

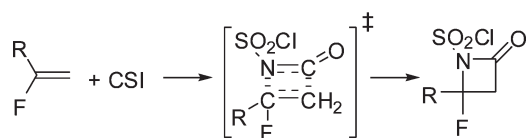
## Reaction of Chlorosulfonyl Isocyanate with Fluorosubstituted Alkenes: Evidence of a Concerted Pathway

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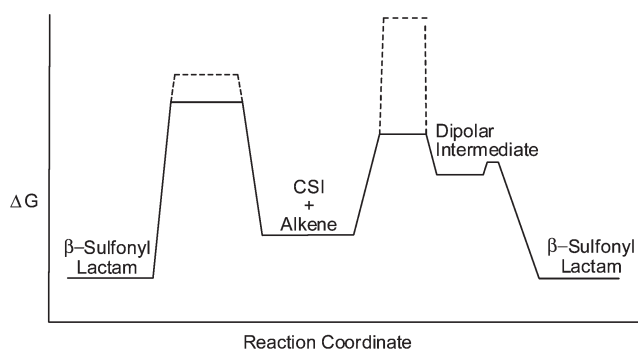


Concerted reactions are indicated for the electrophilic addition of chlorosulfonyl isocyanate with monofluoroalkenes. A vinyl fluorine atom on an alkene raises the energy of a stepwise transition state more than the energy of the competing concerted pathway. This energy shift induces CSI to react with monofluoroalkenes by a one-step process. The low reactivity of CSI with monofluoroalkenes, stereospecific reactions, the absence of 2:1 uracil products with neat fluoroalkenes, and quantum chemical calculations support a concerted pathway.

Chlorosulfonyl isocyanate (CSI) is the most reactive and versatile isocyanate.<sup>1</sup> CSI reacts with alkenes to give chlorosulfonyl  $\beta$ -lactams that are readily reduced to  $\beta$ -lactams.<sup>2,3</sup> This reaction sequence provides a synthetic route to  $\beta$ -lactam antibiotics.<sup>4</sup> We demonstrate in this paper a method to

synthesize  $\beta$ -fluorolactams from CSI. Other methods to prepare  $\beta$ -fluorolactams have been reported.<sup>5a,b</sup>

Reactions of CSI with hydrocarbon alkenes are reported to proceed through an open-ion dipolar intermediate.<sup>1,3,6</sup> Moriconi suggests that some 1,2-disubstituted olefins retain stereochemistry through fast collapse of the dipolar intermediate.<sup>3,6</sup> Ab initio calculations show that [2 + 2] cycloadditions between alkenes and isocyanates can react via a concerted transition state with zwitterionic character.<sup>7</sup> These calculations also found that electron-donating groups on the alkene or electron-withdrawing groups on the isocyanate lower the activation energy and induce the nature of the reaction to become less synchronous.<sup>7</sup> Calculations support a concerted process for the cycloaddition of isocyanates with aldehydes.<sup>8</sup> Quantum chemical calculations and photoelectron spectral data show that substituting a hydrogen with a fluorine atom on the  $\pi$ -bond of an alkene does not significantly alter the molecular energy of the  $\pi$ -bond,<sup>9</sup> and therefore, the HOMO and LUMO orbital energies for a concerted pathway should not be altered either. On the other hand, the energy for a dipolar stepwise pathway is raised significantly by the vinyl fluorine atom through its strong inductive effect.<sup>10</sup> This perturbation of the free energy profile is described in Figure 1 where the fluorine atom raises the transition state energy significantly for the stepwise process but increases the energy of the concerted pathway by only a modest amount. In Figure 1 the solid line represents the energy profile for hydrocarbon alkenes, and the dashed line describes the pathway for monofluoroalkenes. Therefore, alkenes with a vinyl fluorine atom may allow a concerted process to compete with or completely dominate the stepwise pathway. Both concerted and stepwise pathways might be realized for reactions of CSI with appropriately substituted fluoroalkenes.



