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# Michael Addition Reaction of Fluorinated Nitro Compounds†

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The Michael addition reactions of fluorinated nitro compounds with electron deficient olefins to give γ-fluoro-γ-nitro-esters, nitriles and ketones which bear a fluorinated quaternary carbon center were reported. The reactions were promoted by TMG, affording the desired adducts in acceptable to good yields.

**Keywords** Michael addition reaction, fluorinated nitro compounds, fluorinated quaternary carbon center

## Introduction

The Michael addition reaction has become one of the most popular carbon-carbon bond forming reactions ever since its discovery. Because of the broad spectrum of potential donors and acceptors, this reaction is exceptionally versatile and a wide range of synthetically useful adducts bearing various functional groups can be generated.[1] As nucleophilic donors, nitroalkanes have already drawn enormous attention[2] because of the easy manipulation of the nitro functionality into amines (reduction), hydrides (radical denitration), aldehydes, ketones (Nef reaction), and other valuable building blocks.[3]

It is well-known that, due to the unique nature of the fluorine, the introduction of fluorine into an organic molecule can profoundly change the properties of the molecule in many aspects, including lipophilicity, bioavailability and metabolic stability.[4-14] Especially, the organofluorine derivatives always have different bioactivity compared with the non-fluorine containing compounds. As a result, organofluorine compounds have found their application in pharmaceuticals. According to incomplete statistics, 20% of pharmaceuticals and 30%—40% of agrochemicals on market and 30% of the leading 30 blockbuster drugs on sale contain at least one fluorine atom.[15,16]

More specifically, many medicines or biologically active compounds contain a fluorinated quaternary carbon center, such as Fludrocortisone, Advair Diskus (3.6 $\times 10^9$ $ US sales in 2008, top 4), BMS-204352 and Flurithromycin (Figure 1).[14] Recently, incorporation of a fluorine atom to α-position of carbonyl compounds has aroused much attention and plenty of synthetic methodologies for fluorinated ketones have been developed.[17-19] However, research on the construction of fluorinated nitro quaternary carbon center is still rare. Generally speaking, there are two common strategies for the introduction of the fluorine atom: (a) direct fluorination of organic compounds with kinds of electrophilic or nucleophilic fluorinating reagents and (b) the use of easily available simple fluorine-containing building blocks. We have synthesized fluoronitroalkanes as useful building blocks for Henry reactions.[20] Meanwhile

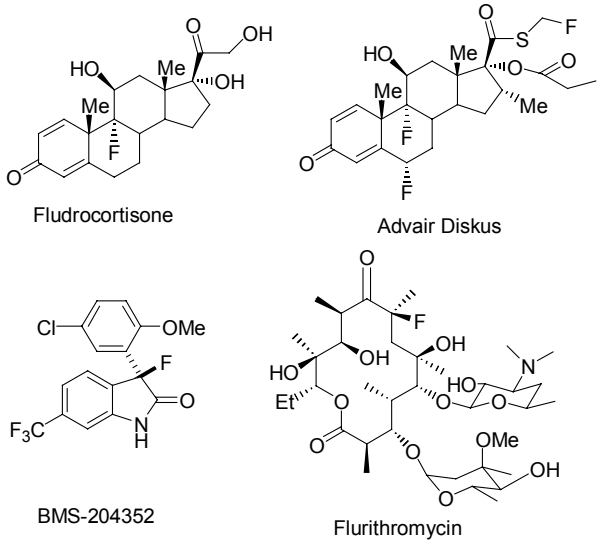


**Figure 1** Examples of medicines and biologically active compounds containing a fluorinated quaternary carbon center.

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† Dedicated to Professor Weiyuan Huang on the occasion of his 90th birthday.

  

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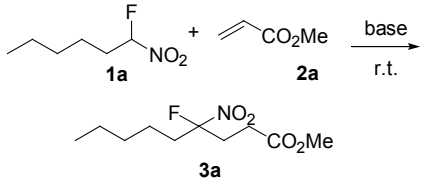
we envisioned fluoronitroalkane could also be a good donor in Michael addition reaction. Herein we wish to report our recent research of the Michael addition reaction of fluoronitroalkanes to give fluorine-containing quaternary carbon center adducts.

