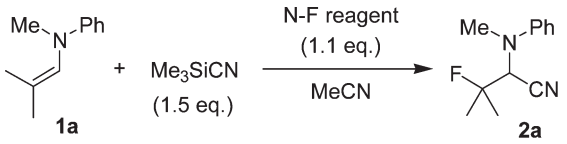


FIGURE 1. Fluorinating reagents.

TABLE 1. Reaction of Enamine 1a.[a]



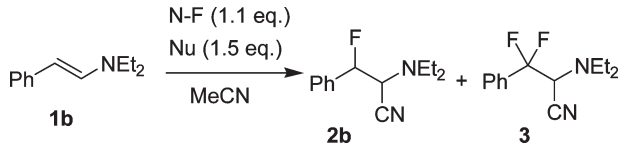
entry	reagent	additive	yield of **2a**,[b] %
1	Selectfluor		50−75
2	NFSI		79[c]
3	Py-F		35[d]
4	Selectfluor	Py	89
5	Selectfluor	NEt_3	41[d]
6	Selectfluor	dabco	23[d]
7	NFSI	Py	89
8	NFSI	NEt_3	70[d]

[a]Conditions: for Selectfluor, −30 °C, 30 min, then 15 min at 0 °C; for NFSI and Py-F, 1 h at 0 °C. [b]Isolated yield unless mentioned otherwise. [c]Byproduct 3-methyl-2-[methyl(phenyl)amino]butanenitrile (ca. 10%) was formed. [d]Determined by NMR spectroscopy with trichloroethylene as internal standard.

The overall result of this stepwise reaction corresponds to fluorocyantion of the C=C bond. It should be pointed out that in the literature addition reactions of cyanogen fluoride to alkenes have not been reported.[14]

Fluorinating reagents shown in Figure 1 were used in initial experiments. Thus, a mixture of enamine **1a** and TMSCN was treated with the fluorinating reagent either at −30 to 0 °C (for most reactive Selectfluor) or at 0 °C (for NFSI and Py-F) (entries 1−3, Table 1). Though the product **2a** was formed in good yields with Selectfluor and NFSI, the reactions with the former provided irreproducible yields, while with the latter the formation of up to 10% of byproduct originating from the addition of HCN to the enamine was noted. It was observed that these reactions proceed much cleaner when pyridine (1.2 equiv) was added, whereas triethylamine and dabco were ineffective. Pyridine may serve for the stabilization of intermediate fluoroiminium carbocation[15] and/or as a scavenger of trimethylsilyl cation arising after consumption of TMSCN.[16] At the same time,

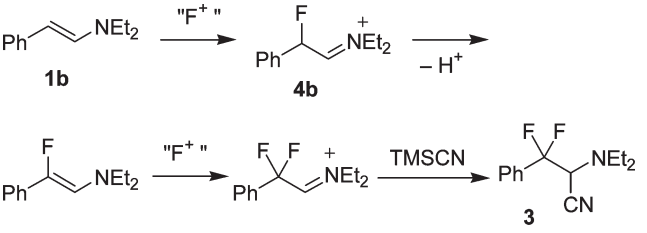
TABLE 2. Reaction of Enamine 1b



no.	reagent	Nu	conditions	ratio[a] **2b**:**3**	yield of **2b**, % (dr)
1	Selectfluor/Py	TMSCN	−30→0 °C	1:15	
2	NFSI/Py	TMSCN	0 °C	1:9	
3	Selectfluor	$BnNEt_3CN$	−30→0 °C	>20:1	85 (3.2: 1)
4	NFSI	$BnNEt_3CN$	−30→0 °C	>20:1	36 (1.8: 1)

[a]Determined by NMR spectroscopy of crude product.

SCHEME 1. Mechanism of Difluorination



the formation of *N*-fluoropyridinium cation seems unlikely due to its decreased activity as fluorinating reagent toward enamine **1a** (entry 3).

When enamine **1b** was subjected to optimized conditions for fluorocyanation, which required only 1.1 equiv of fluorinating reagent, the desired product **2b** was formed in less than 10% yields, with the major product being difluorinated amine **3** (entries 1 and 2, Table 2). The formation of product **3** likely occurs through the deprotonation of initially formed fluoroiminium intermediate **4b** to generate fluoroenamine followed by a second fluorination step[17] (Scheme 1).