**FIGURE 1.** Free energy diagram for reaction of CSI with hydrocarbon alkenes and fluorocarbon alkenes. Concerted reactions to the left and stepwise reactions to the right.

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CSI is a sluggish electrophile and reacts poorly in solution with alkenes that contain an electron-withdrawing vinyl fluorine.<sup>11</sup> We found that neat reactions of CSI with these less reactive fluoroalkenes proceed smoothly and in good yield. Neat reactions of CSI with these monofluoroalkenes allow for the synthesis of  $\beta$ -fluorolactams under “green chemistry” conditions. Thus, dialkylsubstituted monofluoroalkenes like the 1-fluorocyclohexenes (**1**, **2**), 3-fluorohex-3-enes **3E** and **3Z**, and the trialkylsubstituted fluorocyclohexene (**4**) react with CSI to give chlorosulfonyl  $\beta$ -fluorolactams (Scheme 1). A stereospecific reaction of CSI with **3E** and **3Z** is consistent with a concerted process for this series of fluoroalkenes. Product regiochemistry was confirmed by the carbonyl <sup>13</sup>C NMR three bond coupling with fluorine ( $J_{C-F} = 3-6$  Hz). The nitrogen of the  $\beta$ -lactams is bonded to the carbon with the fluorine since the developing positive charge in the concerted transition state prefers to be on the carbon stabilized by back-bond resonance from fluorine.

The regiochemistry of the  $\beta$ -sulfonyl fluorolactam products did not change when a third alkyl group was incorporated as in fluoroalkene **4**.  $\beta$ -Lactam products (**10 cis** and **10 trans**) show a 3 Hz coupling typical for three bond fluorine to carbonyl splitting. Assignment of the carbons from **10 cis** and **10 trans** was based on the magnitude of the carbon-fluorine coupling and from DEPT and HSQC experiments. The *cis/trans* stereochemistry of **10** was assigned using a 1-dimension ROESY experiment. Irradiating the upfield methyl adjacent to the carbonyl of the major isomer enhanced the methyl on the methine carbon. Irradiating the upfield methyl of the minor isomer enhanced the methine hydrogen on the minor isomer. Irradiating the methine hydrogens of each isomer separately confirmed the experiments irradiating the methyl groups above.

The best conditions to obtain  $\beta$ -sulfonyl fluorolactams (**11** and **12**) were with fluoroalkenes **5** and **6** and CSI in methylene chloride at room temperature (Scheme 1). Product **11**, as a neat liquid, decomposes in 1–2 days at room temperature but is stable in solution for about 1 week. Product **6** is a crystalline solid that decomposes in less than 15 min at room temperature but is stable in solution for 1 day. Reactions at high molar concentrations of **5** or **6** with CSI, approaching the neat concentrations used for fluoroalkenes **1**, **2**, **3E**, **3Z**, and **4**, did not give uracil products **13**. At these high concentrations we would expect capture of a dipolar intermediate by a second molecule of CSI to give uracil products like those reported for the reaction of CSI with hydrocarbon alkenes that can support stable dipolar intermediates.<sup>1a,2a,12</sup> Thus we suggest that fluoroalkenes **1–6** react by a concerted pathway.

Quantum chemical calculations at the MP2/6-311G(d,p) level of theory<sup>13a–e,14</sup> also support our claim of a one-step process for reaction of CSI with fluoroalkenes as described in

