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Nuchleophilic Bromodifluoromethylation of Iminium Ions

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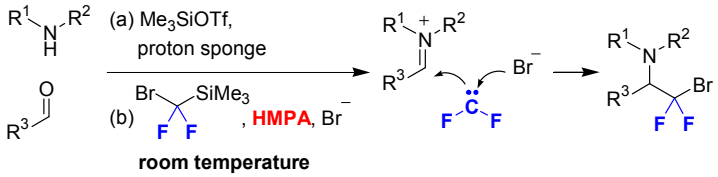


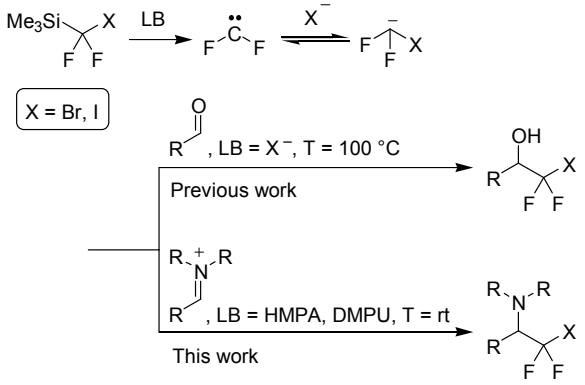
Abstract. A method for bromodifluoromethylation of iminium ions using Me_3SiCF_2Br is described. The reaction involves room temperature activation of the silicon reagent by HMPA to generate difluorocarbene which upon interacting with excess of bromide ion provides bromodifluoromethyl carbanionic species. The iminium electrophiles are generated in situ from aldehydes, secondary amines, proton sponge, and silyl triflate. The reaction can be extended for introduction of chlorodifluoromethyl and iododifluoromethyl groups.

Introduction

Methods for the synthesis of organofluorine compounds have witnessed intensive growth in recent years.[1] While major efforts were focused on the introduction of a fluorine atom and the CF_3-group, methodology for the synthesis of *gem*-difluorinated compounds remains limited.[2] For example, it is difficult to obtain compounds bearing interhalogenated methyl group, CF_2X (X = Br, I). At the same time, this fragment can serve as a halogen bond donor,[3] which may be important for medicinal chemistry and crystal engineering, whereas the C-X bond can be further involved into radical or ion-radical processes[4] finally affording *gem*-difluorinated products.

Existing methods for direct introduction of CF_2X group involve electrophilic bromodifluoromethylation of terminal alkynes,[5] radical atom transfer additions,[6] formal nucleophilic addition to carbonyl compounds using halogenation of Julia-Kocienski intermediates.[7] Recently we reported a first method for direct nucleophilic bromo- and iododifluoromethylation of simple aldehydes using corresponding silicon reagents Me_3SiCF_2X (X = Br, I).[8] The latter reaction likely involves the intermediacy of difluorocarbene and proceeds at high temperatures (100 °C), which is required for activation of Si-C bond by weakly basic bromide and iodide anions (Scheme 1). However, these conditions are too drastic to be applicable to labile electrophiles such as iminium ions. Herein we propose a protocol for nucleophilic addition of the CF_2X group to iminium salts using corresponding silicon reagents which is carried out room (or lower) temperatures. The key finding is that silanes Me_3SiCF_2X can be readily activated by neutral Lewis bases.

Scheme 1. Nucleophilic halodifluoromethylation.

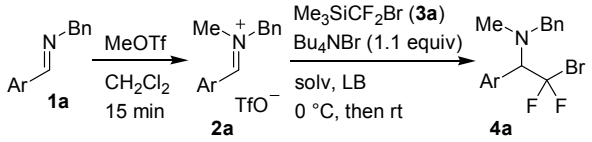


Results and Discussion

Iminium salt **2a** generated by methylation of imine **1a** with methyl triflate in dichloromethane was selected as a model substrate, and its reaction with (bromodifluoromethyl)trimethylsilane (**3a**) in the presence of tetrabutylammonium bromide (1.1 equiv) was evaluated (Table 1). While no reaction occurred in dichloromethane, the use of amide solvents at the bromodifluoromethylation step provided product **4a** (entries 3-6).[9] Subsequent studies aimed at reducing the amount of the amides allowed to identify HMPA as a Lewis basic activator, which is effective even in

stoichiometric quantities (entries 9-10). Fortunately, only slight excess of the silicon reagent (1.5 equiv) proved to be sufficient to achieve 89% isolated yield of **4a** (entry 10).