## Results and Discussion

We prepared five fluorinated nitro compounds **1a**—**1e** which we have used in Henry reaction.[20] In order to screen the appropriate base for the Michael addition reaction, the reaction of 1-fluoro-1-nitrohexane (**1a**) and methyl acrylate (**2a**) was chosen as the model reaction. Among the three bases screened, *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) was found to be the most effective catalyst while $Et_3N$ failed to promote the reaction, and in the reaction with 1,5-diazabicyclo[4.3.0]-non-5-ene (DBU) several fluorated compounds were detected by $^{19}F$ NMR along with the desired adduct (Table 1, Entries 1—3). We then studied the effect of the solvent (Table 1, Entries 4—7). Dipolar solvents, such as dichloromethane (DCM) and acetonitrile, turned out to give better results than the nonpolar solvent such as *p*-xylene. Decreasing the load of the base led to sharp decrease of the yield (Table 1, Entries 8, 9). The influence of the concentration of the reactant was also studied (Table 1, Entries 10, 11). Best results were given in 0.4 mol/L, while an increase or decrease in concentration both led to apparently drop in yield.

**Table 1** Optimization of reaction conditions[a]




| Entry | Base | Solvent | Time/h | Yield[b]/% |
|---|---|---|---|---|
| 1 | $Et_3N$ | Ethyl acetate | 40 | NR |
| 2 | DBU | Ethyl acetate | 40 | 15 |
| 3 | TMG | Ethyl acetate | 40 | 71 |
| 4 | TMG | DCM | 24 | 89 |
| 5 | TMG | THF | 24 | 68 |
| 6 | TMG | *p*-Xylene | 24 | 65 |
| 7 | TMG | Acetonitrile | 24 | 85 |
| 8[c] | TMG | DCM | 24 | 30 |
| 9[d] | TMG | DCM | 24 | 53 |
| 10[e] | TMG | DCM | 24 | 52 |
| 11[f] | TMG | DCM | 24 | 59 |

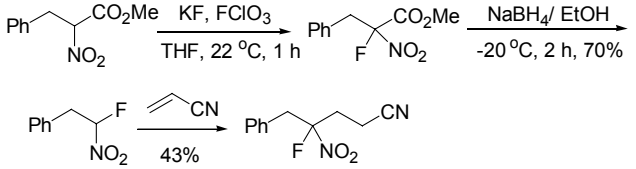
[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **1a**, 0.2 mmol of **2a**, and 0.1 mmol of base in 0.5 mL solvent. [b] Yield based on $^{19}F$ NMR. [c] 0.02 mmol TMG. [d] 0.04 mmol TMG. [e] 0.2 mL DCM. [f] 1 mL DCM. DCM＝dichloromethane, THF＝tetrahydrofuran, DBU＝1,5-diazabicyclo[4.3.0]-non-5-ene, TMG＝*N*,*N*,*N*′,*N*′-tetramethylguanidine.

Afterwards, all of the five nitro compounds **1a**—**1e** obtained previously were used to react with methyl acrylate in the presence of TMG in DCM (Table 2, Entries 1—5). It was found that 1-fluoro-1-nitrohexane (**1a**) was the most active and gave the corresponding Michael adduct in 85% isolated yield (Table 2, Entry 1). Low yields (46%) of Michael addition products were obtained when nitro compounds **1d** and **1e** were used (Table 2, Entries 4, 5). The reactions with acrylonitrile gave similar results. Linear chain aliphatic 1-fluoro-1-nitrohexane (**1a**) gave a better yield (72%) than others (45%—62%) (Table 2, Entries 6—10).

Two selected fluorinated nitro compounds (**1a** and **1c**) were used to react with methyl vinyl ketone (MVK), to give the Michael adducts smoothly (Table 2, Entries 11, 12). In order to study the steric effect of the Michael acceptor, we also performed the reaction of **1c** with (*E*)-4-phenylbut-3-en-2-one. The reaction showed to be ineffective which can hardly get the adduct, indicating that it is quite sensitive to the substituent group on the $\beta$ position of the electron deficient olefin.

