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Metal-Catalyzed Benzylic Fluorination as a Synthetic Equivalent to 1,4-Conjugate Addition of Fluoride

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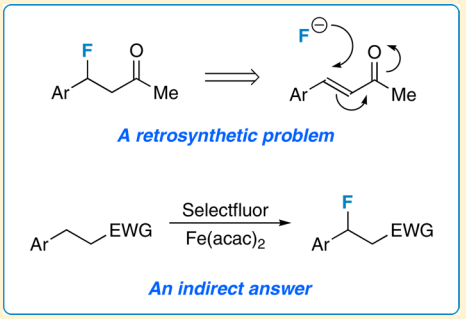
Supporting Information

ABSTRACT: We explore in detail the iron-catalyzed benzylic fluorination of substrates containing aromatic rings and electron-withdrawing groups positioned β to one another, thus providing direct access to β-fluorinated adducts. This operationally convenient process can be thought of not only as a contribution to the timely problem of benzylic fluorination but also as a functional equivalent to a conjugate addition of fluoride, furnishing products in moderate to good yields and in excellent selectivity.



Over the past decade the demand for fluorine-enriched compounds has risen dramatically. Consequently, a host of fluorination strategies has evolved to aid the modern chemist in their syntheses.[1] Despite a large repertoire of practical fluorination methods, the 1,4-addition of fluoride to α,β-unsaturated carbonyl-containing compounds represents a long-standing problem. Of medicinal interest, hydrogen atoms β to a carbonyl are often labile and susceptible to enzymatic decomposition (e.g., in fatty acid catabolism).[2] Accordingly, the replacement of a single hydrogen atom by fluorine has been shown to increase the chemical integrity of the parent molecule, improving its lifetime *in vivo*.[3] It therefore stands to reason that a practical β-fluorination may prove to be a valuable transformation. Unfortunately, previous efforts exploring the use of cuprates (copper fluorides) have yet to afford a notable success, resulting in trace yields or limited selectivity.[4] Perhaps this is no surprise; computationally, employing hybrid-DFT theory, the addition of dimethylcuprate is predicted to be *much* more thermodynamically favorable than the addition of CuF_2^- (Figure 1). We envisioned an *indirect* approach in the absence of the alkene to circumvent this issue.[5,6] Recently, our lab published an iron(II)-catalyzed system for the chemoselective benzylic fluorination of several alkylbenzenes using Selectfluor as a fluorinating agent.[7] Our paper was among the first to provide a more general solution to what is proving to be a very timely problem.[8] In this note, we explore in detail the iron-catalyzed benzylic fluorination of substrates containing aromatic rings and electron-withdrawing groups beta (β) to one another to yield β-fluorinated products (Figure 2). This process can be thought of as a functional solution to the long-standing problem of mild conjugate addition of fluoride, affording products in good to moderate yields and in excellent selectivity. We surmised that this system could also be used as a surrogate to harsh, traditional methods involving nucleophilic-conjugate addition with hydrohalic acids,[9,10] providing a direct, convenient route for site-specific β-fluorination. Remarkably, under our conditions α-fluorinated byproducts were not observed despite the well-documented background reaction between Selectfluor and various ketones.[11] Also, several functional groups known for intolerance to Selectfluor persisted through the reaction conditions very well. Finally, it should be noted that the reaction is operationally simple and reliable.

We began our studies by examining several well-known, saturated variants of "Michael acceptors" under catalytic conditions. To our satisfaction, a host of β-fluorinated products were obtained in good yields and in outstanding selectivity (Table 1). Some noteworthy observations include (1) α-substituted carbonyls demonstrated a preference for *syn* addition of fluorine; (2) nitriles, aldehydes, and free acids were tolerated under our reaction conditions despite a perceived high propensity for deleterious side reactions with Selectfluor and various metal catalysts;[12] (3) for substrates possessing multiple benzylic positions **3**, **5**, **9**, and **12**, fluorination of the *least* substituted carbon is preferred; (4) difluorination and (5) α-fluorination are negligible. In addition, 1,3-aryl sulfones, ketones, and oxazolidinones were successfully β-fluorinated, the latter a being potentially useful auxiliary for developing an asymmetric variant of our reaction. An important note is that the use of other iron(II) and iron(III) salts or the corresponding $Fe(acac)_3$ failed to yield any appreciable quantities of fluorinated product.