### SCHEME 1. Reaction of Alkenes with CSI

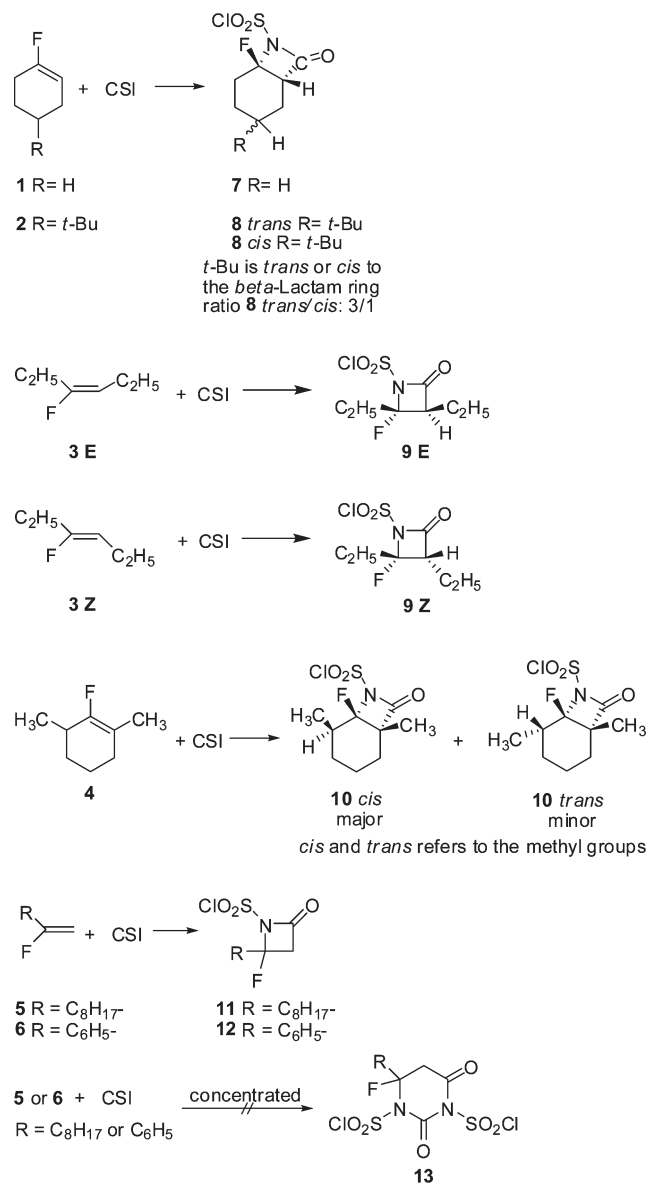


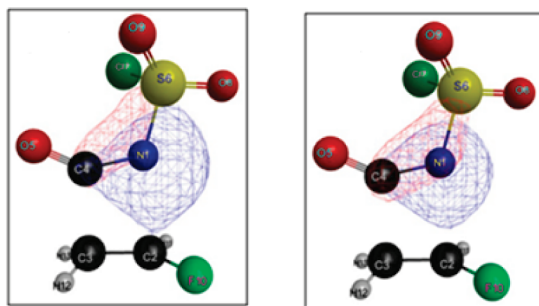
Figure 1. Transition states for the concerted pathway and a portion of a stepwise pathway were calculated for reaction of CSI with vinyl fluoride (Supporting Information). Intrinsic reaction coordinate calculations were performed to trace the minimum energy paths connecting the transition states to the corresponding local minima, i.e., reactants and products. The calculated stepwise transition state that connects to a high energy intermediate is 56.9 kcal/mol above the separated reactants (Supporting Information, structures 1 and 2 and Table S1). This stepwise transition state was found to be 26.6 kcal/mol higher in energy than the concerted transition state. Furthermore, the calculated stepwise transition state and intermediate have the nitrogen interacting with the fluorine-bearing carbon of vinyl fluoride, and that intermediate was also higher in energy than the concerted transition state (Supporting Information, Tables S1 and S2). The stepwise pathway does not include the expected intermediate with the carbonyl carbon of CSI attached to the terminal carbon of vinyl fluoride. All attempts to locate that

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**FIGURE 2.** (Left) C–N  $\pi$  bond orbital. (Right) Lone pair orbital on the nitrogen atom.

intermediate resulted in separation to CSI and vinyl fluoride or collapse to the  $\beta$ -lactam product. The hydrocarbon ethylene has a stepwise transition state 27 kcal/mol higher than that of the concerted transition state presumably from the high energy required to form a primary cation (Supporting Information, Table S2).