The synthesis of 4-fluoro-4-nitro-5-phenylpentanenitrile (**3g**) was previously reported by Takeuchi and coworkers.[21] In their study, the fluorinated nitro substance [fluoro(nitro)methyl]benzene was obtained by electrophilic fluorination reaction and sequent decarboxylation of ethyl $\alpha$-nitro carboxylic ester. 4-Fluoro-4-nitro-5-phenylpentanenitrile (**3g**) was obtained by Michael addition reaction in a similar way (Scheme 1). We found that the fluorinated nitro compounds can be synthesized from the nitro compounds with only one electron withdrawn group, thus avoiding tedious decarboxylation steps.

**Scheme 1** The procedure designed by Takeuchi




## Conclusions

In summary, a series of novel $\alpha$-fluoronitroalkanes were prepared and applied to the Michael addition reaction with methyl acrylate, acrylonitrile and MVK. The Michael adducts with a fluorine-containing quaternary center were obtained in acceptable to good yields. This method provides a practical method for the preparation of biologically useful fluorinated derivatives.

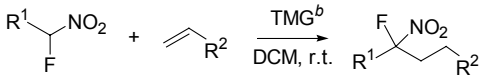
## Experimental

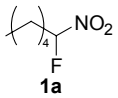
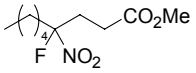
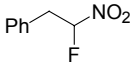
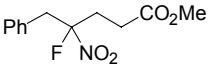
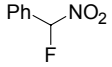
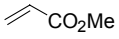
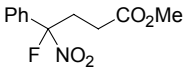
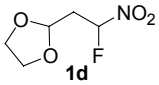
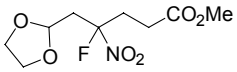
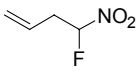
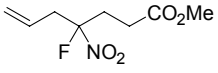
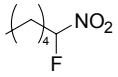
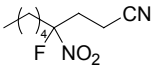
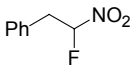
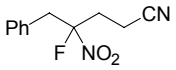
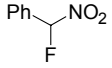
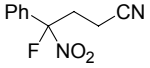
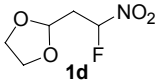
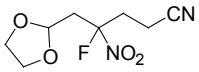
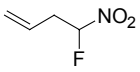
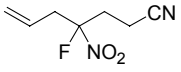
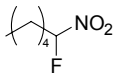
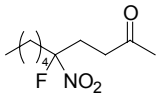
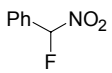
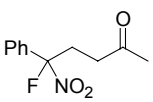
### General information for the Michael addition reaction

All reagents were used as received from commercial

**Table 2** Michael addition of fluorinated nitro compounds[a]




| Entry | Fluorinated nitro compound | Electron deficient olefin | Product | Time/h | Yield[c]/% |
|---|---|---|---|---|---|
| 1 |  **1a** | |  **3a** | 19 | 85 |
| 2 |  **1b** | |  **3b** | 22 | 81 |
| 3 |  **1c** |  **2a** |  **3c** | 23 | 70 |
| 4 |  **1d** | |  **3d** | 23 | 46 |
| 5 |  **1e** | |  **3e** | 23 | 46 |
| 6 |  **1a** | |  **3f** | 20 | 72 |
| 7 |  **1b** | |  **3g** | 26 | 61 |
| 8 |  **1c** |  **2b** |  **3h** | 24 | 62 |
| 9 |  **1d** | |  **3i** | 24 | 48 |
| 10 |  **1e** | |  **3j** | 27 | 45 |
| 11 |  **1a** |  **2c** |  **3k** | 24 | 70 |
| 12 |  **1c** | |  **3i** | 24 | 49 |

[a] Conditions: fluorinated nitro compounds (1.0 equiv.), electron deficient olefin (1.0 equiv.) and TMG (0.5 equiv.) stirred at room temperature in DCM. [b] TMG＝*N*,*N*,*N*′,*N*′-tetramethylguanidine. [c] Isolated yield.

