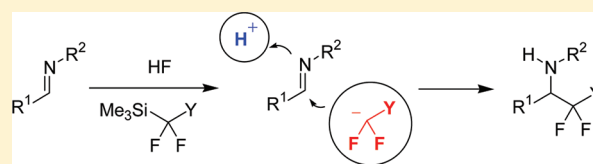


## Reactions of Sulfur- and Phosphorus-Substituted Fluoroalkylating Silicon Reagents with Imines and Enamines under Acidic Conditions

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## Supporting Information

**ABSTRACT:** Nucleophilic fluoroalkylation reactions of imines and enamines with  $\alpha$ -phenylthio,  $\alpha$ -phenylsulfonyl, and  $\alpha$ -diethylphosphoryl substituted fluorinated silanes have been investigated. The reactions are promoted by hydrofluoric acid generated *in situ* from potassium hydrodifluoride and trifluoroacetic acid. Sulfur reagents worked well with both imines and enamines, whereas phosphorus reagent efficiently coupled only with enamines.



Organofluorine compounds have attracted significant attention in recent years due to their increasing role in pharmaceutical and agrochemical industries.<sup>1</sup> Among different methodologies for the synthesis of fluorinated molecules that have been investigated,<sup>2</sup> nucleophilic fluoroalkylation reactions have emerged as a general and reliable approach for the direct introduction of fluorinated groups.<sup>3,4</sup>

Fluoroalkyl organosilicon reagents have become particularly widespread as equivalents of fluorinated carbanions, which is associated with their availability, stability, convenience of handling, and favorable reactivity. Most studies were carried out using trimethyl(trifluoromethyl)silane and higher alkyl analogues.<sup>3a–c</sup> However, within the past few years the chemistry of silanes substituted with sulfur and phosphorus groups began its development.<sup>5–7</sup> Indeed, the major feature of these substituents is that a carbon–heteroatom bond (e.g., C–S bond) can be further functionalized or reduced to a C–H bond, thereby providing compounds inaccessible by other means.<sup>8</sup>

Typically, trimethylsilyl-capped fluoroalkylating reagents exhibit nucleophilic properties only in the presence of Lewis basic activators capable of generating reactive five-coordinate intermediate.<sup>3a–c,9</sup> These reactions are performed under aprotic conditions since the fluorinated carbanion can readily abstract a proton from the medium. Recently we found that *N*-alkyl substituted imines and enamines, which are unreactive under conventional Lewis basic conditions, can undergo nucleophilic trifluoromethylation in the presence of hydrofluoric acid.<sup>10</sup> While anhydrous HF is highly dangerous, in our protocol it is generated *in situ* by mixing easily available and convenient chemicals. Furthermore, reactions can be performed in conventional glassware with no noticeable deterioration of glass surface. Herein we demonstrate that acidic conditions can be applied for  $\alpha$ -phenylthio,  $\alpha$ -phenylsulfonyl, and  $\alpha$ -diethylphosphoryl substituted silicon reagents 1–3 (Figure 1).

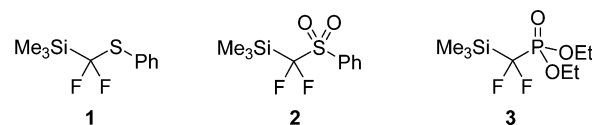


Figure 1. Silicon reagents.

The general mechanism for HF-mediated fluoroalkylation is shown in Scheme 1. Hydrofluoric acid is generated from potassium hydrodifluoride and trifluoroacetic acid in acetonitrile. The interaction of the substrate A (imine 4 or enamine 5) with HF leads to the equilibrium formation of iminium ions along with the hydrodifluoride anion. Then, the hydrodifluoride activates the silicon reagent to generate five-coordinate intermediate 6, which subsequently interacts with iminium ions. It is believed that the transfer of fluorinated carbanion from silicon to the iminium electrophile proceeds in a concerted fashion. Otherwise, if the free carbanion were formed, it would likely be rapidly quenched with acid present in the mixture.<sup>11</sup> However, five-coordinate silicon complex 6 can undergo protonation, and this side reaction leads to irreversible consumption of the silicon reagent.

We studied those compounds that cannot be fluoroalkylated using conventional naked-fluoride mediated methodology,<sup>3a–c</sup> that is, imines bearing at nitrogen alkyl or benzyl group (4) and enamines (5), as substrates in nucleophilic fluoroalkylation reactions. First, their reactions with phenylthio and phenylsulfonyl substituted fluorinated silanes (reagents 1 and 2) were investigated, and results are summarized in Table 1.

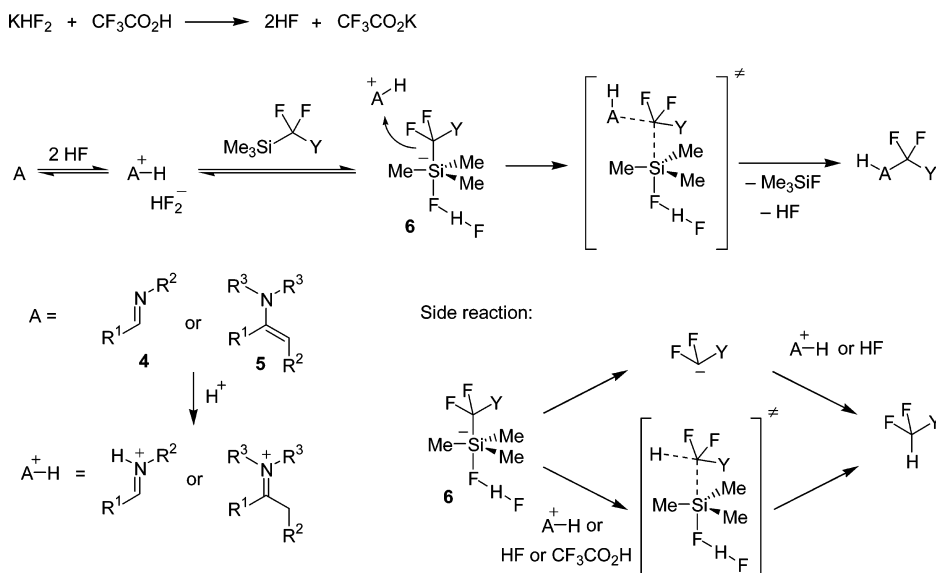
The reactions were performed under standard conditions: overnight at room temperature using 1.5 equiv of the silicon reagent and 1.5 equiv of generated HF. The reaction mixtures

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Scheme 1. Reaction Mechanism



were typically homogeneous except for a few cases where final product precipitated out of solution. As follows from the results, the sulfonyl reagent **2** provides higher yields compared to sulfide reagent **1** (see entries 3–6). This can be explained by the greater susceptibility of silane **2** to basic activation owing to stronger electron-withdrawing effect of the phenylsulfonyl group compared to that of the phenylsulfide counterpart. Enamines **5a–f** gave high yields of products in all cases examined. Indeed, enamines are expected to be intrinsically more reactive than imines, since under acidic conditions the former more readily generate iminium cations.