Table 1. Bromodifluoromethylation of iminium salt 2a.



Ar = 4-$MeOC_6H_4$

#	solv[a]	**3**, equiv	LB (equiv)	Time, h	Yield of **4a**, %[b]
1	CH_2Cl_2	3.0	–	18	0
2	MeCN	3.0	–	18	0
3	HMPA	3.0	–	18	42
4	DMF	3.0	–	18	46
5	NMP	3.0	–	18	61
6	DMPU	3.0	–	24	82 (77[c])
7	DMPU	3.0	HMPA (3.0)	20	68
8	CH_2Cl_2	1.5	DMPU (3.0)	2	7
9	CH_2Cl_2	3.0	HMPA (3.0)	2	97 (89[c])
10	**CH_2Cl_2**	**1.5**	**HMPA (3.0)**	**2**	**95 (89[c])**
11	CH_2Cl_2	1.5	HMPA (0.1)	4	4
12[d]	CH_2Cl_2	1.5	HMPA (3.0)	5	78

[a] HMPA – hexamethylphosphoramide; DMF – dimethylformamide; NMP – *N*-methyl-2-pyrrolidone; DMPU – *N,N′*-dimethyl-*N,N′*-trimethyleneurea.

[b] Determined by ^{19}F NMR of reaction mixtures with $PhCF_3$ as an internal standard.

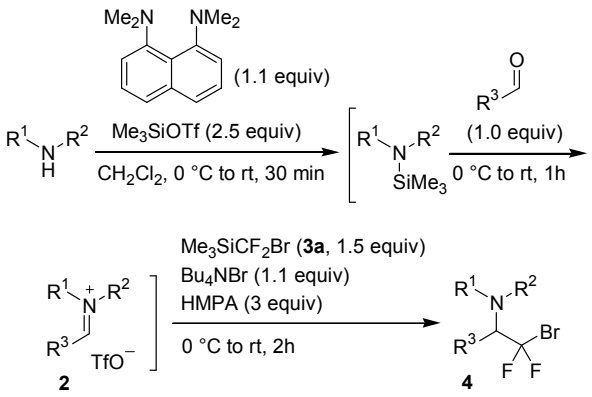
[c] Isolated yield.

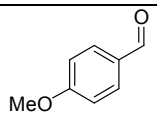
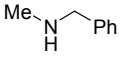
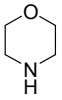
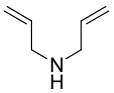
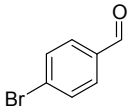
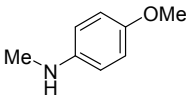
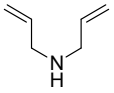
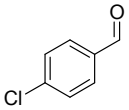
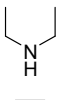
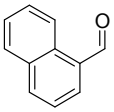
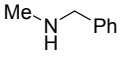
[d] 0.5 equiv of Bu_4NBr was used.

In order to apply this protocol to iminium ions that could not be conveniently prepared by alkylation of corresponding Schiff bases, we developed a procedure for their in situ generation. Thus, treatment of secondary amines with silyl triflate and 1,8-bis(dimethylamino)naphthalene (proton sponge) in dichloromethane followed by interaction with aldehydes during one hour led to

iminium salts **2**.[10,11] Subsequent addition of the silane, bromide ion, and HMPA effected bromodifluormethylation (Table 2).

Table 2. Coupling of amines, aldehydes and silane 3.



#	Aldehyde	Amine	**4**	Yield of **4**, %[a]
1			**4a**	88
2			**4b**	88
3			**4c**	85
4[b]			**4d**	76
5			**4e**	87
6			**4f**	94
7			**4g**	63 (79[c])
8[b]			**4h**	80
9			**4i**	74

[a] Isolated yield.

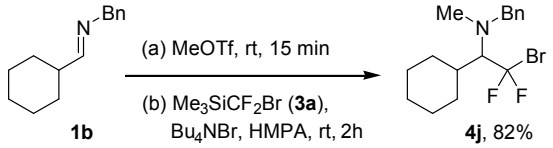
[b] The iminium ion was generated for 24 h.

[c] Yield determined by ^{19}F NMR. The decrease of yield upon isolation is due to volatility of the product.