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sources, unless specified otherwise, or prepared as described in the literature. $^1$H NMR spectra were recorded on a Bruker AM 300 (300 MHz) spectrometer with TMS as an internal standard (negative for upfield). $^{19}$F NMR spectra were recorded on a Bruker AM 300 (282 MHz) with $CFCl_3$ as an external standard (negative for upfield). $^{13}$C NMR spectra were recorded on a Bruker AV-400 (100 MHz) spectrometer with $CDCl_3$ as an internal standard (negative for upfield). MS and HRMS were recorded on a Hewlett-Packard HP-5989A spectrometer and a Finnigan MAT-8483 mass spectrometer. Infrared spectra were measured with a Perkin-Elmer 983 spectrometer. Column chromatography was performed using silica gel (mesh 300—400). All solvents were purified by standard methods.

**General procedure and spectra data**

To a solution of methyl acrylate (0.45 g, 3.0 mmol) in DCM (6 mL) were added *α*-fluoronitro compounds (3.0 mmol) and TMG (0.173 g, 1.5 mmol). The reaction mixture was stirred at room temperature for the time as given in Table 1 and then the solvent was removed under vacuum. 1 mol•L$^{-1}$ hydrochloric acid (3 mL) was added to neutralize the base. The mixture was extracted with $CH_2Cl_2$ (3 mL×3). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, $V$∶$V$=97∶3) to yield the desired addition product.

Methyl 4-fluoro-4-nitrononanoate (**3a**): colorless oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 3.70 (s, 3H), 2.50—2.27 (m, 6H), 1.32—1.27 (m, 6H), 0.90 (t, $J$=6.9 Hz, 3H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −129.8 (m); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 171.6, 121.4 (d, $J$=240.0 Hz), 51.9, 36.9 (d, $J$=21.9 Hz), 32.0 (d, $J$=21.9 Hz), 30.9, 27.0 (d, $J$=2.9 Hz), 22.1, 21.7 (d, $J$=3.3 Hz), 13.7; IR (neat) $v$: 2958, 2874, 1744, 1566, 1439, 1320, 1204, 841 cm$^{-1}$; HRMS (ESI) calcd for $C_{10}H_{18}FNO_4$ [M+Na]$^+$ 258.1112, found 258.1113.

Methyl 4-fluoro-4-nitro-5-phenylpentanoate (**3b**): white solid; m.p. 56—58 ℃; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.35—7.30 (m, 3H), 7.22—7.17 (m, 2H), 3.68 (s, 3H), 3.53—3.38 (m, 2H), 2.80—2.40 (m, 3H), 2.39—2.20 (m, 1H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −128.8 (m); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 171.6, 130.9, 130.2, 128.8, 128.3, 120.7 (d, $J$=243.0 Hz), 52.1, 43.2 (d, $J$=21.0 Hz), 31.6 (d, $J$=21.0 Hz), 27.0 (d, $J$=4.1 Hz); IR (KBr) $v$: 2955, 1732, 1564, 1440, 1206 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{14}FNO_4$ [M+Na]$^+$ 278.0799, found 278.0799.

Methyl 4-fluoro-4-nitro-4-phenylbutanoate (**3c**): colorless oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.68—7.65 (m, 2H), 7.49—7.47 (m, 3H), 3.70 (s, 3H), 3.18—2.87 (m, 2H), 2.56—2.35 (m, 2H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −128.6 (dd, $J$=23.7, 18.3 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 171.6, 132.8 (d, $J$=23.0 Hz), 131.1 (d, $J$=1.2 Hz), 129.0 (d, $J$=1.6 Hz), 125.2 (d, $J$=8.7 Hz), 119.1 (d, $J$=239.0 Hz), 52.1, 32.4 (d, $J$=21.0 Hz), 27.5 (d, $J$=3.3 Hz); IR (neat) $v$: 3002, 2955, 1747, 1570, 1453, 1353, 1201, 1075, 694 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{12}FNO_4$ [M+Na]$^+$ 264.0643, found 264.0646.