Moreover, β-fluorinations of several pharmaceutically efficacious scaffolds including cyclamen (**3**), the 3-phenylpropylester (**9**), chalcone (**10**), and the indane (**11**) were achieved. Among these structures, indane (**11**) proved a particularly interesting case. By crude ^{19}F NMR, both *trans* and *cis* diastereomers are

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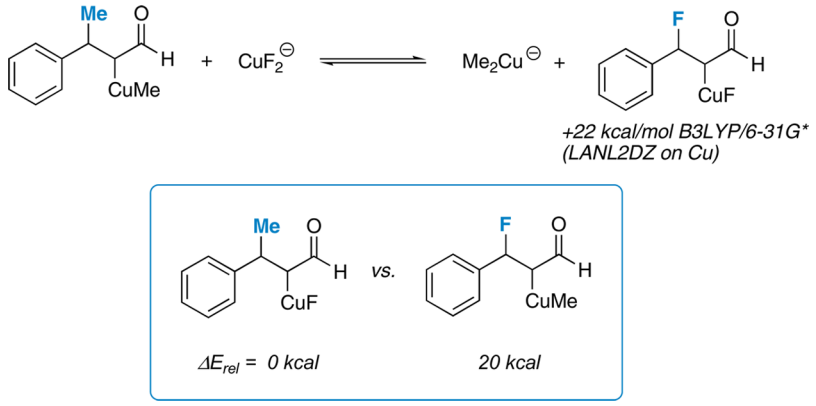


Figure 1. Computational analysis of cuprates in fluoride conjugate addition.

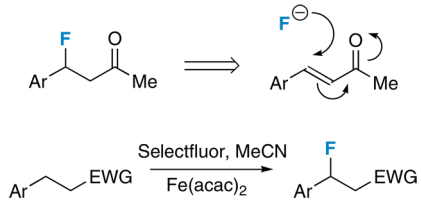
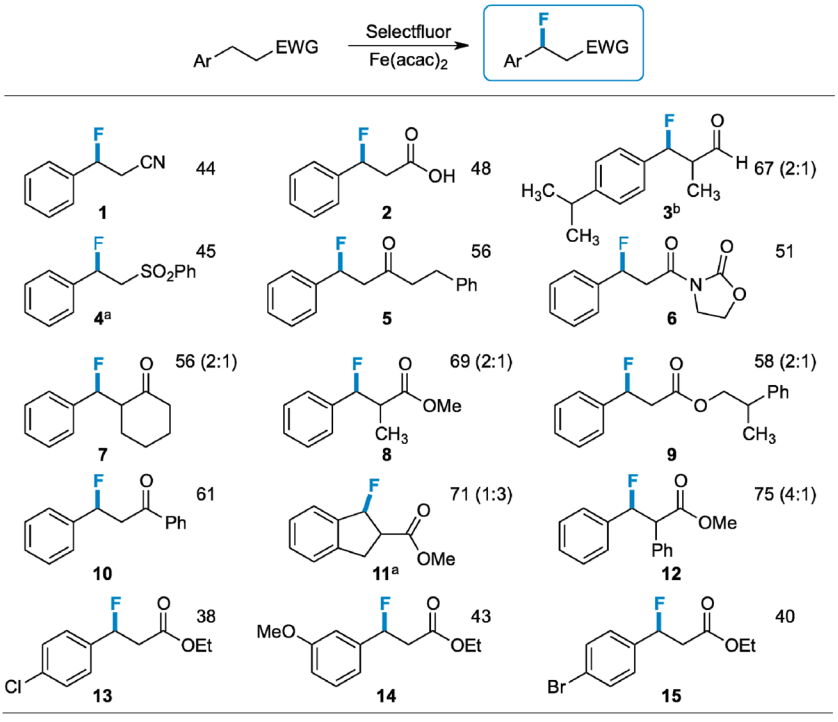


Figure 2. A synthetic equivalent to fluoride conjugate addition.

produced in a 3:1 ratio. However, upon purification by silica gel chromatography, only the *cis* diastereomer can be isolated (31%). In the case of the *anti* diastereomer, a rapid dehydrofluorination occurs to give the unsaturated indene as characterized by ^{1}H NMR. The instability of the *trans* isomer relative to *cis* is rationalized given the ease of *syn*-elimination based on precedent in related systems (see Figure 3).[13] Degradation of the *cis*-diastereomer may be likewise expected, albeit at a much slower rate.