According to this protocol, a variety of iminium ions generated from aromatic aldehydes and alkyl, allyl, benzyl and aryl substituted secondary amines were bromodifluoromethylated affording products **4** in good to excellent yields. In this one-pot protocol, the complete generation of moisture sensitive iminium ion is believed to be a limiting factor. For example, in case of moderately reactive aldehyde/amine couples such as those in entry 4 (non-nucleophilic amine) and entry 8 (hindered aldehyde), longer time (24 hours) is needed for the formation of iminium salts. Interestingly, when diallylamine was used, no cyclopropanation products were detected.

Unfortunately, the one-pot procedure was unsuccessful for a combination of cyclohexanecarboxaldehyde and *N*-benzylmethylamine, presumably owing to enolization problem. Nevertheless, product **4j** could be obtained when the intermediate iminium ion was generated by methylation of imine **1b** (Scheme 2).

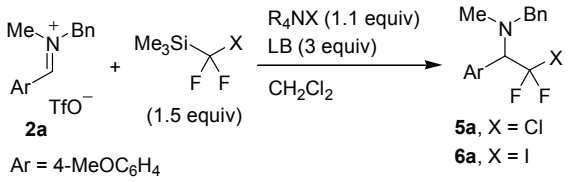
Scheme 2. Synthesis of product 4j.



1b **4j**, 82%

It was interesting to extend the same methodology to chloro- and iododifluoromethylation. Starting from iminium salt **2a** generated by imine methylation, for the chloro-substituted silane Me_3SiCF_2Cl (**3b**), good yield of product **5a** was achieved only after 48 hours (Table 3, entry 4). In contrast, iodinated counterpart Me_3SiCF_2I (**3c**), the use of less donating DMPU (*N,N′*-dimethyl-*N,N′*-trimethyleneurea) was found to be optimal[12] (entry 7).

Table 3. Variation of the silicon reagent.



#	X[a]	LB	t, °C	Time, h	Yield, %
1	Cl	TMU[b]	0 °C → rt	2	traces
2	Cl	DMAP[b]	0 °C → rt	2	traces
3	Cl	HMPA	0 °C → rt	2	12[c]
4	**Cl**	**HMPA**	**0 °C → rt**	**48**	**89[d]**
5	I	HMPA	0 °C → rt	2	66[d]
6	I	HMPA	–42 °C	2	53[c]
7	**I**	**DMPU**	**0 °C → rt**	**2**	**75[d]**

[a] $BnNEt_3Cl$ (for X = Cl) or Bu_4NI (for X = I) were used.

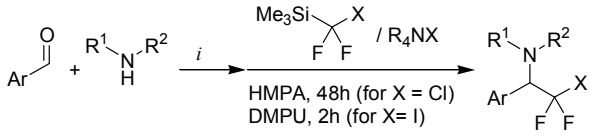
[b] TMU – tetramethylurea; DMAP – 4-(*N*,*N*-dimethylamino)pyridine.

[c] Yield determined by ^{19}F NMR.

[d] Isolated yield.

Chloro- and iododifluoromethylation was also evaluated according to one-pot protocol (Scheme 3), but the yields of products **5a** and **6a** were lower than those achieved with an authentic iminium ion **2a**.

Scheme 3 One-pot chloro- and iododifluoromethylation.



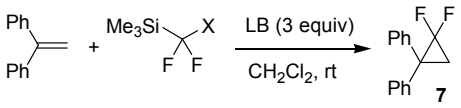
i: 1,8-bis(dimethylamino)naphthalene/Me_3SiOTf

Ar = 4-$MeOC_6H_4$	R^1 = Me, R^2 = Bn	X = Cl	**5a**, 55%
Ar = 4-$MeOC_6H_4$	R^1 = Me, R^2 = Bn	X = I	**6a**, 64%
Ar = 4-ClC_6H_4	R^1, R^2 = Et, X = Cl	X = I	**6b**, 88%