To avoid this side reaction it is necessary to increase the rate of trapping of iminium ion **4b** by the cyanide nucleophile. Indeed, addition of Selectfluor to a mixture of enamine **1b** and benzyltriethylammonium cyanide cleanly gave amine **2b** as the sole product, the difluorinated amine **3** was not detected in the crude sample. The amine **2b** was isolated in 85% yield as a mixture of diastereoisomers (entry 3). A similar experiment with NFSI also afforded only monofluorinated compound in reduced yield, while significant amounts of starting **1b** remained unreacted. We tested the combination Selectfluor/cyanide anion for the reaction with enamine **1a**, and found only 36% conversion to the fluorocyantion product.

Various enamines were subjected to fluorocyantion reactions (Table 3). For enamines **1c**−**f** bearing two substituents at the β-position, reactions were performed with Selectfluor or NFSI and TMSCN (entries 1−6). Reasonable yields of products were achieved, though for compounds **1e**,**f** the use of triethylamine instead of pyridine gave better results. For the enamines **1g**−**j** containing a β-hydrogen atom the combination Selectfluor/$BnNEt_3CN$ was used affording fluorocyanation

(13) Organocatalytic fluorination reactions proceeding through enamine intermediates: (a) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703–3706. (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710. (d) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991–0993. (e) Jiang, H.; Falcicchio, A.; Jensen, K. L.; Paixão, M. W.; Bertelsen, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 7153–7157.

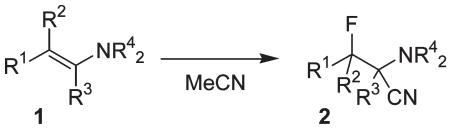
(14) At the same time, the interaction of enamines with bromocyane, as well as with bromine followed by potassium cyanide, has been described, see: De Kimpe, N.; Verhe, R.; De Buyck, L.; Schamp, N. *Chem. Ber.* **1983**, *116*, 3846–3857.

(15) Earlier, upon the interaction of glycals with Selectfluor the stabilization of β-fluorooxocarbenium ion with the bicyclic nitrogen base, which is formed from Selectfluor, was observed; see ref 10d.

(16) (a) Arshadi, M.; Johnels, D.; Edlund, U.; Ottosson, C.-H.; Cremer, D. *J. Am. Chem. Soc.* **1996**, *118*, 5120–5131. (b) Bassindale, A. R.; Stout, T. *Tetrahedron Lett.* **1985**, *26*, 3403–3406.

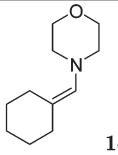
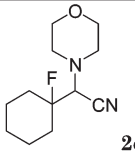
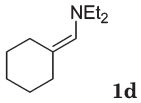
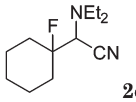
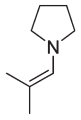
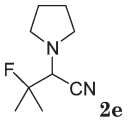
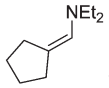
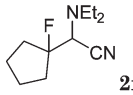
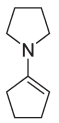
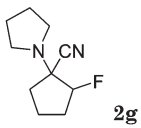
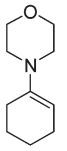
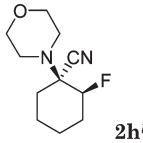
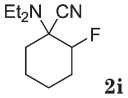
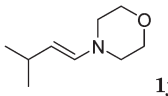
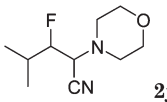
(17) The difluorination of enamines followed by hydrolysis of iminum cation to give either dilfuoroketones or difluorosemiaminals was described; see refs 12a and 12b.