Although applicable to a wide survey of functional groups, yields trended for highly electron-withdrawing "Michael acceptors" in the general order COOMe > COOH > SO_2Ph > CN > NO_2 (trace amounts). This correlates nicely with relative σ substituent values, advocating an increased reactivity of more oxidizable, electron-rich benzylic hydrogens toward fluorination, an unsurprising finding assuming the possible involvement of free radicals during the reaction.[14,15] To elucidate the potential for radicals in our reaction, we envisioned the use of the strained cycloalkane norcarane **16** as a radical clock. Although not a benzylic substrate per se, the cyclopropane ring is similarly activating. Homolytic cleavage of a C3 C−H bond should lead to product **17** following a rapid opening of the cyclopropyl ring and trapping with fluorine (Figure 4).[16] In a similar fashion, α,β-unsaturated aryl ester **18**

Table 1. Survey of Conjugate Addition Products



[a]Yield determined by ^{19}F NMR using 3-chlorobenzotrifluoride as an internal standard. [b]Isolated as the major benzylic product with minor flourinated isomers. All reactions were run at room temperature for 24 h unless otherwise stated. Diastereoselectivity is reported as (*syn*:*anti*).

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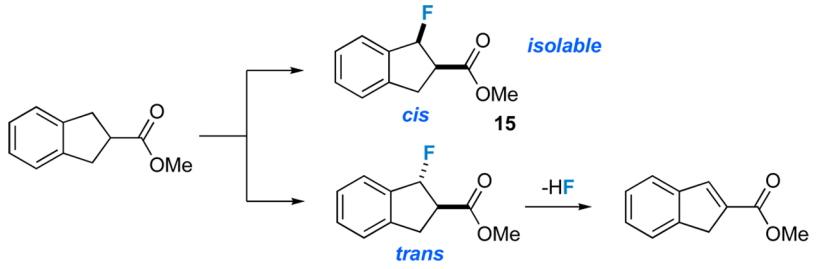

Figure 3. Dehydrofluorination of the *trans*-diastereomer.

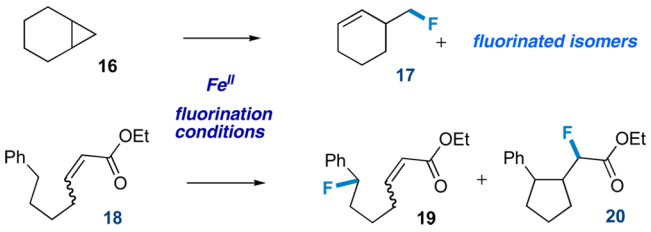

Figure 4. Preliminary evidence for the involvement of radicals during fluorination.

should be a propitious substrate to probe the generation of benzylic radicals. It is expected that formation of the corresponding benzyl radical could lead to the standard fluorinated product **19** and/or to the more diagnostic product **20** through a cyclization reaction. In both cases, these putative radical-derived products were observed by ^{19}F NMR analysis of our reaction mixtures and identified by comparison to known literature values.[17,18] In the case of **16**, it should be noted that the primary fluoride **17** is still the predominant product. Whereas the formation of **17** is incompatible with an anionic mechanism, the formation of cyclized product **20** is incompatible with a cationic mechanism.

In conclusion, a convenient, mild route for the direct preparation of β-fluorinated, 3-phenyl propanoids has been presented. This protocol is operationally reliable and highly chemoselective and has been shown to tolerate a diverse array of functional groups. What is more, we demonstrate the ability of our reaction to act as a surrogate in the 1,4-conjugate addition of fluoride, thus providing an alternative to corrosive hydrofluoric acid protocols.