The fluoroalkylation with phosphorus reagent **3** was evaluated in reaction with imine **4c** under standard conditions, and the desired product **9** was formed in only 30% yield (Scheme 2). The low yield may be associated with competitive protodesilylation of the silane. Attempts to improve the yield were unsuccessful. On the contrary, enamines reacted well and afforded products **10** in good yields (Table 2).

It was interesting to evaluate the stability of reagents **1–3** in the presence of generated hydrofluoric acid (Scheme 3). In a typical experiment, silane was added to a homogeneous solution of  $\text{KHF}_2$  and  $\text{CF}_3\text{CO}_2\text{H}$  in  $d_3$ -acetonitrile at room temperature, and the mixture was monitored by  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectroscopy. The protodesilylation of sulfonyl silane **2** to give  $\text{CHF}_2\text{SO}_2\text{Ph}$  proceeded quite rapidly, and 90% conversion was achieved within 5 h. Silanes **1** and **3** reacted much slower, and only 30% decomposition was noted after 24 h. While protodesilylation of phosphonate **3** leading to  $\text{CHF}_2\text{P}(\text{O})(\text{OEt})_2$  was the sole decomposition pathway, the reaction of phenylthio substituted silane **1** was more complex, and only 6% of protodesilylated compound ( $\text{CHF}_2\text{SPh}$ ) was produced along with some unidentified nonfluorinated species. The slow decomposition of phosphonate **3** was surprising in view of poor yield in its reaction with imine **4c** (Scheme 2). The latter result may be explained by supposing that the protodesilylation of a five-coordinate intermediate originating from silane **3** prevails over the interaction with iminium electrophile (see side reaction in Scheme 1). Furthermore, the difference in reactivities of silanes **1** and **3** toward imines may be due to greater steric hindrance of the  $\text{P}(\text{O})(\text{OEt})_2$  group compared to that of  $\text{SPh}$  group, which is manifested upon

concerted interaction of the five-coordinate intermediate with iminium electrophile.

To demonstrate the utility of products obtained after fluoroalkylation of imines and enamines, we performed the desulfurization of sulfide and sulfonyl groups (Scheme 4). Thus, the sulfone fragment was removed from product **7g** by treatment with magnesium in methanol,<sup>12</sup> furnishing  $\alpha$ -difluoromethyl substituted secondary amine **11**. The phenylthio group was abstracted under radical conditions using tributyltin hydride,<sup>13</sup> affording after acidic treatment the crystalline amine hydrochloride **12**.

In summary, we demonstrated that fluoroalkylating reagents bearing phenylthio, phenylsulfonyl, and diethylphosphoryl groups can be effectively applied in HF-mediated nucleophilic fluoroalkylations. In contrast to phosphoryldifluoromethylsilane, which works only with the most reactive substrates such as enamines, the sulfur reagents are effective for fluoroalkylation of imines and enamines. The products can be readily desulfurized thereby providing access to amines containing the difluoromethyl group.

## EXPERIMENTAL SECTION

**[Difluoro(phenylthio)methyl](trimethyl)silane (1).** Obtained according to literature procedure.<sup>14</sup>

**[Difluoro(phenylsulfonyl)methyl](trimethyl)silane (2).** Obtained from  $\text{PhSO}_2\text{CF}_2\text{Br}$ <sup>15</sup> according to modified literature procedure.<sup>16</sup> *n*-Butyl lithium (13.2 mL of 2.5 M solution in hexane, 33.1 mmol) was added dropwise to a solution of  $\text{PhSO}_2\text{CF}_2\text{Br}$  (5.0 g, 18.2 mmol) and  $\text{Me}_3\text{SiCl}$  (4.7 mL, 35 mmol) in tetrahydrofuran (60 mL) at  $-100^\circ\text{C}$ , and the mixture was stirred for 1 h at  $-70^\circ\text{C}$ . The mixture was allowed to warm to room temperature, and the volatile materials were evaporated using conventional rotary evaporator. The residue was diluted with hexane (20 mL), filtered followed by washing with hexane, and concentrated under vacuum. The crude product was distilled under vacuum to give 3.8 g of the silicon reagent (78% yield). Bp  $114\text{--}115^\circ\text{C}/2\text{ Torr}$ . NMR spectra were identical to reported data.<sup>16</sup>

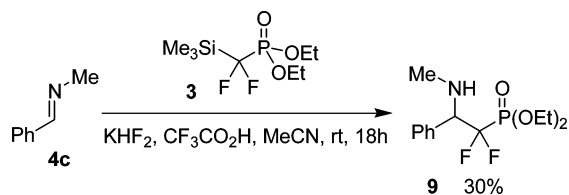
**Diethyl (Difluoro(trimethylsilyl)methyl)phosphonate (3).** Magnesium turnings (486 mg, 20 mmol), tetrahydrofuran (30 mL), and  $\text{Me}_3\text{SiCl}$  (5.37 mL, 40 mmol) were added to a Schlenk flask, and the mixture was cooled to  $-100^\circ\text{C}$ . Diethyl (bromodifluoromethyl)phosphonate<sup>17</sup> (2.52 g, 10 mmol) was added, and the mixture was stirred for 1 h at  $-78^\circ\text{C}$ . The temperature was allowed to rise to  $-25^\circ\text{C}$ .