The described halodifluoromethylation reactions are believed to proceed through the intermediacy of difluorocarbene.[8] It is of special note that by combining silanes Me_3SiCF_2X with amides, *the generation of difluorocarbene occurs at room temperature under virtually non-basic conditions*. For comparison, in previous reports, the decomposition of Me_3SiCF_2X (X = F, Cl, Br)

to difluorocarbene was carried out either with highly reactive activators (fluoride, acetate) at room (or lower) temperature[13] or with non-basic chloride and bromide ions at 100 °C.[14] To make use of our mild activation conditions, we demonstrated the possibility of difluorocyclopropantion of alkenes to be triggered simply by a proper amide additive (HMPA or DMPU) (Table 4). Indeed, difluorocyclopropanation of 1,1-diphenylethylene with bromo- and iodo-substituted silanes took place at room temperature within two hours. To obtain a good isolated yield of product **7**, three equivalents of brominated silane were employed (entry 3). However, chlorinated silane Me_3SiCF_2Cl gave only small amount of cyclopropane **7** while most of the silane (ca. 70%) remained unreacted. The latter phenomenon was unexpected, since Me_3SiCF_2Cl successfully reacted with iminium salt (*vide supra*). Such a discrepancy may suggest that, contrary to bromo- and iodo-substituted silanes, for which generation of difluorocarbene is fast, the reaction of Me_3SiCF_2Cl with iminium ion proceeds as direct transfer of chlorodifluoromethyl group from pentacoordinate siliconate species.

Table 4. Difluorocyclopropanation reactions.



#	X	Equiv of silane	LB	Time, h	Yield of **7**, %
1	Cl	1.5	HMPA	48	7[a]
2	Br	1.5	HMPA	2	54[a]
3	Br	3	HMPA	2	83[b]
4	I	1.5	DMPU	2	39[a]

[a] Yield determined by ^{19}F NMR.

[b] Isolated yield.

In summary, a method for direct bromodifluoromethylation of iminium ions with Me_3SiCF_2Br furnishing α-bromodifluoromethyl-substituted amines[18] has been described. A one-pot procedure involving generation of iminium ions from aldehydes and secondary amines with their successive coupling with the silane has been developed. The method can also be extended to the introduction of CF_2Cl and CF_2I groups using corresponding silicon reagents. The activation of silanes by neutral

Lewis bases such as HMPA and DMPU is believed to be the key factor responsible for reaction efficiency.

Experimental section

General Methods. All reactions were performed in Schlenk flasks under an argon atmosphere. CH_2Cl_2 was distilled from CaH_2 prior to use. HMPA, DMPU, TMU were distilled under vacuum from CaH_2 and stored over MS 4Å. Column chromatography was carried out employing silica gel (230−400 mesh). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography visualizing with UV and/or acidic aq. $KMnO_4$ solution. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and time-of-flight (TOF) mass analyzer. The measurements were done in a positive ion mode (interface capillary voltage – 4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to m/z 3000. *N*-[(4-methoxyphenyl)methylene]-1-phenylmethanamine (**1a**),[15] *N*-[cyclohexylmethylene]-1-phenylmethanamine (**1b**),[16] (bromodifluoromethyl)trimethylsilane (**3a**)[14d] and (iododifluoromethyl)trimethylsilane (**3c**)[8] were obtained according to literature procedures.

*(Chlorodifluoromethyl)trimethylsilane (**3b**)*. Obtained from silane **3a** by modified literature procedure.[17] (Bromodifluoromethyl)trimethylsilane (13.0 g, 64 mmol) was added to a suspension of LiCl (4.1 g, 96 mmol) in diglyme (32 mL) at room temperature, and the mixture was stirred for 18 h at room temperature. The reaction mixture was cooled with ice/water bath, and stirred for additional 2 h. Then, the volatile components were distilled off under vacuum (10 Torr) collecting into a cold trap (liquid nitrogen) [upon distillation the distilling flask was slowly warmed from 0 to 35 °C]. To the collected liquid, $BnNEt_3Cl$ (228 mg, 1 mmol) was added, and the mixture was subjected to distillation at atmospheric pressure affording 7.56 g (74% yield) of the product as a clear colorless liquid. Bp 86–88 °C. NMR spectra were identical to the reported data.[17]

General procedure 1. *Halodifluoromethylation of iminium salts generated from aldehydes and amines [preparation of **4a-i, 5a, 6a,b**]*. Amine (0.55 mmol) and TMSOTf (1.25 mmol, 230 μL) were added to a solution of 1,8-bis(dimethylamino)naphthalene (0.55 mmol, 118 mg) in CH_2Cl_2 (1

