Facile Synthesis of Quaternary α-Fluoronitriles by Cobalt-Catalyzed Hydrocyanation of Monofluoroalkenes

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Abstract An exclusively regioselective hydrocyanation of monofluoroalkenes has been developed, with which a series of aliphatic quaternary α-fluoronitriles were synthesized in a facile and efficient manner. This novel method is featured with mild conditions, good functional groups compatibilities, and high reactivity.

Key words quaternary α-fluoronitriles, hydrocyanation, monofluoroalkenes, cobalt catalysis, radical

The fluorine atom has a tiny atomic radius and the strongest electronegativity of the periodic table of elements.1 These natural characters make the introduction of fluorine into organic structure dramatically change its properties, such as metabolic stability, lipophilicity, bioavailability, and binding affinity.2 Meanwhile, nitriles have been extensively used as one of the most versatile intermediates in organic synthesis, enabling diverse chemical transformations. As one of the alternative precursors of β-fluoroamines, which serves as the key moieties in bioactive and pharmaceutical compounds,3 the efficient synthesis of α-fluoronitriles have inspired wide attentions of organofluorine chemists. Despite the importance of α-fluoronitriles, there are only few synthetic methods reported so far, especially for the quaternary α-fluoronitriles. The common method to afford quaternary α-fluoronitriles is direct fluorination by the construction of C-F bonds, via either dehydroxylate fluorination of cyanoaldronitriles4 (Scheme 1, Path I) or electrophilic fluorination of in situ generated carbanion5 (Scheme 1, Path II). However, the instability of cyanoaldrons for the dehydroxylate fluorination and the requirement of electron-drawing group (EWG) adjacent to the cyano group for the electrophilic fluorination definitely hampered their utility for synthetic applications. Thus, an alternative method has been developed by C–C bond formation via nucleophilic addition of tertiary α-fluoronitrile carbanion to electrophiles6 (Scheme 1, Path III–IV), in which the reaction types and substrate scope was correspondingly limited. Indeed, the diverse construction of quaternary α-fluoronitriles, especially bearing no other activating group on the quaternary carbon center, remains still an unsolved issue to be addressed.

As we are very much inspired by the exploration for facile synthetic methods for the various monofluorinated compounds with new molecular platforms, the construction of quaternary α-fluoronitrile has accordingly aroused our research interests.7 Considering that alkenes served normally as one kind of simple and basal materials for further transformation to diverse complex molecules, we envisioned that monofluoroalkenes may play as a potential molecular platform to construct various monofluorine-containing compounds.8 As is known, the metal-hydride hydrogen atom transfer (MHAT) process is used as a strong strategy for the hydrofunctionalization of alkenes by an in situ generation of hydrogenated carbon radical or metal species, followed by various radical captures or metal-catalyzed functionalizations.9 Accordingly, we speculated that a...
CoIII–H-promoted radical hydrocyanation of monofluoroalkenes would pave a new approach for effective construction of quaternary \( \alpha \)-fluoronitriles, by a strategical cleavage of C–CN bonds. Herein, we describe an exclusively regioselective hydrocyanation of monofluoroalkenes, with which a series of aliphatic quaternary \( \alpha \)-fluoronitriles were synthesized in a facile and efficient manner. This novel method is featured with mild conditions, well functional groups compatibilities, and high reactivity.