Table 1. Reactions of Imines and Enamines with Sulfur Reagents 1 and 2

<div><div><div><div><div><math>R^1</math></div><div><math>\text{N}=\text{C}(\text{R}^2)</math></div></div><div><b>4</b></div></div><div><div><div><math>\text{Me}_3\text{Si}</math></div><div><math>\text{C}(\text{F})(\text{F})\text{Y}</math></div></div><div>(1.5 equiv)</div></div><div><div><math>\text{R}^1</math></div><div><math>\text{CH}(\text{NH}-\text{R}^2)</math></div><div><math>\text{C}(\text{F})(\text{F})\text{Y}</math></div></div><div><b>7</b></div></div></div> <div><div><div><math>\text{R}^3</math></div><div><math>\text{N}(\text{R}^3)</math></div><div><math>\text{C}(\text{R}^1)=\text{C}(\text{R}^2)</math></div></div><div><b>5</b></div></div> <div><div><math>\text{KHF}_2</math> (0.75 equiv), <math>\text{CF}_3\text{CO}_2\text{H}</math> (1.25 equiv)</div><div><math>\text{MeCN}</math>, rt, 18 h</div></div> <div><div><div><math>\text{R}^3</math></div><div><math>\text{N}(\text{R}^3)</math></div><div><math>\text{C}(\text{R}^1)(\text{F})(\text{F})\text{C}(\text{R}^2)\text{Y}</math></div></div><div><b>8</b></div></div>										
#	substrate	silane	product	yield (%) <sup>a</sup>	#	substrate	silane	product	yield (%) <sup>a</sup>	
1		4a	2		85	9		1		85
2		4b	1		71	10	5a	2		85
3		4c	1		72	11		1		79
4		4c	2		77	12		1		81
5		4d	1		60	13		1		90
6		4d	2		70	14		2		87
7		4e	1		75	15		2		78
8		4f	2		73					

<sup>a</sup>Isolated yield.

## Scheme 2. Reaction of Imine 4c with Reagent 3



°C during 3 h, and mixture was kept overnight at −25 °C. The volatile materials were evaporated using a conventional rotary evaporator. The residue was treated with ether/hexane (1:1, 10 mL) and water (20 mL), the aqueous phase was extracted with ether/hexane (1:1, 3 × 5 mL), and the combined organic phase was dried over MgSO<sub>4</sub>. The

solvent was evaporated, and the residue was distilled under vacuum to give 2.0 g of the title compound (yield 77%). Bp 56–57 °C/1 Torr. NMR spectra were identical to the reported data.<sup>7a</sup>

**N-(Furan-2-ylmethylene)cyclohexanamine (4a).** Obtained according to literature procedure.<sup>18</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.04–1.36 (m, 3H), 1.40–1.82 (m, 7H), 2.92–3.14 (m, 1H), 6.30–6.40 (m, 1H), 6.53–6.67 (m, 1H), 7.35–7.46 (m, 1H), 7.98–8.07 (m, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 24.6, 25.3, 34.1, 69.8, 111.2, 113.3, 144.1, 147.0, 151.5.

**Propyl-(3,4,5-trimethoxybenzylidene)amine (4b).** Obtained according to literature procedure.<sup>10a</sup>

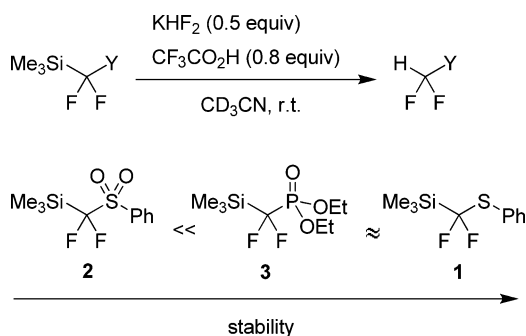
**N-Benzylidenemethanamine (4c).** Obtained according to literature procedure.<sup>19</sup> <sup>1</sup>H NMR spectra were identical to the reported data.<sup>20</sup>

Table 2. Reactions of Enamines with Phosphorus Reagent 3

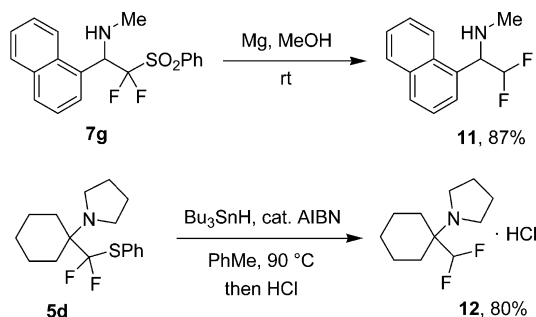
#	substrate	product	yield (%) <sup>a</sup>
1			71
2			78
3			84

<sup>a</sup>Isolated yield.

Scheme 3. Stability of Silanes in the Presence of HF



Scheme 4. Desulfurization Reactions



**N-(2,2-Dimethylpropylidene)-1-phenylmethanamine (4d).** Obtained according to literature procedure.<sup>21</sup> NMR spectra were identical to the reported data.<sup>22</sup>

**N-[1-Naphthylmethylene]methanamine (4e).** Obtained according to literature procedure.<sup>23</sup> <sup>1</sup>H NMR spectra were identical to the reported data.<sup>24</sup>

**Cyclopropyl-naphthalen-1-ylmethylene-amine (4f).** Obtained according to literature procedure.<sup>10a</sup>

**4-Cyclohex-1-en-1-ylmorpholine (5a).** Obtained according to literature procedure.<sup>25</sup> <sup>1</sup>H NMR spectra were identical to the reported data.<sup>26</sup>

**1-(2-Methylprop-1-en-1-yl)pyrrolidine (5b).** Obtained according to literature procedure.<sup>27</sup> NMR spectra were identical to the reported data.<sup>26b</sup>

**4-(1-Phenylvinyl)morpholine (5c).** Obtained according to literature procedure.<sup>28</sup> <sup>1</sup>H NMR spectra were identical to the reported data.<sup>29</sup>

**1-Cyclohex-1-en-1-ylpyrrolidine (5d).** Obtained according to literature procedure.<sup>25</sup> <sup>1</sup>H NMR spectra were identical to the reported data.<sup>30</sup>

**Methyl 3-(Pyrrolidin-1-yl)but-2-enoate (5e).** Obtained according to literature procedure.<sup>31</sup> NMR spectra were identical to the reported data.<sup>32</sup>