mL) at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 30 min at room temperature. Then, the mixture was cooled to 0 °C, aldehyde (0.50 mmol) was added. The cooling bath was removed and the mixture was stirred at room temperature (1 h for preparation of **4a-c,e-g,i**, **5a,b**, **6a**; 24 h for preparation of **4d,h**). For reaction with silanes, the obtained solution of iminium salt was cooled to 0 °C, and ammonium salt (0.55 mmol; Bu_4NBr for X = Br, Bu_4NI for X = I, $BnNEt_3Cl$ for X = Cl), silicon reagent Me_3SiCF_2X (0.75 mmol), a Lewis base (1.50 mmol, HMPA for X = Br and Cl, DMPU for X = I) were successively added. The cooling bath was removed and the mixture was stirred at room temperature (2 h for X = Br and I, 48 h for X = Cl). For the work-up, the mixture was concentrated under vacuum and the residue was quenched with 0.3 M aqueous NH_4OAc (5 mL). The aqueous phase was extracted with hexane/methyl *tert*-butyl ether (1:1, 10 mL; 3×3 mL). The combined organic phases were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography.

General procedure 2. *Halodifluoromethylation of iminium salts generated by methylation of imines [preparation of **4a,j, 5a, 6a**]*. MeOTf (0.55 mmol, 53 μL) was added to a solution of imine (**1a,b**, 0.5 mmol) in CH_2Cl_2 (1 mL) at 0 °C. The cooling bath was removed and the solution was stirred for 15 min at room temperature to give a solution of iminium salts **2a,b**. Reactions of the iminium salts **2a,b** with silanes was performed identically to General procedure 1.

*Benzyl[2-bromo-2,2-difluoro-1-(4-methoxyphenyl)ethyl]methylamine (**4a**).* General procedure 1: 162.0 mg (88%). General procedure 2: 164.8 mg (89%). Colorless oil. Bp 135–140 °C (bath temp.)/0.31 Torr. R_f 0.39 (EtOAc/hexanes, 1:10). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.43–7.22 (m, 7H), 7.01–6.89 (m, 2H), 4.30 (t, *J* = 13.8, 1H), 3.85 (s, 3H), 3.80 (d, *J* = 13.6, 1H), 3.53 (d, *J* = 13.6, 1H), 2.32 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 159.8, 138.9, 131.2 (t, *J* = 1.5), 128.9, 128.5, 127.4, 125.8 (t, *J* = 313.9), 124.7, 113.9, 75.0 (dd, *J* = 21.6, 19.7), 59.9, 55.4, 39.0 (t, *J* = 2.3). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −48.1 (dd, *J* = 161.0, 12.8, 1F), −49.3 (dd, *J* = 161.0, 14.8, 1F). Anal. Calcd. for $C_{17}H_{18}BrF_2NO$ (370.23): C, 55.15; H, 4.90; N, 3.78. Found: C, 55.19; H, 4.74; N, 3.81.

*4-[2-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethyl]morpholine (**4b**).* 148.5 mg (88%). White crystals. Mp 34–37 °C. Bp 129–132 °C (bath temp.)/0.26 Torr. R_f 0.30 (EtOAc/hexanes, 1:5). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 8.6, 2H), 6.92 (d, *J* = 8.6, 2H), 3.98 (dd, *J* = 13.4, 10.6, 1H), 3.83 (s, 3H), 3.70 (t, *J* = 4.6, 4H), 2.72–2.47 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 159.9, 131.2, 125.3 (dd, *J* = 310.7, 312.7), 124.6, 113.9, 77.2 (t, *J* = 20.8), 67.2, 55.3, 51.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −47.3 (dd, *J* = 162.8, 10.6, 1F), −48.6 (dd, *J* = 162.8, 13.4, 1F). Anal. Calcd. for $C_{13}H_{16}BrF_2NO_2$ (336.17): C, 46.45; H, 4.80; N, 4.17. Found: C, 46.34; H, 4.88; N, 4.14.

*[2-Bromo-2,2-difluoro-1-(4-methoxyphenyl)ethyl]bis(prop-2-en-1-yl)amine (**4c**).* 147.4 mg (85%). Pale-yellow oil. Bp 107–108 °C (bath temp.)/0.22 Torr. R_f 0.53 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 8.6, 2H), 6.92 (d, *J* = 8.6, 2H), 5.85 (dddd, *J* = 15.0, 10.1, 7.8, 4.8, 2H), 5.30–5.13 (m, 4H), 4.46 (t, *J* = 14.3, 1H), 3.84 (s, 3H), 3.49 (dd, *J* = 14.3, 4.8, 2H), 2.86 (dd, *J* = 14.3, 7.8, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 159.6, 136.4, 131.1 (t, *J* = 1.5), 126.0 (t, *J* = 313.0), 125.0, 117.8, 113.9, 70.7 (dd, *J* = 22.2, 19.4), 55.3, 54.2 (t, *J* = 1.5). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −48.9 (dd, *J* = 161.1, 14.3, 1F), −50.2 (dd, *J* = 161.1, 14.3, 1F). Anal. Calcd. for $C_{15}H_{18}BrF_2NO$ (346.21): C, 52.04; H, 5.24; N, 4.05. Found: C, 52.07; H, 5.19; N, 4.04.