At the beginning, our study commenced with methyl 2-(2-fluoroallyl)isoindoline-1,3-dione (1) as the initial substrate, tosyl cyanide (0.15 mmol, 1.5 equiv) as the cyano source, and PhSiH3 as the hydride source in the presence of a catalytic amount of CoIISal\( \text{t-Bu, t-Bu} \), 10 mol%) in EtOH. To our delight, the desired quaternary \( \alpha \)-fluoronitrile 2 was obtained smoothly in 47% yield when 0.3 equivalent of \( \text{t-BuOOf} \) was added to the reaction as oxidant to generate the active catalyst (Table 1, entry 1). Considering this metal-hydride hydrogen atom transfer (MHAT) process was initiated only by CoIII–H species, different kinds of oxidants were examined under such reaction conditions at first (entries 2–6). The resulting data show that a number of added oxidants, including \( \text{t-BuOOf}, \text{PhCO}_2\text{O} \), Selectfluor, NFSI, and BIOH, could start this radical reaction and provide the desired product 2 in tolerable yields, but \( \text{t-BuOOf} \) favored the hydrocyanation of monofluoroalkene with a slightly higher yield (entry 2). In order to adjust the rate of Co–H species generation to match the rate of radical capture, various Si–H reagents, including, activated HSi(OEt)3, HSiMe(OEt)2, and PMHS or non-activated PhSiMeH and Ph2SiH2 were carefully investigated in this cobalt catalytic system (entries 7–11). The results revealed that the non-activated Si–H reagents adapted this reaction conditions better, and PhSiH3 still gave the best yield of aliphatic qua-

### Table 1  Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Si–H</th>
<th>Oxidant</th>
<th>Solvent (mL)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhSiH3</td>
<td>t-BuOOf-Bu</td>
<td>EtOH</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>PhSiH3</td>
<td>PhCO2Or-Bu</td>
<td>EtOH</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>PhSiH3</td>
<td>Selectfluor</td>
<td>EtOH</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>PhSiH3</td>
<td>NFSI</td>
<td>EtOH</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>PhSiH3</td>
<td>BIOH</td>
<td>EtOH</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>PhSi(OEt)2</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>PhSiMe(OEt)2</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>PMHS</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>PhSiMeH2</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>acetone (0.9)/EtOH (0.1)</td>
<td>34</td>
</tr>
<tr>
<td>13</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>DCE (0.9)/EtOH (0.1)</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>DME (0.9)/EtOH (0.1)</td>
<td>38</td>
</tr>
<tr>
<td>15</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>MeCN (0.9)/EtOH (0.1)</td>
<td>15</td>
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<tr>
<td>16</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>34</td>
</tr>
<tr>
<td>17</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>PhSiH3</td>
<td>t-BuOOf</td>
<td>EtOH</td>
<td>84 (82)</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1 (0.1 mmol, 1.0 equiv), TsCN (1.5 equiv), CoIISal\( \text{t-Bu, t-Bu} \) (10 mol%), Si–H (1.0 equiv), oxidant (0.3 equiv), solvent (1 mL), r.t., 12 h. Yields were determined by \( ^{19} \text{F NMR spectroscopy using PhCF}_3 \) as an internal standard; numbers in parentheses were yields of isolated products. PMHS = Poly(methylhydroxiloxane).

*b TsCN (3.0 equiv) was used.

*c PhSiH3 (1.5 equiv) was used.

*d PhSiH3 (2.5 equiv) was used.
ternary α-fluoronitrile 2. Meanwhile, the optimization of solvents indicated mixed solvents were unhelpful for this reaction (entries 12–15), and only DCM (0.9 mL)/EtOH (0.1 mL) gave a similar yield as in entry 2. While increasing the loading of TsCN to 0.3 mmol slightly decreased the yield (entry 16), to our satisfaction, the enhancement of the equivalent of both Ts–CN (0.3 mmol) and PhSiH₃ (0.15 mmol) could clearly improve the yield of target product to 60% (entry 17). This result indicated that the loading of Si–H reagent should be closely related to Ts–CN and was crucial for the transformation. Finally, further increment of the loading of PhSiH₃ to 2.5 equivalents furnished the aliphatic quaternary α-fluoronitriles 2 in 82% isolated yield (entry 18).