The concerted transition state is not orthogonal as reported for ketene cycloadditions where the orbitals mix by a [ $\pi^2(s) + \pi^2(a)$ ] process.<sup>15</sup> A six-electron process, involving the lone pair on nitrogen represented as [ $\pi^2(s) + \pi^2(s) + n^2(s)$ ], would allow for a concerted cyclization where the alkene carbon atoms and the O=C=N– moiety of CSI are in the same plane. Calculated localized molecular orbitals of the cyclic 2 + 2 transition state for the cycloaddition of CSI to vinyl fluoride show significant mixing between the C–N  $\pi$ -bond in CSI and the nitrogen lone pair electrons (Figure 2).

Our data support a concerted reaction of CSI with these less reactive fluoroalkenes because (i) reactions with **3E** and **3Z** are stereospecific; (ii) neat reactions of CSI with **1**, **2**, **3E**, **3Z**, **4**, **5**, and **6** do not give uracil products; and (iii) a concerted pathway is supported by quantum chemical calculations. A stepwise pathway is untenable since it is prohibitively high in energy. The expected dipolar intermediate with the carbonyl attached to the fluoroalkene could not be located.

## Experimental Section

Diethylaminosulfur trifluoride was added to cyclohexanones in methylene chloride to give mixtures of 1,1-difluorocyclohexanes and 1-fluorocyclohexenes. After water workup, the methylene chloride was removed by distillation, and the mixture was distilled through a vigreux column to give enriched 1-fluorocyclohexenes **1**, **2**, and **4** containing various amounts of 1,1-difluorocyclohexanes. Acyclic fluoroalkenes **3E**,<sup>16</sup> **3Z**,<sup>16</sup> **5**,<sup>16</sup> and **6**<sup>17</sup> were prepared as described in the literature. The  $\beta$ -fluorolactam products were isolated by chromatography (column or preparative thin layer), or in one case by recrystallization. Spectral data (NMR, IR) of crude reaction mixtures did not show other minor stereo- or regioisomer products. The following procedure is representative.

To 156 mg (1.00 mmol) of 4-*tert*-butyl-1-fluorocyclohexene (**2**) in a small round-bottom flask was added 155 mg (96  $\mu$ L, 1.10 mmol) of chlorosulfonyl isocyanate (CSI). The stirred mixture was heated to 65–70 °C for 1 h and then cooled. Methylene chloride (2–3 mL) was added, followed by dropwise addition of

ice–water. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic extractions were washed with 2% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated. <sup>19</sup>F NMR analysis on the crude mixture showed **8** *cis/trans* to be formed in a ratio of 1.0/3.0, respectively. Column chromatography (10 g silica gel) of the crude mixture with hexanes/chloroform gave 194 mg, 65%, of pure **8** *cis/8* *trans* in a ratio of 1.0/2.6 respectively. **8** *trans/cis*: <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>)  $\delta$  0.89 (s, 9H); 1.20–2.30 (m, 6H); [*trans* 2.55–2.75 (m) and *cis* 2.78–2.90 (m), 1H]; [*cis* 3.50 (m) and *trans* 3.67 (dm,  $J$  = 13 Hz), 1H]. <sup>19</sup>F NMR 376 MHz (CDCl<sub>3</sub>) *trans*  $\delta$  –117.7 (m) and *cis* –114.1 (m), ratio 3/1, respectively on the crude reaction mixture. <sup>13</sup>C NMR 100.6 MHz (CDCl<sub>3</sub>) **8** *trans*  $\delta$  19.2 (d,  $J$  = 8 Hz); 21.6 (s); 26.4 (d,  $J$  = 26 Hz); 26.7 (s); 33.2 (s); 40.0 (s); 57.5 (d,  $J$  = 21 Hz); 105.2 (d,  $J$  = 248 Hz); 161.7 (d,  $J$  = 6 Hz). **8** *cis*  $\delta$  21.2 (d,  $J$  = 9 Hz); 22.9 (s); 26.9 (s); 29.4 (d,  $J$  = 26 Hz); 32.9 (s); 43.2 (s); 55.5 (d,  $J$  = 22 Hz); 105.1 (d,  $J$  = 246 Hz); 162.9 (d,  $J$  = 4 Hz). IR (KBr) neat mixture *trans* 1826 cm<sup>–1</sup>, *cis* 1838 cm<sup>–1</sup>. Exact mass [MH]<sup>+</sup> calcd for C<sub>11</sub>H<sub>18</sub>NO<sub>3</sub>FSCl 298.067996; found 298.068000.