*N-[2-Bromo-1-(4-bromophenyl)-2,2-difluoroethyl]-4-methoxy-N-methylaniline (**4d**).* 165.0 mg (76%). Colorless oil. R_f 0.28 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 8.4, 2H), 7.26 (d, *J* = 8.4, 2H), 7.00–6.85 (m, 4H), 5.35 (t, *J* = 13.5, 1H), 3.81 (s, 3H), 2.71 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 153.7, 144.4, 132.2 (t, *J* = 1.5), 131.8, 130.5 (t, *J* = 2.1), 124.2 (dd, *J* = 316.1, 314.1), 122.7, 117.3, 114.8, 73.6 (dd, *J* = 22.4, 20.5), 55.7, 34.6 (t, *J* = 2.2). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −49.0 (dd, *J* = 163.6, 13.5, 1F), −50.4 (dd, *J* = 163.6, 13.5, 1F). HRMS (ESI) Calcd. for $C_{16}H_{16}Br_2F_2NO$ (M+H): 433.9541. Found: 433.9533.

*[2-Bromo-1-(4-bromophenyl)-2,2-difluoroethyl]bis(prop-2-en-1-yl)amine (**4e**).* 171.0 mg (87%). Colorless oil. Bp 100–101 °C (bath temp.)/0.24 Torr. R_f 0.63 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (d, *J* = 8.1, 2H), 7.22 (d, *J* = 8.1, 2H), 5.91–5.72 (m, 2H), 5.30–5.12 (m, 4H), 4.47 (t, *J* = 13.9, 1H), 3.46 (dd, *J* = 14.3, 4.8, 2H), 2.86 (dd, *J* = 14.3, 7.4, 2H). ^{13}C{^{1}H} NMR (75

MHz, $CDCl_3$) δ: 136.0, 132.2, 131.7, 131.4 (t, *J* = 1.5), 125.2 (t, *J* = 313.2), 122.7, 118.2, 70.5 (t, *J* = 20.9), 54.1 (t, *J* = 1.5). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −49.1 (dd, *J* = 162.5, 13.9, 1F), −50.5 (dd, *J* = 162.5, 13.9, 1F). Anal. Calcd. for $C_{14}H_{15}Br_2F_2N$ (395.08): C, 42.56; H, 3.83; N, 3.55. Found: C, 42.62; H, 3.89; N, 3.54.

*[2-Bromo-1-(4-chlorophenyl)-2,2-difluoroethyl]diethylamine (**4f**).* 152.9 mg (94%). Colorless oil. Bp 70–75 °C (bath temp.)/0.16 Torr. R_f 0.42 (EtOAc/hexanes, 1:20). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.35 (br, 4H), 4.40 (dd, *J* = 15.5, 11.6, 1H), 2.82 (dq, *J* = 14.2, 7.1, 2H), 2.49 (dq, *J* = 13.7, 7.1, 2H), 1.06 (t, *J* = 7.1, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 134.3, 133.0 (d, *J* = 2.2), 131.1 (t, *J* = 1.8), 128.6, 125.6 (dd, *J* = 315.1, 313.0), 72.5 (dd, *J* = 21.5, 19.7), 45.0 (t, *J* = 1.5), 13.9. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −48.8 (dd, *J* = 161.1, 11.6, 1F), −50.8 (dd, *J* = 161.1, 15.5, 1F). Anal. Calcd. for $C_{12}H_{15}BrClF_2N$ (326.61): C, 44.13; H, 4.63; N, 4.29. Found: C, 44.09; H, 4.75; N, 4.28.