With the optimized reaction conditions in hand, we next explored the compatibilities with various monofluoroalkenes in this cobalt catalytic system (Scheme 2). As expected, the monofluoroalkenes with a longer carbon chain could adapt this radical reaction well affording 4, which indicated that a directing group was not necessary for this transformation. Furthermore, the monofluoroalkenes installed with benzamide group were also compatible with the optimized conditions, affording the desired products 2 and 5 in acceptable to good yields. Meanwhile, the benzoate-derived monofluoroalkenes were also suitable substrates for this transformation (6–15, 18). Notably, diverse monofluoroalkenes containing different phenyl rings which were equipped with various functional groups, such as methyl (7), isopropyl (8), methoxy (9), phenyl (10), ester (12), cyano (13), and trifluoromethyl (11, 14), could all provide the corresponding products in moderate to good yields. To our interests, the substrates installed with ortho-functional groups on the phenyl rings, no matter methoxy (15) or bromo (18), could also furnish the desired quaternary α-fluoronitrile smoothly, albeit in slightly decreased yields. Inspired by these interesting results, this novel transformation has also been explored for late-stage modification of complex bioactive molecules. Accordingly, several monofluoroalkenes containing diversified pharmaceutical structures have been synthesized and subjected into the

Scheme 2  Scope of monofluoroalkenes. Reagents and conditions: monofluoroalkene (0.1 mmol, 1.0 equiv), TsCN (3.0 equiv), CoIISalt-t-Bu,t-Bu (10 mol%), PhSiH₃ (2.5 equiv), t-BuOOH (0.3 equiv), EtOH (1 mL), r.t., 12 h. Isolated yields are shown. * Reactions run with 0.5 mmol of 1.
hydrocyanation conditions. To our excitement, such monofluoroalkenes derived from diverse drugs, such as isoxepac (16), flurbiprofen (17), gemfibrozil (19), and loxoprofen (20), all were compatible well with this transformation in acceptable yields.

In order to confirm the hydride source of this hydrocyanation reaction, PhSiD_3 has been used as hydride source to subject to the standard conditions by replacement of PhSiH_3, affording the corresponding product 2-D in 62% yield with 99% deuterium incorporation (Scheme 3). This result clearly indicated that the hydrogen atom for hydrocyanation comes from the Si–H species via a MHAT process.

Based on previous reports and the above deuterium experiment result, a possible mechanism is proposed as shown in Scheme 4. Initially, the Co^II_ species is oxidized to the active Co^III_ species, which generates the Co^III–H species by interaction with PhSiH_3. Subsequently, the insertion of monofluoroalkene into the Co^III–H bond affords alkylated cobalt species A. The following homolytic cleavage of C–Co^III_ bond provides carbon radical B, followed by a radical capture by TsCN to furnish the final product 2 and produces Ts radical. Finally, the Ts' (or t-BuOOH) oxidizes Co^III_ species to Co^II_ species and completes the catalytic cycle.

In summary, we have reported an exclusively regioselective hydrocyanation of monofluoroalkenes. This method paves a novel way to construct a series of aliphatic quaternary α-fluoronitriles, and featured with mild conditions, good functional groups compatibilities, and high reactivity. Further explorations for regio- and stereoselective construction of monofluorine-containing quaternary carbon center are underway in our laboratory.

Chemical shifts were reported in ppm from the solvent resonance as the internal standard (CDCl_3, δ = 7.26, δ = 77.16. Standard abbreviations were used to indicate multiplicities. Coupling constants were reported in hertz (Hz). High-resolution mass spectra were recorded on P-SIMS-Gly of Bruker Daltonics Inc. using ESI-TOF (electrospray ionization-time of flight). The monofluoroalkenes were synthesized according to following methods. Anhydrous solvents and commercially available reagents were purchased and used without further purification. Flash column chromatography was carried out using silica gel (200–300 mesh) with the indicated solvent system. All reactions were conducted in oven-dried Schlenk tubes.