**Enamine 5f. Mixture of 4-(1-Isopropylvinyl)morpholine (5f-A) and 4-(1,2-Dimethylprop-1-enyl)morpholine (5f-B); Ratio A:B = 2:1.** A solution of TiCl<sub>4</sub> (8.55 g, 45 mmol) in hexane (10 mL) was added dropwise to a solution of morpholine (24.8 g, 285 mmol) in hexane (100 mL) at 0 °C. Then, a solution of isopropyl methyl ketone (4.3 g, 50 mmol) in hexane (20 mL) was added, and the mixture was refluxed for 1 h and cooled to room temperature. The mixture was filtered washing with small amount of hexane, the filtrate was concentrated, and the mixture was distilled under vacuum to give 5.4 g (70% yield) of a mixture of enamines (5f-A and 5f-B, 2:1). Bp 90–92 °C/35 Torr. The product contains ca. 10% of unidentified impurity. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ isomer 5f-A, 1.07 (d, 6H, J = 6.6), 2.38 (sept, 1H, J = 6.6), 3.87 (s, 1H), 4.00 (s, 1H), 2.73–2.93 (m, 4H); isomer 5f-B, 1.6 (s, 6H), 1.73 (s, 3H), 2.48–2.61 (m, 4H); both isomers, 3.60–3.78 (m). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 9.6, 18.7, 19.4, 22.4, 29.3, 48.9, 50.2, 66.9, 67.4, 84.9, 122.0, 137.5, 162.5. <sup>1</sup>H NMR spectrum was identical to the reported data for a mixture of regioisomers.<sup>33</sup>

**Fluoroalkylation of Imines and Enamines (General Procedure).** Trifluoroacetic acid (48 μL, 0.625 mmol) was added to a mixture of the substrate (0.5 mmol) and KHF<sub>2</sub> (29 mg, 0.375 mmol) in acetonitrile (1.5 mL) at 0 °C, and the suspension was stirred for 5 min. Silicon reagent (0.75 mmol) was added, the cooling bath was removed, and the mixture was stirred for 18 h at room temperature. For the workup, saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (1 mL) was added dropwise, and the mixture was stirred for an additional 2 min, diluted with water (7 mL), and extracted with ether/hexane (1:1, 3 × 4 mL). The combined organic phase was filtered through Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum to give the crude material, which was purified by one of the following methods.

**Method A.** Column chromatography on silica gel.

**Method B.** A solution of HCl in dioxane (150 μL, 4 M, 0.6 mmol) was added dropwise to a solution of crude material in diethyl ether (2 mL), which caused the precipitation of the hydrochlorided salt. The solvent was decanted, and the salt was washed with ether (2 × 1 mL). The residue was treated with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (2 mL), the aqueous phase was extracted with ether/hexane (1:1, 3 × 3 mL), the combined organic phase was filtered through Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum. The residue was dissolved in ether containing 0.5 vol % of triethylamine, passed through a short silica gel pad, and concentrated to give analytically pure product.

**Method C.** Concentrated aqueous HCl (1 mL) was added to a solution of crude product in diethyl ether (2 mL). The mixture was diluted with water (3 mL) and vigorously shaken. The aqueous phase was washed with ether/hexane (1:1, 10 × 1.5 mL) and then treated dropwise with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> until basic reaction. The aqueous phase was extracted with ether/hexane (1:1, 3 × 6 mL), and the combined organic phase was filtered through Na<sub>2</sub>SO<sub>4</sub>, concentrated under vacuum. The residue was dissolved in ether containing 0.5 vol % of triethylamine, passed through a short silica gel pad, and concentrated to give analytically pure product.

**N-[2,2-Difluoro-1-(2-furyl)-2-(phenylsulfonyl)ethyl]-cyclohexanamine (7a).** Purified by method A; 157 mg, 85% yield. Mp 106–108 °C. Chromatography hexanes/EtOAc 10:1. R<sub>f</sub> 0.25 (hexanes/EtOAc 10:1). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.00–1.30 (m, 5H), 1.45–1.82 (m, 5H), 1.82–2.05 (m, 1H), 2.30–2.52 (m, 1H), 4.85 (dd, 1H, J = 20.9, 6.6), 6.28–6.50 (m, 2H), 7.42 (br, 1H), 7.57 (t, 2H, J = 7.7), 7.71 (t, 1H, J = 7.7), 7.99 (d, 2H, J = 7.7). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 24.4, 24.7, 25.8, 32.2, 33.9, 53.9 (dd, J = 23.4, 19.2), 54.4, 110.2, 110.5, 121.4 (dd, J = 296.0, 290.3), 128.9, 130.5, 134.3, 134.8, 143.1, 148.3. <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>): δ –112.5 (dd, 1F, J



= 234.2, 20.9), -101.7 (dd, 1F,  $J$  = 234.2, 6.6). Anal. Calcd for  $C_{18}H_{21}F_2NO_3S$  (369.43): C, 58.52; H, 5.73; N, 3.79. Found: C, 58.69; H, 5.79; N, 3.76.

**N-[2,2-Difluoro-2-(phenylthio)-1-(3,4,5-trimethoxyphenyl)-ethyl]-N-propylamine (7b).** Purified by method A; 141 mg, 71% yield. Chromatography hexanes/EtOAc 5:1.  $R_f$  0.27 (hexanes/EtOAc 5:1). Oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  0.92 (t, 3H,  $J$  = 7.3), 1.39–1.61 (m, 2H), 1.77 (br, 1H), 2.52 (t, 2H,  $J$  = 6.9), 3.85 (s, 9H), 4.08 (dd, 1H,  $J$  = 12.3, 7.5), 6.67 (s, 2H), 7.20–7.43 (m, 3H), 7.56 (d, 2H,  $J$  = 6.4).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  11.5, 22.9, 49.4, 56.0, 60.6, 68.5 (dd,  $J$  = 24.3, 23.3), 105.9, 126.6, 128.7, 129.4, 129.8 (t,  $J$  = 284.2), 131.2 (d,  $J$  = 1.4), 136.0, 138.0, 152.9.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -80.9 (dd, 1F,  $J$  = 206.6, 12.3), -76.8 (dd, 1F,  $J$  = 206.6, 7.5). Anal. Calcd for  $C_{20}H_{25}F_2NO_3S$  (397.48): C, 60.43; H, 6.34; N, 3.52. Found: C, 60.55; H, 6.40; N, 3.40.