*1-(2-Bromo-2,2-difluoro-1-phenylethyl)pyrrolidine (**4g**).* 92.0 mg (63%). Colorless oil. Bp 107–110 °C (bath temp.)/0.18 Torr. R_f 0.29 (EtOAc/hexanes, 1:20). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.51–7.33 (m, 5H), 3.88 (dd, *J* = 13.4, 6.2, 1H), 2.77–2.49 (m, 4H), 1.89–1.63 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 135.0 (t, *J* = 2.7), 129.9 (t, *J* = 1.1), 128.8, 128.3, 125.6 (dd, *J* = 313.0, 307.9), 76.8 (dd, *J* = 22.1, 20.6), 52.6, 23.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −46.7 (dd, *J* = 162.8, 6.2, 1F), −48.8 (dd, *J* = 162.8, 13.4, 1F). Anal. Calcd. for $C_{12}H_{14}BrF_2N$ (290.15): C, 49.67; H, 4.86; N, 4.83. Found: C, 49.54; H, 4.84; N, 5.03.

*1-[2-Bromo-2,2-difluoro-1-(naphthalen-1-yl)ethyl]pyrrolidine (**4h**).* 136.0 mg (80%). Pale-pink oil. Bp 120–125°C (bath temp.)/0.13 Torr. R_f 0.47 (EtOAc/hexanes, 1:20). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, *J* = 8.4, 1H), 7.99 (d, *J* = 7.3, 1H), 7.96–7.86 (m, 2H), 7.65–7.47 (m, 3H), 4.88 (dd, *J* = 14.8, 5.0, 1H), 2.88–2.59 (m, 4H), 1.97–1.67 (m, 4H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ: 134.0, 132.5, 131.3 (t, *J* = 2.9), 129.3, 129.1, 127.9 (d, *J* = 2.5), 126.5, 126.2 (dd, *J* = 315.3, 308.5), 125.6, 125.2, 123.3, 70.8 (m), 52.7 (t, *J* = 1.5), 23.6. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −44.6 (br d, *J*

= 160.5, 1F), −48.0 (dd, *J* = 161.0, 14.8, 1F). Anal. Calcd. for $C_{16}H_{16}BrF_2N$ (340.21): C, 56.49; H, 4.74; N, 4.12. Found: C, 56.34; H, 4.91; N, 4.09.

*Benzyl[2-bromo-2,2-difluoro-1-(thiophen-2-yl)ethyl]methylamin (**4i**).* 128.1 mg (74%). Yellow oil. Bp 112–115 °C (bath temp.)/0.18 Torr. R_f 0.54 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49–7.27 (m, 6H), 7.19–7.05 (m, 2H), 4.67 (t, *J* = 13.1, 1H), 3.88 (d, *J* = 13.6, 1H), 3.64 (d, *J* = 13.6, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 138.5, 133.7, 129.0, 128.64 (t, *J* = 1.2), 128.55, 127.5, 126.9, 126.2, 124.6 (t, *J* = 314.1), 70.8 (dd, *J* = 22.6, 21.1), 59.8 (t, *J* = 1.7), 38.6 (t, *J* = 2.2). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −49.3 (dd, *J* = 161.7, 13.1, 1F), −50.3 (dd, *J* = 161.7, 13.1, 1F). Anal. Calcd. for $C_{14}H_{14}BrF_2NS$ (346.23): C, 48.57; H, 4.08; N, 4.05. Found: C, 48.57; H, 4.17; N, 4.08.

*Benzyl(2-bromo-1-cyclohexyl-2,2-difluoroethyl)methylamine (**4j**).* 142.0 mg (82%). Colorless oil. Mp 52–64°C. Bp 114–118 °C (bath temp.)/0.16 Torr. R_f 0.64 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39–7.20 (m, 5H), 4.02 (d, *J* = 13.7, 1H), 3.90 (d, *J* = 13.7, 1H), 3.03 (td, *J* = 10.2, 8.3, 1H), 2.44 (s, 3H), 2.14 (d, *J* = 13.2, 1H), 2.03–1.62 (m, 5H), 1.49–1.05 (m, 5H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 139.8, 128.7, 128.4, 127.2, 127.1 (dd, *J* = 323.4, 321.8), 76.5 (t, *J* = 17.3), 61.0, 38.7, 36.9, 30.9 (dd, *J* = 3.3, 1.7), 30.8 (d, *J* = 1.0), 26.5, 26.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –39.5 (dd, *J* = 159.9, 8.3, 1F), –42.1 (dd, *J* = 159.9, 10.2, 1F). Anal. Calcd. for $C_{16}H_{22}BrF_2N$ (346.25): C, 55.50; H, 6.40; N, 4.05. Found: C, 55.31; H, 6.31; N, 4.04.