EXPERIMENTAL SECTION

General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and benzylic compounds were dried and distilled by standard methods. ^1H spectra were acquired on a 400 MHz NMR in $CDCl_3$; ^{13}C and ^{19}F spectra were taken on a 300 MHz NMR in $CDCl_3$. The ^1H, ^{13}C, and ^{19}F chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard and/or 3-chlorobenzotrifluoride (δ −64.2 ppm relative to $CFCl_3$).[19] NMR data are reported in the following format: chemical shift (multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constants [Hz]). IR data were obtained using an FT-IR and standard NaCl cell. High resolution mass spectra (HRMS) were recorded using ESI-TOF (electrospray ionization-time-of-flight) mass spectrometry. All measurements were recorded at 25 °C unless otherwise stated. Characterization of 3-fluoro-3-phenylpropanenitrile (**1**),[20] methyl-3-fluoro-2-methyl-3-phenylpropanoate (**8**),[21] and 3-fluoro-1,3-diphenylpropan-1-one (**10**)[7] were consistent with the literature precedents. Compounds **4** and **11** are reported as crude spectra due to product decomposition. Spectral data was processed with ACD/NMR Processor Academic Edition.[22]

General Procedure for the Syntheses of β-Fluorinated Products. An oven-dried, 10-mL, round-bottom flask equipped with a stir bar was placed under an atmosphere of N_2. Selectfluor (195.0 mg, 0.55 mmol, 2.2 equiv) and $Fe(acac)_2$ (6.0 mg, 0.025 mmol, 0.1 equiv) were added followed by MeCN (3.0 mL). 3-Phenylpropiononitrile (32.8 mg, 0.25 mmol, 1 equiv) was then added, and the mixture allowed to stir overnight. The product was extracted into CH_2Cl_2 and washed with water. The organics were dried with $MgSO_4$ and filtered through Celite. The solvents were removed by rotary evaporation, and the residue was subjected to column chromatography on silica with a mixture of ethyl acetate/hexanes as eluent to afford 3-fluoro-3-phenylpropanenitrile as a clear oil (16.4 mg, 44%).

Computational Methods. The Gaussian 09[23] package and Spartan '10 were used for all calculations. Chemical shifts of the products were computed using Gaussian at the B3LYP/6-311++G** level.[24] Geometry optimizations of organocopper complexes were determined at the B3LYP/6-31G* (LANL2DZ on Cu) level.

Compound Characterization. 3-Fluoro-3-phenylpropanenitrile (1). Spectral and analytical data were in agreement with previous reports.[20] Yield: (16.4 mg, 44%).

3-Fluoro-3-phenylpropanoic Acid (2). Amorphous solid; ^1H NMR ($CDCl_3$) δ 7.46−7.40 (m, 5H), 5.95 (ddd, 1H, J = 46.7, 9.0, 4.0 Hz), 3.12 (ddd, 1H, J = 25.4, 16.4, 8.9 Hz), 2.89 (ddd, 1H, J = 32.4, 16.2, 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 177.5 (s), 138.4 (d, J = 19.0 Hz), 128.9 (s), 128.7 (s), 128.4 (d, J = 30.7 Hz), 126.4 (s), 125.6 (d, J = 5.9 Hz), 90.4 (d, J = 172.7 Hz), 30.2 (d, J = 90.0 Hz); ^{19}F NMR ($CDCl_3$) δ −172.4 (ddd, 1F, J = 45.4, 33.0, 13.4 Hz); IR (CH_2Cl_2) 3065, 1717 cm^{-1}; HRMS (ESI^+) calcd for $C_9H_9FO_2Na^+$ 191.0485, found 191.0491. Yield: (20.2 mg, 48%).