**N-[2,2-Difluoro-1-phenyl-2-(phenylthio)ethyl]-N-methylamine (7c).** Purified by method A; 101 mg, 72% yield. Chromatography hexanes/EtOAc 15:1.  $R_f$  0.30 (hexanes/EtOAc 15:1). Oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.94 (br, 1H), 2.43 (s, 3H), 4.11 (dd, 1H,  $J$  = 12.3, 8.3), 7.30–7.52 (m, 8H), 7.56–7.68 (m, 2H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  34.5, 70.3 (dd,  $J$  = 24.8, 23.2), 126.9 (t,  $J$  = 1.9), 128.3, 128.5, 128.8, 128.9, 129.5, 129.8 (t,  $J$  = 283.9), 135.2, 136.2.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -81.3 (dd, 1F,  $J$  = 207.7, 12.3), -77.1 (dd, 1F,  $J$  = 207.7, 8.3). Anal. Calcd for  $C_{15}H_{15}F_2NS$  (279.35): C, 64.49; H, 5.41; N, 5.01. Found: C, 64.48; H, 5.46; N, 4.90.

**N-[2,2-Difluoro-1-phenyl-2-(phenylsulfonyl)ethyl]-N-methylamine (7d).** Purified by method A; 120 mg, 77% yield. Chromatography hexanes/EtOAc 5:1.  $R_f$  0.44 (hexanes/EtOAc 5:1). Oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  2.00 (s, 1H), 2.36 (s, 3H), 4.54 (dd, 1H,  $J$  = 20.2, 5.9), 7.26–7.46 (m, 5H), 7.55 (t, 2H,  $J$  = 7.7), 7.68 (t, 1H,  $J$  = 7.7), 7.98 (d, 2H,  $J$  = 7.7).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  34.0, 64.1 (dd,  $J$  = 23.0, 17.9), 121.7 (dd,  $J$  = 295.0, 287.9), 128.4, 128.87, 128.91, 128.94, 130.5, 133.7, 134.9.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -114.7 (dd, 1F,  $J$  = 237.4, 20.2), -100.4 (dd, 1F,  $J$  = 237.4, 5.9). Anal. Calcd for  $C_{15}H_{15}F_2NO_2S$  (311.35): C, 57.86; H, 4.86; N, 4.50. Found: C, 57.81; H, 5.02; N, 4.32.

**N-Benzyl-N-{1-[difluoro(phenylthio)methyl]-2,2-dimethylpropyl}amine (7e).** Purified by method A; 101 mg, 60% yield. Chromatography hexanes/EtOAc 30:1.  $R_f$  0.26 (hexanes/EtOAc 30:1). Oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.18 (s, 9H), 1.55 (s, 1H), 2.97 (dd, 1H,  $J$  = 16.9, 6.9), 4.00 (d, 1H,  $J$  = 12.4), 4.30 (d, 1H,  $J$  = 12.4), 7.30–7.60 (m, 8H), 7.65–7.78 (m, 2H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  27.9 (t,  $J$  = 2.6), 36.1, 56.0, 71.5 (t,  $J$  = 22.3), 127.2, 127.9 (d,  $J$  = 2.6), 128.36, 128.38, 128.8, 129.3, 133.8 (dd,  $J$  = 292.5, 289.6), 136.4, 140.3.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -75.8 (dd, 1F,  $J$  = 201.3, 16.9), -65.6 (dd, 1F,  $J$  = 201.3, 6.9). HRMS (ESI): calcd for  $C_{19}H_{24}F_2NS$  (M + H) 336.1592, found 336.1590.

**N-Benzyl-N-{1-[difluoro(phenylsulfonyl)methyl]-2,2-dimethylpropyl}amine (7f).** Purified by method A; 129 mg, 70% yield. Chromatography hexanes/EtOAc 10:1.  $R_f$  0.33 (hexanes/EtOAc 10:1). Mp 62–63 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.11 (s, 9H), 1.49 (br, 1H), 3.47 (dd, 1H,  $J$  = 27.5, 3.2), 3.92 (d, 1H,  $J$  = 11.5), 4.39 (d, 1H,  $J$  = 11.5), 7.18–7.42 (m, 3H), 7.49 (d, 2H,  $J$  = 6.8), 7.60 (t, 2H,  $J$  = 7.7), 7.74 (t, 1H,  $J$  = 7.7), 7.95 (d, 2H,  $J$  = 7.7).  $^{13}C$  NMR (50 MHz,  $CDCl_3$ ):  $\delta$  27.6 (dd,  $J$  = 3.6, 1.4), 37.6 (d,  $J$  = 2.1), 55.2, 64.4 (dd,  $J$  = 19.9, 17.7), 125.3 (dd,  $J$  = 300.2, 298.1), 127.1, 128.3, 128.5, 129.1, 130.5 (d,  $J$  = 1.4), 134.3, 134.7, 140.0.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -110.8 (dd, 1F,  $J$  = 229.9, 27.5), -91.9 (d, 1F,  $J$  = 229.9). Anal. Calcd for  $C_{19}H_{23}F_2NO_2S$  (367.45): C, 62.10; H, 6.31; N, 3.81. Found: C, 62.02; H, 6.44; N, 3.72.

**2,2-Difluoro-N-methyl-1-(naphthalen-1-yl)-2-(phenylsulfonyl)ethanamine (7g).** Purified by method B; 136 mg, 75% yield. Mp 116–118 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  2.24 (br, 1H), 2.39 (s, 3H), 5.60 (d, 1H,  $J$  = 22.9), 7.48–7.66 (m, 5H), 7.67–7.81 (m, 2H), 7.84–7.95 (m, 2H), 8.02 (d, 2H,  $J$  = 7.3), 8.15–8.26 (m, 1H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  34.2, 58.2 (br), 122.0 (dd,  $J$  = 297.1, 287.9), 122.8, 125.2, 125.7, 126.2, 126.6, 128.9, 129.0, 129.4, 129.7, 130.6, 132.9, 133.7, 133.8, 135.0.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -116.1 (br d, 1F,  $J$  = 224.7), -99.3 (d, 1F,  $J$  = 224.7). Anal. Calcd

for  $C_{19}H_{17}F_2NO_2S$  (361.41): C, 63.14; H, 4.74; N, 3.88. Found: C, 63.00; H, 4.66; N, 3.72.