Methyl 5-(1,3-dioxolan-2-yl)-4-fluoro-4-nitropentanoate (**3d**): yellow solid; m.p. 45—47 ℃; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 5.10 (t, $J$=5.1 Hz, 1H), 3.97—3.85 (m, 4H), 3.70 (s, 3H), 2.58—2.51 (m, 5H), 2.30—2.28 (m, 1H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −128.8 (m); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 171.6, 118.6 (d, $J$=238.0 Hz), 99.0 (d, $J$=4.9 Hz), 65.0 (d, $J$=6.6 Hz), 52.1, 41.0 (d, $J$=19.8 Hz), 32.4 (d, $J$=21.0 Hz), 26.9 (d, $J$=4.2 Hz); IR (KBr) $v$: 2958, 2903, 1731, 1573, 1441, 1339, 1213, 1144, 986 cm$^{-1}$; HRMS (ESI) calcd for $C_9H_{14}FNO_6$ [M+Na]$^+$ 274.0697, found 274.0698.

Methyl 4-fluoro-4-nitrohept-6-enoate (**3e**): colorless oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 5.78—5.64 (m, 1H), 5.29 (d, $J$=5.4 Hz, 1H), 5.25 (d, $J$=12.9 Hz, 1H), 3.70 (s, 3H), 3.03—2.79 (m, 2H), 2.73—2.45 (m, 3H), 2.36—2.23 (m, 1H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −130.0 (m); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 171.6, 127.4 (d, $J$=3.7 Hz), 122.5, 120.5 (d, $J$=241.0 Hz), 52.1, 41.4 (d, $J$=21.5 Hz), 31.5 (d, $J$=21.5 Hz), 26.9 (d, $J$=4.1 Hz); IR (neat) $v$: 3088, 2957, 1743, 1567, 1440, 1204, 940, 841 cm$^{-1}$; HRMS (ESI) calcd for $C_8H_{12}FNO_4$ [M+Na]$^+$ 228.0643, found 228.0645.

4-Fluoro-4-nitrononanenitrile (**3f**): colorless oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 2.74—2.08 (m, 6H), 1.50—1.58 (m, 1H), 1.33—1.25 (m, 5H), 0.89 (t, $J$=6.9 Hz, 3H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −130.0 (m); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 120.2 (d, $J$=241.0 Hz), 117.2, 36.8 (d, $J$=21.0 Hz), 32.6 (d, $J$=22.3 Hz), 30.8, 22.1, 21.7 (d, $J$=2.9 Hz), 13.7, 11.2 (d, $J$=15.3 Hz); IR (neat) $v$: 2960, 2873, 2254, 1568, 1440, 1356, 1139, 840 cm$^{-1}$; HRMS (ESI) calcd for $C_9H_{15}FN_2O_2$ [M+Na]$^+$ 225.1010, found 225.1011.

4-Fluoro-4-nitro-5-phenylpentanenitrile (**3g**): yellow oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.37—7.34 (m, 3H), 7.23—7.17 (m, 2H), 3.53—3.36 (m, 2H), 2.80—2.66 (m, 1H), 2.51—2.28 (m, 3H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −129.7 (m).

4-Fluoro-4-nitro-4-phenylbutanenitrile (**3h**): colorless oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.64 (d, $J$=7.8 Hz, 2H), 7.52—7.47 (m, 3H), 3.22—2.89 (m, 2H), 2.58—2.38 (m, 2H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −130.7 (dd, $J$=21.7, 19.7 Hz); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 131.6 (d, $J$=23.0 Hz), 131.7 (d, $J$=1.3 Hz), 129.3 (d, $J$=1.6 Hz), 125.0 (d, $J$=9.1 Hz), 118.0 (d, $J$=240.0 Hz), 117.2, 33.1 (d, $J$=21.5 Hz), 11.7(d, $J$=4.6 Hz); IR $v$: 3067, 2970, 2907, 2254, 1573, 1498, 1453, 1159, 762.651 cm$^{-1}$; HRMS (ESI) calcd for $C_{10}H_9FN_2O_2$ [M+Na]$^+$ 231.0540, found 231.0541.