Reactions of fluoroalkenes **1**, **3E**, **3Z**, and **4** with CSI were done similarly and the following data were obtained. **7**: isolated (50%) by column chromatography on silica gel with hexanes/methylene chloride. <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>)  $\delta$  1.59–1.72 (m, 3H); 1.81–1.99 (m, 2H); 2.01–2.21 (m, 2H); 2.69–2.80 (m, 1H); 3.52–3.63 (m, 1H). <sup>19</sup>F NMR 376 MHz (CDCl<sub>3</sub>)  $\delta$  –112.8 (m). <sup>13</sup>C NMR 100.6 MHz (CDCl<sub>3</sub>)  $\delta$  15.5 (d,  $J$  = 8 Hz); 16.0 (s); 18.4 (s); 24.7 (d,  $J$  = 25 Hz); 53.5 (d,  $J$  = 21 Hz); 102.9 (d,  $J$  = 248 Hz); 160.1 (d,  $J$  = 4 Hz). IR (KBr) neat 1832 cm<sup>–1</sup>. Exact mass [MH]<sup>+</sup> calcd for C<sub>7</sub>H<sub>10</sub>NO<sub>3</sub>FSCl 242.00539; found 242.00470. **9E**: isolated (50%) by column chromatography as described above. <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>)  $\delta$  1.18 (t,  $J$  = 7.4 Hz, 6H); 1.65–1.98 (m, 2H); 2.03–2.23 (m, 1H); 2.54–2.68 (m, 1H); 3.42–3.52 (m, 1H). <sup>19</sup>F NMR 376 MHz (CDCl<sub>3</sub>)  $\delta$  –119.4 (ddd,  $J$  = 30.5, 13.7, and 9.2 Hz). <sup>13</sup>C NMR 100.6 MHz (CDCl<sub>3</sub>)  $\delta$  7.6 (d,  $J$  = 4 Hz); 11.6 (s); 18.5 (d,  $J$  = 2 Hz); 24.7 (d,  $J$  = 28 Hz); 63.1 (d,  $J$  = 24 Hz); 108.2 (d,  $J$  = 247 Hz); 162.2 (d,  $J$  = 5 Hz). IR (KBr) neat 1830 cm<sup>–1</sup>. Exact mass [MH]<sup>+</sup> calcd for C<sub>7</sub>H<sub>12</sub>NO<sub>3</sub>FSCl 244.0210; found 244.0202. **9Z**: isolated (55%) by column chromatography as described above. <sup>1</sup>H NMR 400 MHz (CDCl<sub>3</sub>)  $\delta$  1.11 (t,  $J$  = 7.6 Hz, 3H); 1.14 (t,  $J$  = 7.4 Hz, 3H); 1.78–1.99 (m, 2H); 2.10–2.29 (m, 1H); 2.47–2.60 (m, 1H); 3.36–3.43 (m, 1H). <sup>19</sup>F NMR 376 MHz (CDCl<sub>3</sub>)  $\delta$  –137.3 (dt,  $J$  = 27.5 and 6.9 