**N-[2,2-Difluoro-1-(1-naphthyl)-2-(phenylsulfonyl)ethyl]-cyclopropanamine (7h).** Purified by method A; 141 mg, 73% yield. Chromatography hexanes/EtOAc 5:1.  $R_f$  0.22 (hexanes/EtOAc 5:1). Mp 113–115 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  0.30–0.55 (m, 3H), 0.62–0.75 (m, 1H), 1.95–2.10 (m, 1H), 2.56 (d, 1H,  $J$  = 8.7), 5.65–5.95 (m, 1H), 7.43–7.78 (m, 7H), 7.89 (t, 2H,  $J$  = 8.0), 7.95–8.03 (m, 2H), 8.19–8.27 (m, 1H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  6.0, 7.2, 28.8, 56.5 (br), 122.4 (dd,  $J$  = 294.2, 291.4), 122.9, 125.2, 125.8, 126.8, 128.8, 129.0, 129.3, 130.5, 131.0, 132.7, 133.8, 134.4, 134.8.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -115.1 (br d, 1F,  $J$  = 239.5), -99.5 (d, 1F,  $J$  = 239.5). Anal. Calcd for  $C_{21}H_{19}F_2NO_2S$  (387.44): C, 65.10; H, 4.94; N, 3.62. Found: C, 65.28; H, 4.99; N, 3.57.

**4-{1-[Difluoro(phenylthio)methyl]cyclohexyl}morpholine (8a).** Purified by method A; 139 mg, 85% yield. Mp 68–70 °C. Chromatography hexanes/EtOAc/NEt<sub>3</sub> 20:1:0.005.  $R_f$  0.2 (hexanes/EtOAc 20:1).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.18–1.41 (m, 1H), 1.43–1.85 (m, 7H), 2.00–2.20 (m, 2H), 2.94 (br, 4H), 3.67 (br, 4H), 7.30–7.50 (m, 3H), 7.56–7.68 (m, 2H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  20.6, 25.9, 28.8, 46.9, 64.6 (t,  $J$  = 18.5), 68.5, 126.7 (t,  $J$  = 1.1), 128.8, 129.5, 134.8 (t,  $J$  = 294.4), 136.6.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -76.6 (s, 2F). Anal. Calcd for  $C_{17}H_{23}F_2NOS$  (327.43): C, 62.36; H, 7.08; N, 4.28. Found: C, 62.55; H, 7.09; N, 4.08.

**4-{1-[Difluoro(phenylsulfonyl)methyl]cyclohexyl}morpholine (8b).** Purified by method B; 153 mg, 85% yield. Mp 167–169 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.20–1.84 (m, 6H), 1.95–2.35 (m, 4H), 2.60–3.11 (br, 4H), 3.34–3.91 (br, 4H), 7.60 (t, 2H,  $J$  = 7.7), 7.74 (t, 1H,  $J$  = 7.7), 7.95 (d, 2H,  $J$  = 7.7).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  20.2, 25.5, 28.5 (t,  $J$  = 3.0), 46.8 (t,  $J$  = 2.8), 64.9 (t,  $J$  = 16.9), 68.3, 126.8 (t,  $J$  = 300.5), 129.0, 130.6, 134.5, 134.8.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -101.7 (s, 2F). Anal. Calcd for  $C_{17}H_{23}F_2NO_2S$  (359.43): C, 56.81; H, 6.45; N, 3.90. Found: C, 56.97; H, 6.35; N, 3.75.

**1-{1-[Difluoro(phenylthio)methyl]-2-methylpropyl}pyrrolidine (8c).** Purified by method C; 113 mg, 79% yield. Oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.04 (d, 3H,  $J$  = 6.9), 1.11 (dd, 3H,  $J$  = 6.4, 4.1), 1.79–1.94 (m, 4H), 2.20–2.40 (m, 1H), 2.94–3.20 (m, 5H), 7.33–7.50 (m, 3H), 7.62–7.73 (m, 2H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  20.1 (dd,  $J$  = 5.8, 1.2), 21.1, 25.0, 27.5, 49.0, 69.7 (t,  $J$  = 23.6), 128.6, 128.9, 129.6, 134.7 (t,  $J$  = 293.7), 135.9.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -75.7 (dd, 1F,  $J$  = 197.1, 17.0), -66.6 (br d, 1F,  $J$  = 197.1). Anal. Calcd for  $C_{15}H_{21}F_2NS$  (285.40): C, 63.13; H, 7.42; N, 4.91. Found: C, 63.03; H, 7.37; N, 4.82.

**4-[2,2-Difluoro-1-methyl-1-phenyl-2-(phenylsulfonyl)ethyl]morpholine (8d).** Purified by method A; 155 mg, 81% yield. Chromatography hexanes/EtOAc/NEt<sub>3</sub> 5:1:0.005.  $R_f$  0.29 (hexanes/EtOAc 5:1). Mp 93–95 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.91 (s, 3H), 2.45–2.83 (m, 4H), 3.56–3.85 (m, 4H), 7.29–7.44 (m, 3H), 7.45–7.59 (t, 2H,  $J$  = 7.8), 7.60–7.77 (m, 3H), 7.77–7.92 (d, 2H,  $J$  = 7.8).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  14.7, 47.7 (d,  $J$  = 2.9), 67.3, 68.5 (dd,  $J$  = 18.4, 15.6), 124.4 (dd,  $J$  = 308.6, 302.3), 127.9, 128.4, 128.9, 129.0, 130.2, 134.4, 134.8, 137.4 (d,  $J$  = 4.6).  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -101.4 (d, 1F,  $J$  = 231.0), -92.3 (d, 1F,  $J$  = 231.0). HRMS (ESI): calcd for  $C_{19}H_{21}F_2NNaO_2S$  (M + Na) 404.1102, found 404.1106.