2-(2-Fluoroallyl)isoindoline-1,3-dione (1); Typical Procedure 1 (TP 1)
The starting material 2-fluoroprop-2-en-1-ol was synthesized according to a reported procedure from methyl 2-fluorocrylate (3.2 g, 50 mmol). After removing the solvent carefully, the crude 2-fluoroprop-2-en-1-ol was dissolved in THF (0.5 M). At 0 °C, to the solution was added NaH (60% in mineral oil, 1 equiv) slowly and the mixture was stirred for 5 min. Then TsCl (1.1 equiv) in THF was added dropwise and the reaction was stirred overnight. H_2O (100 mL) and EtOAc (100 mL) were added to the reaction mixture, then the aqueous phase was extracted with EtOAc (3 × 100 mL) and the organic layers were combined, washed with brine, and dried (Na_2SO_4). The organic layer was concentrated for flash column chromatography on silica gel with an eluent of PE and EtOAc (10:1 to obtain the crude 2-fluoroprop-2-ethyl tosylate. Next, phthalimide (7.36 g, 50 mmol) was dissolved in THF and the solution was cooled to 0 °C. After stirring for 5 min, the tosylate from the last step was added to the reaction mixture and allowed to stay overnight at r.t. After quenching with H_2O (100 mL), EtOAc (100 mL) was added to the mixture, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine, and dried (Na_2SO_4). The mixture was concentrated for column chromatography on silica gel with an eluent of PE and ETOAc to obtain the final product 1; total yield: 3.6 g (35%). Similarly, 5a was prepared from N-phenylbenzamide and 2-fluoroprop-2-en-1-ol.

2-Fluoroallyl Benzoate (6a); Typical Procedure 2 (TP 2)
The starting material 2-fluoroprop-2-en-1-ol was synthesized according to a reported procedure from methyl 2-fluorocrylate (5.2 g, 50 mmol), and then the crude 2-fluoroprop-2-en-1-ol was stirred with PhCOCI (7.03 g, 50 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 M) at 0 °C. NEt_3 (10.1 g, 50 mmol, 2.0 equiv) was added to the reaction mixture and the mixture was stirred overnight. After total consumption of the starting material, the mixture was concentrated under vacuum. The residue was then purified by flash column chromatography (PE:EtOAc 10:1) to give the target product 6a; yield: 6.5 g (72%).

Vinyl fluorides 7a–20a were prepared from suitable starting materials based on the above typical procedure 2.

2-(2-Fluoroallyl)-1,3,5-trimethylbenzene (3a)
2,4,6-Trimethylphenylmagnesium bromide (1 M in THF, 2.23 g, 10 mmol, 1 equiv) was stirred at r.t. Anhyd THF (30 mL) and 2-fluoroallyl 4-methylbenzenesulfonate (2.3 g, 10 mmol, 1 equiv) were added sequentially to the reaction mixture. The mixture was stirred at 60 °C for 4 h. Afterwards, the mixture was quenched withaq 1 M HCl. The organic phase was washed withaq 1 M HCl, and the aqueous phase was extracted with ETOAc (3 × 50 mL). The organic layers were com-
2-(2-Fluoroallyl)isoindoline-1,3-dione (1)

Purified by silica gel chromatography (PE) to give the target product 3a; yield: 540 mg (30%).

2-(2-Fluoroallyl)-1,3,5-trimethylbenzene (3a)

HRMS (ESI): m/z [M + Na+] calcd for C_{13}H_{16}FO_3Na+: 217.0635; found: 217.0652.

2-Fluoroallyl 4-Methoxybenzoate (9a)

HRMS (ESI): m/z [M + H+] calcd for C_{11}H_{11}FO_2: 223.1129; found: 223.1137.

2-Fluoroallyl 4-Isopropylbenzoate (8a)

HRMS (ESI): m/z [M + Na+] calcd for C_{11}H_{11}FO_2Na+: 217.0635; found: 217.0652.

N-(2-Fluoroallyl)-N-phenylbenzamide (5a)

HRMS (ESI): m/z [M + H+] calcd for C_{17}H_{19}FNO: 239.1078; found: 239.1083.