3-Fluoro-3-(4-isopropylphenyl)-2-methylpropanal (3). Clear oil; ^1H NMR ($CDCl_3$) δ 9.90 (dd, 1H, J = 2.2, 0.9 Hz), 9.76 (t, 1H, J = 1.2 Hz), 7.50−7.10 (m, 8H), 5.87 (dd, 1H, J = 46.7, 4.7 Hz), 5.57 (dd, 1H, J = 46.5, 8.3 Hz), 3.10−2.75 (m, 4H), 1.25 (d, 6H, J = 7.0 Hz), 1.25 (d, 6H, J = 8.3 Hz), 1.17 (dd, 3H, J = 7.2, 0.8 Hz), 0.96 (d, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 202.2 (d, J = 3.7 Hz), 201.8 (d, J = 4.4 Hz), 195.6 (s), 150.92 (s), 150.0 (s), 149.4 (s), 137.6 (s), 134.9 (d, J = 20.5 Hz), 134.4 (d, J = 20.5 Hz), 130.3 (s), 126.9 (s), 126.8 (s), 126.7 (s), 126.4 (s), 126.4 (s), 125.6 (s), 125.5 (s), 94.6 (d, J = 172.6 Hz), 92.6 (d, J = 176.4 Hz), 52.5 (d, J = 23.4 Hz), 52.0 (d, J = 23.4 Hz), 34.1 (s), 33.9 (d, J = 4.4 Hz), 23.9 (s), 23.8 (s), 13.3 (s), 11.0 (s), 10.4 (d, J = 6.6 Hz), 8.07 (d, J = 5.1 Hz; ^{19}F NMR ($CDCl_3$) δ −171.5 (dd, 1F, J = 47.4, 15.5 Hz), δ −186.9 (dd, 1F, J = 46.4, 24.7 Hz); IR (CH_2Cl_2) 1679 cm^{-1}; HRMS (ESI^+) calcd for $C_{13}H_{17}FONa^+$ 231.1161, found 231.1169. Yield: (34.9 mg, 67%).

(1-Fluoro-2-(phenylsulfonyl)ethyl)benzene (4). Amorphous solid; ^1H NMR ($CDCl_3$) δ 8.0−7.63 (m, 10H), 6.11 (ddd, 1H, J = 47.5, 9.4, 2.5 Hz), 3.83 (ddd, 1H, J = 22.8, 13.4, 1.7 Hz), 3.49 (ddd, 1H, J = 31.7, 15.3, 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 139.1 (s), 137.5 (s), 133.9 (s), 133.8 (s), 129.4 (s), 129.3 (s), 128.9 (s), 128.8 (s), 128.3 (s), 128.1 (s), 126.9 (s), 125.5 (d, J = 6.6 Hz), 88.5 (d, J = 177.1 Hz), 62.7 (d, J = 26.4 Hz); ^{19}F NMR ($CDCl_3$) δ −172.1 (ddd, 1F, J = 46.4, 32.0, 13.4 Hz); IR (CH_2Cl_2) 1087, 1151 cm^{-1}; HRMS (ESI^+) calcd for $C_{14}H_{13}FO_2SNa^+$ 287.0518, found 287.0512. Yield: (29.7 mg, 45%).

1-Fluoro-1,5-diphenylpentan-3-one (5). Amorphous solid; ^1H NMR ($CDCl_3$) δ 7.45−7.15 (m, 10H), 6.01 (ddd, 1H, J = 46.9, 8.9, 4.1 Hz), 3.2 (ddd, 1H, J = 14.7, 8.3, 2.5 Hz), 3.0−2.7 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 205.8 (s), 142.6 (s), 140.7 (s), 139.2 (s), 139.0 (s),

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128.9 (s), 128.7 (s), 128.6 (s), 128.5 (s), 128.3 (s), 126.2 (s), 125.5 (s), 125.4 (s), 90.1 (d, J = 165 Hz), 50.1 (d, J = 25.6 Hz), 42.2 (s), 29.4 (s); ^{19}F NMR ($CDCl_3$) δ −173.4 (ddd, 1F, J = 47.4, 32.0, 14.4 Hz); IR (CH_2Cl_2) 1715 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{17}H_{17}FONa^+$ 279.1161, found 279.1168. Yield: (35.9 mg, 56%).