5-(1,3-Dioxolan-2-yl)-4-fluoro-4-nitropentanenitrile (**3i**): colorless oil; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 5.10 (q, $J$=4.5 Hz, 1H), 4.03—3.85 (m, 4H), 2.77—2.50 (m, 5H), 2.41—2.31 (m, 1H); $^{19}$F NMR ($CDCl_3$, 282 MHz) $\delta$: −127.7 (m); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 116.6 (d, $J$=253.3 Hz), 116.2, 97.8 (d, $J$=5.3 Hz), 64.1, 64.0,

  

39.6 (d, $J$=19.8 Hz), 31.7 (d, $J$=21.9 Hz), 10.1 (d, $J$=5.8 Hz); IR (neat) $\nu$: 2970, 2254, 1738, 1566, 1365, 1217, 843, 528 $cm^{-1}$; HRMS (ESI) calcd for $C_8H_{11}FNO_4$ $[M+Na]^+$ 241.0595, found 241.0596.

4-Fluoro-4-nitrohept-6-enenitrile (**3j**): colorless oil; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 5.74—5.63 (m, 1H), 5.34 (d, $J$=9.9 Hz, 1H), 5.29 (d, $J$=17.1 Hz, 1H), 3.00—2.88 (m, 2H), 2.77—2.47 (m, 3H), 2.45—2.33 (m, 1H); $^{19}F$ NMR ($CDCl_3$, 282 MHz) $\delta$: −129.5 (m); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$: 126.4 (d, $J$=11.0 Hz), 123.3, 119.3 (d, $J$=246.0 Hz), 117.1, 41.2 (d, $J$=21.0 Hz), 31.0 (d, $J$=21.4 Hz), 11.1 (d, $J$=5.8 Hz); IR (neat) $\nu$: 3088, 2987, 2926, 2254, 1644, 1574, 1439, 1358, 1177, 940, 837 $cm^{-1}$; HRMS (ESI) calcd for $C_7H_9FN_2O_2$ $[M+Na]^+$ 195.0540, found 195.0543.

5-Fluoro-5-nitrodecan-2-one (**3k**): colorless oil; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 2.69—2.59 (m, 1H), 2.55—2.22 (m, 5H), 2.16 (s, 3H), 2.12—1.95 (m, 1H), 1.58—1.42 (m, 1H), 1.13—1.38 (m, 5H), 0.88 (t, $J$=6.6 Hz, 3H); $^{19}F$ NMR ($CDCl_3$, 282 MHz) $\delta$: −129.1 (m); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$: 205.1 (d, $J$=1.3 Hz), 121.7 (d, $J$=240.2 Hz), 37.0 (d, $J$=21.9 Hz), 35.8 (d, $J$=2.9 Hz), 30.8, 30.6 (d, $J$=21.9 Hz), 29.7, 22.1, 21.7 (d, $J$=2.9 Hz), 13.6; IR (neat) $\nu$: 2960, 2935, 2873, 1723, 1564, 1468, 1435, 1360, 1170, 843 $cm^{-1}$; HRMS (ESI) calcd for $C_{10}H_{18}FNO_3$ $[M+Na]^+$ 242.1163, found 242.1159.

4-Fluoro-4-nitro-4-phenylbutan-2-one (**3l**): yellow oil; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$: 7.67—7.64 (m, 2H), 7.48—7.45 (m, 3H), 3.11—2.80 (m, 2H), 2.69—2.46 (m, 2H), 2.17 (s, 3H); $^{19}F$ NMR ($CDCl_3$, 282 MHz) $\delta$: −127.5 (dd, $J$=25.7, 17.5 Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$: 205.1, 133.1 (d, $J$=23.1 Hz), 131.1 (d, $J$=1.2 Hz), 128.9 (d, $J$=1.2 Hz), 125.2 (d, $J$=8.7 Hz), 119.5 (d, $J$=238.5 Hz), 36.4 (d, $J$=2.0 Hz), 31.0 (d, $J$=21.1 Hz), 29.9; IR (neat) $\nu$: 2948, 2911, 1722, 1567, 1452, 1357, 1168, 1001, 715 $cm^{-1}$; HRMS (ESI) calcd for $C_{11}H_{12}FNO_3$ $[M+Na]^+$ 248.0693, found 248.0691.

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