**1-{1-[Difluoro(phenylthio)methyl]cyclohexyl}pyrrolidine (8e).** Purified by method C; 140 mg, 90% yield. Mp 46–48 °C.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.10–1.30 (m, 1H), 1.35–1.81 (m, 11H), 1.96–2.12 (m, 2H), 2.90–3.10 (m, 4H), 7.30–7.46 (m, 3H), 7.50–7.68 (m, 2H).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  21.5, 24.9, 25.6, 29.9 (t,  $J$  = 1.6), 45.1 (t,  $J$  = 1.9), 63.4 (t,  $J$  = 16.9), 127.4, 128.7, 129.3, 136.0 (t,  $J$  = 296.3), 136.6.  $^{19}F$  NMR (282 MHz,  $CDCl_3$ ):  $\delta$  -76.1 (s, 2F). Anal. Calcd for  $C_{17}H_{23}F_2NS$  (311.43): C, 65.56; H, 7.44; N, 4.50. Found: C, 65.67; H, 7.50; N, 4.64.

**Methyl 4,4-Difluoro-3-methyl-4-(phenylsulfonyl)-3-pyrrolidin-1-ylbutanoate (8f).** Purified by method C; 157 mg, 87% yield. Oil.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  1.52–1.68 (m, 4H), 1.82 (s, 3H), 2.72 (d, 1H,  $J$  = 13.7), 2.78–2.88 (m, 2H), 2.93–3.08 (m, 3H), 3.64 (s, 3H), 7.55 (t, 2H,  $J$  = 7.6), 7.68 (t, 1H,  $J$  = 7.6), 7.94 (d, 2H,  $J$  = 7.6).  $^{13}C$  NMR (75 MHz,  $CDCl_3$ ):  $\delta$  20.1 (dd,  $J$  = 3.9, 2.2), 24.1, 37.6

(d,  $J = 5.0$ ), 46.4 (t,  $J = 2.2$ ), 51.5, 63.4 (dd,  $J = 19.3$ , 17.7), 125.0 (dd,  $J = 305.7$ , 303.0), 128.9, 130.2, 134.6, 135.0, 170.2.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -103.8 (d, 1F,  $J = 237.4$ ), -97.8 (d, 1F,  $J = 237.4$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{F}_2\text{NO}_4\text{S}$  (361.40): C, 53.17; H, 5.86; N, 3.88. Found: C, 53.20; H, 5.83; N, 3.84.

**4-[1-(Difluoro(phenylsulfonyl)methyl)-1,2-dimethylpropyl]-morpholine (8g).** Purified by method B; 136 mg, 78% yield. Mp 105–107 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.84 (dd, 3H,  $J = 6.4$ , 4.1), 0.94 (d, 3H,  $J = 6.9$ ), 1.77 (d, 3H,  $J = 3.7$ ), 2.52–2.69 (m, 1H), 2.90–3.13 (m, 4H), 3.67–3.8 (m, 2H), 3.86–3.98 (m, 2H), 7.53–7.62 (m, 2H), 7.64–7.73 (m, 1H), 7.93 (d, 2H,  $J = 7.78$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.2 (dd,  $J = 3.8$ , 5.5), 17.8, 17.9 (d,  $J = 1.1$ ), 30.0 (dd,  $J = 1.7$ , 3.9), 47.6, 67.3, 68.0 (t,  $J = 18.5$ ), 126.4 (d,  $J = 311.5$ ), 128.8, 129.9 (d,  $J = 2.2$ ), 134.0, 136.4.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -102.2 (d, 1F,  $J = 228.9$ ), -79.6 (d, 1F,  $J = 228.9$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{23}\text{F}_2\text{NO}_3\text{S}$  (347.42): C, 55.31; H, 6.67; N, 4.03. Found: C, 55.10; H, 6.74; N, 3.98.

**Diethyl [1,1-Difluoro-2-(methylamino)-2-phenylethyl]-phosphonate (9).** Purified by method B. For final purification, the product was fractionally flash chromatographed using small silica gel column eluting with ether containing 0.5 vol % of triethylamine; 46 mg, 30% yield. Mp 42–44 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.22–1.37 (m, 6H), 1.84 (s, 1H), 2.34 (s, 3H), 4.01–4.33 (m, 5H), 7.30–7.45 (m, 5H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.2 (d,  $J = 3.5$ ), 16.3 (d,  $J = 3.5$ ), 34.2, 64.1 (d,  $J = 6.9$ ), 64.5 (d,  $J = 6.9$ ), 66.4 (ddd,  $J = 15.6$ , 19.0, 23.3), 119.5 (td,  $J = 267.2$ , 210.2), 128.3, 128.4, 129.2, 134.6 (m).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -122.0 (ddd, 1F,  $J = 302.3$ , 104.8, 19.1), -112.2 (ddd, 1F,  $J = 302.3$ , 101.9, 10.6).  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.18 (dd,  $J = 101.9$ , 104.8). Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{F}_2\text{NO}_3\text{P}$  (307.27): C, 50.81; H, 6.56; N, 4.56. Found: C, 50.60; H, 6.32; N, 4.30.

**Diethyl (Difluoro(1-morpholinocyclohexyl)methyl)-phosphonate (10a).** Purified by method B; 126 mg, 71% yield. Mp 57–60 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.19–1.80 (m, 14H), 1.92–2.08 (m, 2H), 2.93 (br, 4H), 3.62 (br, 4H), 4.16–4.31 (m, 4H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.4 (d,  $J = 5.4$ ), 20.3, 25.7, 28.0 (t,  $J = 3.3$ ), 47.1 (t,  $J = 3.0$ ), 62.7 (q,  $J = 16.7$ ), 64.4 (d,  $J = 7.5$ ), 68.6, 126.9 (td,  $J = 271.2$ , 191.9).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -112.4 (d,  $J = 108.2$ ).  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.05 (t,  $J = 108.2$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{28}\text{F}_2\text{NO}_4\text{P}$  (355.36): C, 50.70; H, 7.94; N, 3.94. Found: C, 50.76; H, 8.03; N, 3.77.