*Benzyl[2-chloro-2,2-difluoro-1-(4-methoxyphenyl)ethyl]methylamine (**5a**).* General procedure 1: 89.4 mg (55%). General procedure 2: 145.5 mg (89%). Pale-yellow oil. Bp 128–129 °C (bath temp.)/0.31 Torr. R_f 0.36 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48–7.23 (m, 7H), 6.99 (d, *J* = 8.7, 2H), 4.31 (dd, *J* = 13.6, 12.1, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 13.6, 1H), 3.55 (d, *J* = 13.6, 1H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ: 159.7, 138.9, 131.1 (t, *J* = 1.8), 128.8, 128.5, 127.4, 124.6 (d, *J* = 1.3), 113.8, 73.0 (dd, *J* = 23.8, 22.4), 59.8 (t, *J* = 1.7), 55.3, 39.0 (t, *J* = 2.1). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –54.2 (dd, *J* = 165.0, 12.1), –55.3 (dd, *J* = 165.0, 13.6).

Anal. Calcd. for $C_{17}H_{18}ClF_2NO$ (325.78): C, 62.67; H, 5.57; N, 4.30. Found: C, 62.83; H, 5.84; N, 4.27.

*Benzyl[2,2-difluoro-2-iodo-1-(4-methoxyphenyl)ethyl]methylamine (**6a**).* General procedure 1: 132.9 mg (64%). General procedure 2: 156.1 mg (75%). White crystals. Mp 63–65 °C (hexanes). R_f 0.33 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48–7.26 (m, 7H), 6.96 (d, *J* = 8.6, 2H), 4.21 (t, *J* = 15.0, 1H), 3.86 (s, 3H), 3.79 (d, *J* = 13.4, 1H), 3.53 (d, *J* = 13.4, 1H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 159.8, 138.8, 131.4 (t, *J* = 1.6), 129.0, 128.4, 127.4, 124.2, 113.9, 109.1 (t, *J* = 321.1), 77.5 (dd, *J* = 20.6, 18.2), 59.9 (t, *J* = 1.9), 55.3, 39.0 (t, *J* = 2.4). ^{19}F NMR (282 MHz, $CDCl_3$) δ: −41.4 (dd, *J* = 177.7, 15.0, 1F), −42.3 (dd, *J* = 177.7, 15.0, 1F). Anal. Calcd. for $C_{17}H_{18}F_2INO$ (417.23): C, 48.94; H, 4.35; N, 3.36. Found: C, 49.07; H, 4.51; N 3.21.

*[1-(4-Chlorophenyl)-2,2-difluoro-2-iodoethyl]diethylamine (**6b**).* 164.1 mg (88%). Colorless oil. R_f 0.49 (EtOAc/hexanes, 1:20). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 8.6, 2H), 7.29 (d, *J* = 8.6, 2H), 4.27 (t, *J* = 15.0, 1H), 2.81 (dq, *J* = 14.0, 7.1, 2H), 2.45 (dq, *J* = 14.0, 7.1, 2H), 1.09 (t, *J* = 7.1, 6H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ: 134.3, 132.3, 131.3 (t, *J* = 1.7), 128.6, 109.6 (t, *J* = 321.3), 74.9 (dd, *J* = 20.8, 17.9), 45.0 (t, *J* = 1.6), 13.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −42.2 (dd, *J* = 177.9, 15.0, 1F), −43.2 (dd, *J* = 177.9, 15.0, 1F). HRMS (ESI) Calcd. for $C_{12}H_{16}ClF_2IN$ (M+H): 373.9979. Found: 373.9975.

*(2,2-Difluoro-1-phenylcyclopropyl)benzene (**7**).* Me_3SiCF_2Br (1.50 mmol, 304 mg) and HMPA (1.50 mmol, 260 μL) were successively added to a solution of 1,1-diphenylethylene (0.5 mmol, 90 mg) in CH_2Cl_2 at 0 °C. The cooling bath was removed and the mixture was stirred at room temperature 2 h. Saturated aqueous Na_2CO_3 (5 mL) was added, and the mixture was extracted with hexane/methyl *tert*-buthyl ether (1:1, 10 mL; 3×3 mL). The combined organic phases were filtered through Na_2SO_4, concentrated under vacuum, and the residue was purified by column chromatography affording 95.7 mg (83% yield) of compound **7** as a colorless oil. NMR spectra were identical to the reported data.[13a]

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Supporting Information

Copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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