2-Fluoroallyl Benzoate (6a)


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**2-Fluoroallyl 4-(Trifluoromethyl)benzoate (11a)**

Purified by silica gel chromatography (PE/EtOAc 30:1); colorless oil.

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.19 (d, J = 8.1 \text{ Hz}, 2 \text{ H}), 7.73 (d, J = 8.2 \text{ Hz}, 2 \text{ H}), 4.90 (dd, J = 15.7, 3.3 \text{ Hz}, 1 \text{ H}), 4.88 (dd, J = 14.6, 2.3 \text{ Hz}, 2 \text{ H}), 4.74 (dd, J = 47.0, 3.3 \text{ Hz}, 1 \text{ H})\).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)): \(\delta = 148.11, 160.05 (d, J = 258.3 \text{ Hz}), 134.99 (q, J = 32.9 \text{ Hz}), 132.86, 130.34, 126.67 (q, J = 37.8 \text{ Hz}), 123.7 (q, J = 273.4 \text{ Hz}, 95.17 (d, J = 17.2 \text{ Hz}, 62.38 (d, J = 33.8 \text{ Hz})\).

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_{12}\)H\(_7\)F\(_7\)O\(_2\): 239.0716; found: 239.0714.

**19F NMR (376 MHz, CDCl\(_3\)):** \(\delta = –63.21, –105.40 (dq, J = 47.5, 14.9 \text{ Hz})\).

**Purified by silica gel chromatography (PE/EtOAc 30:1); colorless oil.**

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**2-Fluoroallyl 2-Methoxybenzoate (15a)**

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_8\)H\(_7\)F\(_1\)O\(_2\): 249.0533; found: 249.0514.

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**2-Fluoroallyl Methyl Terephthalate (12a)**

Purified by silica gel chromatography (PE/EtOAc 20:1); colorless oil.

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 8.15–8.07 (m, 4 \text{ H}), 4.89 (dd, J = 15.7, 3.3 \text{ Hz}, 1 \text{ H}), 4.86 (d, J = 14.5 \text{ Hz}, 2 \text{ H}), 4.73 (dd, J = 47.1, 3.3 \text{ Hz}, 1 \text{ H}), 3.95 (s, 3 \text{ H})\).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)): \(\delta = 166.33, 165.20, 160.10 (d, J = 258.2 \text{ Hz}), 134.41, 133.34, 129.90, 129.77, 95.11 (d, J = 17.2 \text{ Hz}, 62.27 (d, J = 33.8 \text{ Hz}), 52.63\).

**19F NMR (376 MHz, CDCl\(_3\)):** \(\delta = –107.67 \text{ to} –113.92 (m)\).

**Purified by silica gel chromatography (PE/EtOAc 10:1); colorless oil.**

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**2-Fluoroallyl 4-Cyanobenzoate (13a)**

Purified by silica gel chromatography (PE/EtOAc 30:1); colorless oil.

\(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.22–7.14 (m, 2 \text{ H}), 4.81 (dd, J = 15.9, 3.3 \text{ Hz}, 1 \text{ H}), 4.73–4.44 (m, 3 \text{ H}), 3.95 (s, 3 \text{ H}), 2.37 (s, 3 \text{ H})\).

\(^1^C\) NMR (126 MHz, CDCl\(_3\)): \(\delta = 173.30, 160.11 (d, J = 258.0 \text{ Hz}), 159.78 (d, J = 248.4 \text{ Hz}), 141.34 (d, J = 7.5 \text{ Hz}), 135.50, 130.96 (d, J = 3.8 \text{ Hz}), 129.03 (d, J = 2.7 \text{ Hz}), 128.55, 128.08 (d, J = 13.6 \text{ Hz}, 2 \text{ H}), 127.80, 123.67 (d, J = 3.4 Hz), 115.37 (d, J = 23.8 \text{ Hz}), 94.44 (d, J = 16.9 \text{ Hz}), 61.70 (J = 13.4 \text{ Hz}), 44.90, 18.40\).