TABLE 3. Fluorocyanation of Enamines



1 **2**

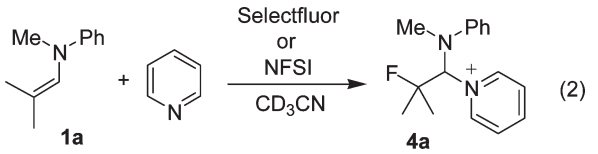
A: 1.1 NFSI, 1.2 pyridine, 1.5 TMSCN, 0 °C, 1h
B: 1.1 Selectfluor, 1.2 base, 1.5 TMSCN, –30 → 0 °C, 0.5 h
C: 1.1 Selectfluor, 1.5 $BnNEt_3CN$, –30 → 0 °C, 0.5 h

#	enamine	method	product	yield of **2**, %[a] (dr)
1	 **1c**	A	 **2c**	84
2	 **1d**	B/Py	 **2d**	60
3	 **1e**	A	 **2e**	65
4		B/NEt_3		70
5	 **1f**	A	 **2f**	65
6		B/NEt_3		76
5	 **1g**	C	 **2g**	87 (1.1 : 1)
6	 **1h**	C	 **2h**[b]	72 (1.9 : 1)
7	 **1i**	C	 **2i**	68 (2.5 : 1)
8	 **1j**	C	 **2j**	42 (1 : 1)

[a]Isolated yield. [b]The structure of the major isomer is shown.

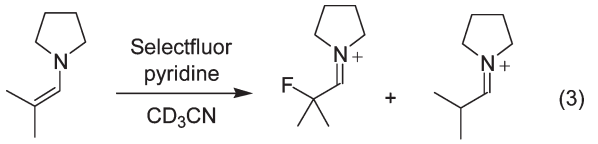
products in good to moderate yields (entries 5−8). It may be proposed that the efficiency of the reaction decreases with the decrease of nucleophilicity of the enamine substrate.[18] The products **2g−j** were formed as mixtures of diastereoisomers. For compound **2h**, the structure of the major isomer was studied by X-ray diffraction analysis that showed trans arrangement of fluorine atom and cyano group (see the Supporting Information for details).

To gain insight on the nature of reaction intermediates and understand the role of pyridine additive, several experiments were performed in an NMR tube in CD_3CN. Thus, when a solution of enamine **1a** and pyridine was treated with either Selectfluor or NFSI, a major cationic species was observed corresponding to the pyridinium salt **4a** according to ^1H, ^{19}F, and ^{13}C NMR spectroscopy[19] (eq 2).



1a **4a** (2)

However, in a similar experiment with enamine **1e**, the β-fluoroiminium ion **5** was observed along with 23% of iminium cation **6**[20] (eq 3). The proton signals of pyridine remained unshifted, but broadening may suggest the equilibrium interaction with the iminium carbocation. Notably, in ^1H and ^{13}C spectra of **5** and **6**, the sp^2-CH iminium fragment contains splitting with the ^{14}N nucleus, which is characteristic of complete involvement of the nitrogen lone pair in conjugation with the adjacent carbocationic center.[21]



1e **5** 3.3 : 1 **6** (3)

It was also interesting to evaluate the compatibility of fluorinating reagents with nucleophilic reagents. No reaction between NFSI and TMSCN in CD_3CN was noted at room temperature for 1 h. In contrast, treatment of Selectfluor with 1.2 equiv of TMSCN caused rapid decomposition of TMSCN to form TMS-fluoride (40% conversion in 15 min at rt), with the fluoroammonium dication being mostly untouched (ca. 95%). In 1 h no TMSCN was observed, whereas 75% of fluoroammonium dication remained unreacted. Conversion of TMSCN to TMS-fluoride (confirmed by ^1H and ^{19}F NMR) likely occurs with the participation of tetrafluoroborate anion.[22]

After mixing of Selectfluor or NFSI with $BnNEt_3CN$ in CD_3CN no signals of initial N−F species were detected even upon the first NMR measurements (a few minutes after mixing). These results suggest that fluorocyanation of the alkene substrate may be successful only if fluorination of the substrate is faster than the decomposition of the fluorinating reagent.

In summary, an approach for the fluorocyantion of enamines has been described. The reaction involves convenient fluorinating reagents along with silylcyanide or cyanide anion, and proceeds through the intermediacy of β-fluoroiminium cationic intermediates. Further studies will be focused

(18) Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209–2218.