**Diethyl (1,1-Difluoro-3-methyl-2-pyrrolidin-1-ylbutyl)-phosphonate (10b).** Purified by method C; 122 mg, 78% yield. Oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.95 (d, 3H,  $J = 6.9$ ), 1.03 (dd, 3H,  $J = 6.4$ , 4.6), 1.26–1.37 (m, 6H), 1.63–1.76 (m, 4H), 2.14–2.30 (m, 1H), 2.75–3.00 (m, 4H), 3.10 (dt, 1H,  $J = 29.3$ , 7.6), 4.06–4.28 (m, 4H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.3 (t,  $J = 6.1$ ), 20.1 (dd,  $J = 7.5$ , 1.2), 21.6, 24.5, 26.0 (dt,  $J = 6.9$ , 2.3), 48.8, 63.6 (m), 64.9 (ddd,  $J = 11.5$ , 20.7, 23.6), 124.0 (ddd,  $J = 277.5$ , 274.7, 218.8).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -121.0 (ddd, 1F,  $J = 297.8$ , 108.3, 29.3), -97.4 (dd, 1F,  $J = 297.8$ , 108.3).  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.71 (dd,  $J = 110.4$ , 106.3). Anal. Calcd for  $\text{C}_{15}\text{H}_{26}\text{F}_2\text{NO}_3\text{P}$  (313.32): C, 49.83; H, 8.36; N, 4.47. Found: C, 49.71; H, 8.23; N, 4.44.

**Diethyl Difluoro(1-(1-pyrrolidin-1-yl)cyclohexyl)-methylphosphonate (10c).** Purified by method C. 143 mg, 84% yield. Oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.08–1.74 (m, 18H), 1.91–2.07 (m, 2H), 2.87–3.04 (m, 4H), 4.13–4.28 (m, 4H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.2 (d,  $J = 6.1$ ), 21.1, 24.8, 25.4, 28.9 (t,  $J = 3.6$ ), 44.9 (t,  $J = 2.8$ , 61.5 (dt,  $J = 17.7$ , 15.5), 64.0 (d,  $J = 7.2$ ), 126.4 (dt,  $J = 273.7$ , 191.8).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -112.2 (d, 2F,  $J = 110.3$ ).  $^{31}\text{P}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13 (t,  $J = 110.3$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{28}\text{F}_2\text{NO}_3\text{P}$  (339.36): C, 53.09; H, 8.32; N, 4.13. Found: C, 52.99; H, 8.34; N, 4.13.

**N-[2,2-Difluoro-1-(1-naphthyl)ethyl]-N-methylamine (11).** A suspension of magnesium turnings (243 mg, 10 mmol) in methanol (15 mL) was treated with dibromoethane (2  $\mu\text{L}$ ), and the mixture was stirred for a few minutes until slow evolution of hydrogen started. Then, a solution of amine **7g** (98 mg, 0.5 mmol) in methanol (3 mL) was added, and the mixture was stirred for 1 h at room temperature. An additional portion of magnesium (243 mg, 10 mmol) was added,

and the mixture was stirred for 1 h. The solvent was evaporated, and the residue was treated with saturated aqueous  $\text{NH}_4\text{Cl}$  (5 mL), extracted with ether (3  $\times$  3 mL), and dried over  $\text{MgSO}_4$ . The solvent was evaporated, and the residue was distilled under vacuum in a short-path apparatus to give 96 mg (87% yield) of amine **11** as colorless liquid. Bp 106–115 °C (bath temperature)/0.35 Torr.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.81 (br, 1H), 2.44 (s, 3H), 4.75 (dt, 1H,  $J = 10.9$ , 5.7), 6.03 (dt, 1H,  $J = 56.8$ , 5.7), 7.48–7.63 (m, 3H), 7.69 (d, 1H,  $J = 7.3$ ), 7.83–7.95 (m, 2H), 8.26 (d, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.5, 62.4 (t,  $J = 21.6$ ), 117.3 (dd,  $J = 245.1$ , 246.2), 122.9, 125.4, 125.65, 125.69, 126.4, 128.9, 129.0, 131.7 (dd,  $J = 4.6$ , 3.0), 132.3, 134.0.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):  $\delta$  -124.5 (ddd, 1F,  $J = 280.8$ , 56.8, 10.9), -122.6 (ddd, 1F,  $J = 280.8$ , 56.8, 5.7). Anal. Calcd for  $\text{C}_{13}\text{H}_{13}\text{F}_2\text{N}$  (221.25): C, 70.57; H, 5.92; N, 6.33. Found: C, 70.71; H, 6.01; N, 6.24.

**1-[1-(Difluoromethyl)cyclohexyl]pyrrolidine Hydrochloride (12).** A solution of amine **5d** (156 mg, 0.5 mmol),  $\text{Bu}_3\text{SnH}$  (202  $\mu\text{L}$ , 0.75 mmol), and azobisisobutyronitrile (5 mg) in toluene (3 mL) was heated for 2 h at 90 °C. Then an additional portion of azobisisobutyronitrile (5 mg) was added, and the mixture was heated for 3 h at 90 °C. The mixture was cooled to room temperature, treated with concentrated aqueous hydrochloric acid (1 mL), and vigorously stirred for 5 min. The organic phase was separated, and the aqueous phase was washed with ether/pentane (1:1, 1 mL). The aqueous phase was treated with saturated aqueous  $\text{Na}_2\text{CO}_3$  until basic reaction and extracted with ether/pentane (1:1, 3  $\times$  2 mL). The combined organic phase was filtered through  $\text{Na}_2\text{SO}_4$ , the solvent was evaporated under ambient pressure until the volume of 2 mL, and HCl in dioxane (150  $\mu\text{L}$ , 4 M solution) was added. The precipitate was filtered, washed with ether/pentane (1:1), and dried to give 96 mg (80% yield) of amine hydrochloride **12**. Mp 168–171 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.24–2.36 (m, 14H), 3.35 (br m), 3.61 (br m), 6.24 (t, 1H,  $J = 51.9$ ), 12.25 (br, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  21.5, 23.45, 23.48, 28.6 (t,  $J = 3.2$ ), 49.0 (t,  $J = 3.7$ ), 64.5 (t,  $J = 16.7$ ), 115.6 (t,  $J = 249.9$ ).  $^{19}\text{F}$  NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  -128.4 (d,  $J = 51.9$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{20}\text{F}_2\text{NCl}$  (239.73): C, 55.11; H, 8.41; N, 5.84. Found: C, 55.17; H, 8.50; N, 5.86.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

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

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

This paper is dedicated to Professor Herbert Mayr on the occasion of his 65th birthday.

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