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_{18}\)H\(_{17}\)F\(_2\)O\(_2\): 327.1040; found: 327.1040.

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**2-Fluoroallyl 3,5-Bis(trifluoromethyl)benzoate (14a)**

Purified by silica gel chromatography (PE/EtOAc 5:1); colorless oil.

**HRMS (EI):** \([M + H]^+\) calcd for C\(_{11}\)H\(_9\)F\(_7\)O\(_2\): 211.0771; found: 211.0765.

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**2-Fluoroallyl 2-(11-Oxo-6,11-dihydrodibenzo-[A–J]oxepin-2-yl)acetate (16a)**

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_{11}\)H\(_9\)F\(_4\)O\(_2\): 257.8705; found: 257.8702.

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**2-Fluoroallyl 5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoate (17a)**

Purified by silica gel chromatography (PE/EtOAc 10:1); colorless oil.

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_{18}\)H\(_{20}\)O\(_3\): 303.1191; found: 303.1205.

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**2-Fluoroallyl 2-(2-Fluoro-[1,1′-biphenyl]-4-yl)propanoate (17a)**

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_{18}\)H\(_{17}\)F\(_2\)O\(_2\): 327.1027; found: 327.1040.

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**2-Fluoroallyl 2-Bromobenzoate (18a)**

**HRMS (ESI):** \([M + H]^+\) calcd for C\(_{10}\)H\(_9\)BrO\(_2\): 211.0771; found: 211.0765.
1H NMR (500 MHz, CDCl3): δ = 7.20 (d, J = 8.1 Hz, 2 H), 7.10 (d, J = 8.1 Hz, 2 H), 4.70 (dd, J = 16.1, 3.3 Hz, 1 H), 4.61–4.36 (m, 3 H), 3.73 (q, J = 7.2 Hz, 1H), 3.10 (dd, J = 13.9, 4.1 Hz, 1 H), 2.49 (dd, J = 13.9, 9.5 Hz, 1 H), 2.37–2.27 (m, 2 H), 2.13–2.00 (m, 2 H), 1.97–1.87 (m, 1 H), 1.70 (dddt, J = 12.6, 10.6, 8.4, 6.4 Hz, 1 H), 1.59–1.40 (m, 1 H), 1.48 (d, J = 7.2 Hz, 3 H).

13C NMR (126 MHz, CDCl3): 128.70, 116.36 (d, J = 166.9 Hz), 55.68 (d, J = 220.3 Hz), 44.13 (d, J = 262.6 Hz), 23.93 (d, J = 24.0 Hz).


2-Fluoro-3-mesityl-2-methylpropanenitrile (3)
Prepared by following GP using I (90 mg, 0.5 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 30:1); colorless oil; yield: 74.5 mg (72%).

1H NMR (400 MHz, CDCl3): δ = 7.33–7.21 (m, 5 H), 7.20–7.10 (m, 5 H), 4.66–4.30 (m, 2 H), 1.86 (d, J = 21.5 Hz, 3 H).

13C NMR (101 MHz, CDCl3): 129.51, 128.83, 127.98, 127.55, 117.12 (d, J = 34.2 Hz), 88.65 (d, J = 183.7 Hz), 55.68 (d, J = 23.8 Hz), 29.84, 24.07 (d, J = 24.3 Hz).

19F NMR (376 MHz, CDCl3): δ = –134.16 (m). HRMS (ESI): m/z [M + H+] calcd for C18H16FNO3: 266.1187; found: 266.1195.

N-(2-Cyano-2-fluoropropyl)-N-phenylbenzamide (5)
Prepared by following GP using 5a (25.5 mg, 0.1 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 10:1); colorless oil; yield: 30.8 mg (46%).

1H NMR (400 MHz, CDCl3): δ = 7.35–7.26 (m, 5 H), 7.22–7.12 (m, 5 H), 4.66–4.30 (m, 2 H), 1.76 (d, J = 24.1 Hz, 3 H).