Hz). <sup>13</sup>C NMR 100.6 MHz (CDCl<sub>3</sub>)  $\delta$  7.8 (d,  $J$  = 4 Hz); 11.7 (s); 17.7 (d,  $J$  = 5 Hz); 27.5 (d,  $J$  = 28 Hz); 60.2 (d,  $J$  = 22 Hz); 107.6 (d,  $J$  = 249 Hz); 162.4 (d,  $J$  = 1.5 Hz). IR (KBr) neat 1833 cm<sup>–1</sup>. Exact mass, negative ion ESI [M<sup>–</sup> – H] calcd for C<sub>7</sub>H<sub>10</sub>NO<sub>3</sub>FSCl 242.0054; found 242.0051. **10** *cis/trans*: *cis* and *trans* refers to the two methyl groups on the cyclohexane ring; isolated (48%) by column chromatography as described above. <sup>1</sup>H NMR 600 MHz (C<sub>6</sub>D<sub>6</sub>)  $\delta$  [*cis* 1.15 (dd,  $J$  = 7.0 and 1.8 Hz) and *trans* 1.26 (d,  $J$  = 7.0 Hz, 3H)]; [*trans* 1.30 (d,  $J$  = 2.9 Hz) and *cis* 1.33 (d,  $J$  = 2.9 Hz, 3H)]; *cis* and *trans* 1.43–1.62 (m, 2H); *cis* and *trans* 1.62–1.73 (m, 2H); *cis* and *trans* 1.80–1.96 (m, 2H); [*cis* 2.26 (m) and *trans* 2.78 (m), 1H]. <sup>19</sup>F NMR 376 MHz (CDCl<sub>3</sub>) *trans*  $\delta$  –135.3 (s); *cis* –138.6 (brd. s), ratio of 1.0/1.1, respectively on the crude reaction mixture. <sup>13</sup>C NMR 150.8 MHz (C<sub>6</sub>H<sub>6</sub>) assignments supported by DEPT and HSQC experiments. **10** *cis*  $\delta$  15.2 (CH<sub>3</sub>, d,  $J$  = 8.4 Hz); 16.1 (CH<sub>3</sub>, d,  $J$  = 7.9 Hz); 16.0 (CH<sub>2</sub>, s); 26.0 (CH<sub>2</sub>, d,  $J$  = 4.5 Hz); 28.7 (CH<sub>2</sub>, s); 31.5 (CH, d,  $J$  = 24.7 Hz); 59.9 (C adj. to the carbonyl, d,  $J$  = 20.2 Hz); 108.7 (d,  $J$  = 256.4 Hz); 166.3 (d,  $J$  = 2.8 Hz). **10** *trans*:  $\delta$  14.4 (CH<sub>3</sub>, d,  $J$  = 9.0 Hz); 14.7 (CH<sub>3</sub>, d,  $J$  = 2.8 Hz); 17.1 (CH<sub>2</sub>, s); 25.6 (CH<sub>2</sub>, d,  $J$  = 7.3 Hz); 28.8 (CH<sub>2</sub>, s); 32.4 (CH, d,  $J$  = 24.1 Hz); 61.8 (C adj. to the carbonyl, d,  $J$  = 18.0 Hz); 111.2 (d,  $J$  = 256.4 Hz); 166.7 (d,  $J$  = 2.8 Hz).