(19) The distinction between aminal (CH-sp^3) or iminium (CH-sp^2) structures can be made based on chemical shifts in ^1H and ^{13}C NMR spectra, see the Supporting Information for details.

(20) The proton required for the formation of iminium ion **6** may arise from adventitious water contained in Selectfluor or solvent.

(21) Mayr, H.; Ofial, A. R.; Würthwein, E.-U.; Aust, N. C. *J. Am. Chem. Soc.* **1997**, *119*, 12727–12733.

(22) However, when TMSCN was combined with $Me_4N\cdot BF_4$ in CD_3CN, no formation of TMS-fluoride was observed and TMSCN remained unaffected. This means that the fluoroammonium dication of Selectfluor somehow activates TMSCN for the interaction with tetrafluoroborate anion. We thank a reviewer for suggesting this control experiment.

on employing other terminating nucleophiles and extending the scope of this process to other alkene substrates.

Experimental Section

General Procedures for Fluorocyantion of Enamines. Method A. Pyridine (40 μL, 0.42 mmol) and enamine (0.35 mmol) were successively added to a solution of TMSCN (70 μL, 0.53 mmol) and NFSI (121.3 mg, 0.39 mmol) in acetonitrile (1.4 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and quenched with saturated aqueous $NaHCO_3$ (1.0 mL). The resulting mixture was diluted with an excess of water and extracted with ether (3 × 5 mL), then the combined organic phase was washed with brine, filtered through Na_2SO_4, concentrated, and azeotropically dried with acetonitrile. The residue was purified by flash chromatography.

Method B. Enamine (0.5 mmol) and Selectfluor (194.7 mg, 0.55 mmol) were successively added to a solution of TMSCN (100 μL, 0.75 mmol) and base (pyridine or NEt_3, 0.6 mmol) in acetonitrile (2.0 mL) at −30 °C. The mixture was stirred for 30 min at −30 °C, the cooling bath was replaced by an ice/water bath, and the mixture was stirred for 15 min at 0 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ (1.0 mL), diluted with an excess of water, and extracted with ether (3 × 5 mL), then the combined organic phase was washed with brine, filtered through Na_2SO_4, concentrated, and azeotropically dried with acetonitrile. The residue was purified by flash chromatography.

Method C. Enamine (0.5 mmol) and Selectfluor (194.7 mg, 0.55 mmol) were successively added to a solution of $BnNEt_3CN$ (163.5 mg, 0.75 mmol) in acetonitrile (2.0 mL) at −30 °C. The mixture was stirred for 30 min at −30 °C, the cooling bath was replaced by an ice/water bath, and the mixture was stirred for 15 min at 0 °C. The mixture was diluted with an excess of water and extracted with ether (3 × 5 mL), then the combined organic phase was washed with brine, filtered through Na_2SO_4, concentrated, and azeotropically dried with acetonitrile. The residue was purified by flash chromatography.

3-Fluoro-3-methyl-2-[methyl(phenyl)amino]butanenitrile (2a): R_f 0.27 (hexanes/EtOAc, 9:1). Mp 30−32 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (d, 3H, J = 22.3 Hz), 1.62 (d, 3H, J = 22.3 Hz), 3.06 (s, 3H), 4.52 (d, 1H, J = 22.3 Hz), 6.89−7.00 (m, 3H), 7.28−7.36 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.5 (d, J = 24.2 Hz), 25.1 (d, J = 24.2 Hz), 35.9 (d, J = 6.3 Hz), 62.0 (d, J = 20.7 Hz), 96.3 (d, J = 180.6 Hz), 114.7 (d, J = 2.3 Hz), 115.8, 120.7, 129.4, 149.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ −144.0 (octet, J = 22.3). Calcd for $C_{12}H_{15}FN_2$ (206.26): C, 69.88; H, 7.33; N, 13.58. Found: C, 69.97; H, 7.29; N, 13.41.

Acknowledgment. This work was supported by the Russian Academy of Sciences (program no. 7) and the Federal program "Scientific and educational personnel of innovative Russia" (project 02.740.11.0258).

Supporting Information Available: Experimental procedures and spectroscopic, analytical, and X-ray data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.