13C NMR (126 MHz, CDCl3): 128.86, 128.34, 128.44, 127.58, 117.12 (d, J = 34.2 Hz), 88.65 (d, J = 183.7 Hz), 55.68 (d, J = 23.8 Hz), 29.84, 24.07 (d, J = 24.3 Hz).

19F NMR (376 MHz, CDCl3): δ = –134.16 (d, J = 43.4 Hz, 21.6 Hz). HRMS (ESI): m/z [M + H+] calcd for C18H16FNO3: 283.1241; found: 283.1254.

2-Cyano-2-fluoropropyl Benzoate (6)
Prepared by following GP using 6a (90 mg, 0.5 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 30:1); colorless oil; yield: 74.5 mg (72%).

1H NMR (400 MHz, CDCl3): δ = 8.25–7.81 (m, 2 H), 7.55 (tt, J = 7.0, 1.3 Hz, 1 H), 7.47–7.34 (m, 2 H), 4.73–4.29 (m, 2 H), 1.79 (d, J = 20.9 Hz, 3 H).

13C NMR (126 MHz, CDCl3): δ = 165.42, 133.95, 130.06, 128.76, 128.70, 116.36 (d, J = 34.4 Hz), 86.31 (d, J = 184.7 Hz), 66.62 (d, J = 25.7 Hz), 22.59 (d, J = 24.0 Hz).


2-Cyano-2-fluoropropyl 4-Methylbenzoate (7)
Prepared by following GP using 7a (97 mg, 0.5 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 30:1); colorless oil; yield: 86.2 mg (78%).

1H NMR (500 MHz, CDCl3): δ = 7.98 (d, J = 8.1 Hz, 2 H), 7.27 (d, J = 8.1 Hz, 2 H), 4.88–4.28 (m, 2 H), 2.43 (s, 3 H), 1.86 (d, J = 20.9 Hz, 3 H).
2-Cyano-2-fluoropropyl 4-Isopropylbenzoate (8)
Prepared by following GP using 8a (111 mg, 0.5 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 30:1); colorless oil; yield: 71.1 mg (60%).


1H NMR (500 MHz, CDCl3): δ = 165.49, 144.85, 130.11, 129.81, 129.48, 116.42 (d, J = 34.5 Hz), 86.36 (d, J = 184.5 Hz), 66.47 (d, J = 25.9 Hz), 22.60 (d, J = 24.2 Hz), 21.89.

19F NMR (376 MHz, CDCl3): δ = −152.39 (pd, J = 21.0, 15.0 Hz).

13C NMR (126 MHz, CDCl3): δ = 164.28, 135.38 (q, J = 32.8 Hz), 131.93, 130.50, 125.84 (q, J = 3.7 Hz), 123.59 (q, J = 273.0 Hz), 116.18 (d, J = 34.4 Hz), 86.21 (d, J = 185.4 Hz), 67.05 (d, J = 25.5 Hz), 22.52 (d, J = 23.9 Hz).

2-Cyano-2-fluoropropyl Methyl Terephthalate (12)
Prepared by following GP using 12a (119 mg, 0.5 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 20:1); colorless oil; yield: 79.5 mg (60%).


1H NMR (500 MHz, CDCl3): δ = 8.28–7.99 (m, 4 H), 4.80–4.37 (m, 2 H), 3.96 (s, 3 H), 1.88 (d, J = 20.9 Hz, 3 H).

19F NMR (471 MHz, CDCl3): δ = −152.35 (pd, J = 20.9, 14.6 Hz).

13C NMR (101 MHz, CDCl3): δ = 166.18, 164.66, 134.82, 132.40, 130.04, 129.88, 116.23 (d, J = 34.5 Hz), 86.22 (d, J = 185.0 Hz), 66.95 (d, J = 25.5 Hz), 52.68, 22.66 (d, J = 24.0 Hz).