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IR (KBr) neat mixture  $1834\text{ cm}^{-1}$ . Exact mass, negative ion ESI  $[M^+ - H]$  calcd for  $C_9H_{12}NO_3FSCl$  268.0210; found 268.0212.

CSI (1.10 mmol) was added to fluoroalkenes **5** or **6** (1.00 mmol) in 0.2–4 mL of methylene chloride at  $0\text{ }^\circ\text{C}$ . The mixture was allowed to warm to room temperature and then stirred for 4 h. Workup was accomplished as described above. Product **11** was obtained 90% pure (NMR) by preparative TLC, and product **12** was isolated pure by recrystallization from ether. Crystals from **12** decomposed in several minutes at room temperature but were sufficiently stable in solution to obtain spectral data. Wet crystals of **12** were kept cold during transportation for X-ray analysis at low temperature. The following data were obtained. **11**: decomposition produced 8% side products during purification by preparative thin layer chromatography on silica gel with chloroform/methanol (95:5); isolated in 33% yield.  $^1\text{H}$  NMR 400 MHz ( $\text{CDCl}_3$ )  $\delta$  0.89 (t,  $J = 7.0$  Hz, 3H); 1.29 (m, 10H); 1.38–1.62 (m, 2H); 2.06–2.26 (m, 1H); 2.44–2.56 (m, 1H); 3.33–3.48 (m, 2H).  $^{19}\text{F}$  NMR 376 MHz ( $\text{CDCl}_3$ )  $\delta$  -120.9 (m). The 8% impurity around -131 to -132 ppm is from decomposition during purification by TLC.  $^{13}\text{C}$  NMR 100.6 MHz ( $\text{CDCl}_3$ )  $\delta$  14.0 (s); 22.5 (s); 23.5 (s); 23.7 (s); 29.0 (s); 29.1 (d,  $J = 14.0$  Hz); 31.7 (s); 48.9 (d,  $J = 25.1$  Hz); 76.8 (d,  $J = 4.8$  Hz); 105.7 (d,  $J = 246.1$  Hz); 158.6 (d,  $J = 3.0$  Hz). IR (KBr) neat  $1831\text{ cm}^{-1}$ . Exact mass, negative ion ESI  $[M^+ - H]$  calcd for  $C_{11}H_{18}NO_3FSCl$  298.0680; found 298.0716. **12**: yield (65%) by  $^{19}\text{F}$  NMR with 4-fluoroanisole as internal standard.  $^1\text{H}$  NMR 400 MHz ( $\text{CDCl}_3$ )  $\delta$  3.62–3.85 (m, 2H); 7.51 (m, 3H); 7.61 (m, 2H).  $^{19}\text{F}$  NMR 376 MHz ( $\text{CDCl}_3$ )  $\delta$  -129.0 (t,  $J = 10.5$  Hz).  $^{13}\text{C}$  NMR 100.6 MHz ( $\text{CDCl}_3$ )  $\delta$  53.4 (d,  $J = 25$  Hz); 103.7 (d,  $J = 246$  Hz); 125.2 (d,  $J = 8$  Hz); 129.2 (s); 130.9 (s); 132.0 (d,  $J = 29$  Hz); 158.9 (d,  $J = 2$  Hz). IR (KBr) neat  $1834\text{ cm}^{-1}$ .

Quantum chemical calculations were performed using second order perturbation theory (MP2, also known as MBPT(2)<sup>13a–c</sup>) and the 6-311G(d,p) basis set.<sup>14</sup> All structures were fully optimized using a quasi-Newton–Raphson approach based upon the quadratic approximation, also known as the trust radius image minimization (TRIM) method.<sup>18</sup> Harmonic

vibrational frequencies were computed to verify each stationary point as either a local minimum (with all real frequencies) or a transition state (with exactly one imaginary vibrational frequency). Free energies were obtained using the computed vibrational frequencies (which were scaled by 0.9748)<sup>19</sup> and the ideal gas + rigid rotor + harmonic oscillator models.<sup>20</sup> Following an approach similar to that of López et al.,<sup>5b</sup> electrostatic free energies of salvation were obtained using the conductor polarization continuum model (C-PCM),<sup>21a–c</sup> with methylene dichloride as the solvent, via single point energy calculations at the MP2/6-311G(d,p) stationary points. Intrinsic reaction coordinate (IRC) calculations<sup>22a–c</sup> using the Gonzalez–Schlegel second order method<sup>23</sup> were performed to trace the minimum energy reaction paths connecting each transition state to reactants and products. All calculations were performed using the GAMESS quantum chemistry code.<sup>24a,b</sup>

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**Supporting Information Available:** Spectral data to characterize the products, X-ray data for **12** in CIF format, and quantum chemical data are in the Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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