2-Cyano-2-fluoropropyl 3,5-Bis(trifluoromethyl)benzoate (14)
Prepared by following GP using 14a (158 mg, 0.5 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 30:1); colorless oil; yield: 68.8 mg (50%).


1H NMR (500 MHz, CDCl3): δ = 8.22–8.09 (m, 2 H), 7.72–7.67 (m, 2 H), 7.65–7.59 (m, 2 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.42 (t, J = 7.3, 6.4, 3.2 Hz, 1 H), 4.75–4.49 (m, 2 H), 1.88 (d, J = 20.9 Hz, 3 H).

19F NMR (471 MHz, CDCl3): δ = −152.39 (pd, J = 21.1, 14.3 Hz).

2-Cyano-2-fluoropropyl 2-(11-Oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl)acetate (16)

Prepared by following GP using 16a (32.6 mg, 0.1 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 1:1); colorless oil; yield: 14.5 mg (41%).

1H NMR (400 MHz, CDCl3): δ = 8.13 (d, J = 2.3 Hz, 1 H), 7.88 (d, J = 7.6 Hz, 1 H), 7.56 (td, J = 7.4, 1.1 Hz, 1 H), 7.50–7.41 (m, 2 H), 7.37 (d, J = 7.2 Hz, 3 H), 1.61 (d, J = 8.4 Hz, 1 H), 5.19 (s, 2 H), 4.63–4.15 (m, 2 H), 3.76 (s, 2 H), 1.76 (d, J = 20.9 Hz, 3 H).

13C NMR (126 MHz, CDCl3): δ = 190.90, 170.35, 160.81, 140.51, 136.40, 135.60, 132.97, 132.70, 129.61, 129.43, 129.77, 126.79, 125.31, 121.42, 116.19 (d, J = 34.2 Hz), 86.09 (d, J = 184.8 Hz), 73.76, 66.49 (d, J = 25.7 Hz), 39.78, 22.46 (d, J = 23.9 Hz).

19F NMR (376 MHz, CDCl3): δ = −152.60 (pd, J = 21.3, 15.3 Hz).


2-Cyano-2-fluoropropyl 2-(2-Fluoro-[1,1-oxepin-2-yl)acetate (17)

Prepared by following GP using 17a (30.2 mg, 0.1 mmol) as substrate. Purification by flash column chromatography (silica gel, PE:EtOAc 1:1); colorless oil; yield: 12.9 mg (39%); dr = 1:1.6.

1H NMR (500 MHz, CDCl3): δ = 7.23 (d, J = 7.8 Hz, 2 H), 7.13 (d, J = 7.8 Hz, 2 H), 4.32 (dd, J = 26.4, 20.2, 13.8 Hz, 2 H), 3.80 (q, J = 7.1 Hz, 1 H), 3.12 (dd, J = 13.9, 3.9 Hz, 1 H), 2.51 (dd, J = 13.8, 9.6 Hz, 1 H), 2.33 (dd, J = 17.3, 7.5 Hz, 2 H), 2.13–2.04 (m, 2 H), 2.02–1.89 (m, 1 H), 1.78–1.70 (m, 1 H), 1.66 (d, J = 21.3 Hz, 3 H), 1.54 (d, J = 7.1 Hz, 3 H), 1.57–1.49 (m, 1 H).

13C NMR (101 MHz, CDCl3): δ = 142.00, 139.45, 137.39, 129.41, 127.74, 116.20 (d, J = 32.4 Hz), 86.16 (dd, J = 184.8, 9.1 Hz), 66.15 (dd, J = 26.2, 2.3 Hz), 51.08, 44.96, 38.32, 35.31, 29.28, 22.37 (dd, J = 24.0, 15.7 Hz), 20.68, 18.22 (dd, J = 8.6, 2.3 Hz).

19F NMR (376 MHz, CDCl3): δ = −147.81 to −162.94 (m).


Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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