3-(3-Fluoro-3-phenylpropanoyl)oxazolidin-2-one (6). Amorphous solid; ^{1}H NMR ($CDCl_3$) δ 7.47−7.35 (m, 5H), 6.05 (ddd, 2H, J = 47.1, 9.0, 3.4 Hz), 4.49−4.39 (m, 2H), 4.16−4.0 (m, 2H), 3.8 (ddd, 1H, J = 16.7, 9.2, 3.0 Hz), 3.36 (ddd, 1H, J = 32.8, 16.7, 3.4 Hz); ^{13}C NMR ($CDCl_3$) δ 169.3 (s), 153.5 (s), 138.7 (d, J = 19.8 Hz), 128.8 (d, J = 2.2 Hz), 128.6 (s), 128.5 (d, J = 8.0 Hz), 125.7 (d, J = 6.6 Hz), 90.0 (d, J = 172 Hz), 62.2 (s), 42.8 (d, J = 27.1 Hz), 42.5 (s); ^{19}F NMR ($CDCl_3$) δ −173.6 (ddd, 1F, J = 47.4, 33.0, 13.4 Hz); IR (CH_2Cl_2) 1706, 1783 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{12}H_{12}FNO_3Na^+$ 260.0699, found 260.0691. Yield: (30.2 mg, 51%).

2-(Fluoro(phenyl)methyl)cyclohexanone (7). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.56−7.25 (m, 10H), 6.09 (dd, 1H, J = 46.5, 4.1 Hz), 5.87 (dd, J = 45.2, 7.7 Hz), 3.26−1.52 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 209.9 (d, J = 2.9 Hz), 209.4 (d, J = 2.9 Hz), 139.2 (d, J = 20.5 Hz), 137.6 (d, J = 20.5 Hz), 130.3 (s), 128.6 (d, J = 2.9 Hz), 128.4 (s), 128.3 (s), 128.1 (s), 128.0 (d, J = 1.5 Hz), 126.6 (d, J = 7.3 Hz), 125.5 (d, J = 8.0 Hz), 92.3 (d, J = 174.2 Hz), 90.8 (d, J = 170.5 Hz), 56.3 (d, J = 5.1 Hz), 56.1 (d, J = 5.9 Hz), 42. Three (s), 29.9 (d, J = 5.1 Hz), 28.1 (s), 27.5 (s), 27.2 (s), 26.6 (d, J = 5.9 Hz), 24.5 (d, J = 2.2 Hz), 23.8 (s); ^{19}F NMR ($CDCl_3$) δ −96.9 (dd, J = 1492.9, 12.4 Hz), −95.2 (dd, J = 990.8, 12.4 Hz), −172.3 (dd, 1F, J = 45.4, 15.5 Hz), −191.6 (dd, 1F, J = 45.4, 21.7 Hz); IR (CH_2Cl_2) 1721 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{13}H_{15}FONa^+$ 229.1005, found 229.1009. Yield: (28.9 mg, 56%).

Methyl 3-Fluoro-2-methyl-3-phenylpropanoate (8). Spectral and analytical data were in agreement with previous reports.[21] Yield: (33.8 mg, 69%).

2-Phenylpropyl 3-Fluoro-3-phenylpropanoate (9). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.44−7.20 (m, 20H), 5.97−5.80 (m, 2H), 4.40−4.20 (m, 4H), 3.25−2.65 (m, 6H), 1.33 (d, 3H, J = 0.8 Hz), 1.31 (d, 3H, J = 0.8); ^{13}C NMR ($CDCl_3$) δ 169.5 (s), 142.9 (d, J = 2.2 Hz), 138.6 (d, J = 19.8 Hz), 128.8 (d, J = 2.2 Hz), 128.7 (s), 128.5 (d, J = 1.5 Hz), 127.3 (s), 126.8 (d, J = 1.5 Hz), 125.6 (dd, J = 6.6, 2.2 Hz), 90.6 (d, J = 171.3 Hz), 69.9 (d, J = 4.4 Hz), 42.4 (dd, J = 28.5, 2.9 Hz), 38.9 (s), 17.7 (s); ^{19}F NMR ($CDCl_3$) δ −172.2 (m, 1F); IR (CH_2Cl_2) 1738 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{13}H_{15}FONa^+$ 229.1005, found 229.1009. HRMS (ESI$^+$) calcd for $C_{18}H_{19}FO_2Na^+$ 309.1267, found 309.1272. Yield: (41.5 mg, 58%).

3-Fluoro-1,3-diphenylpropan-1-one (10). Spectral and analytical data were in agreement with previous reports.[7] Yield: (34.8 mg, 61%).

Methyl 1-Fluoro-2,3-dihydro-1*H*-indene-2-carboxylate (11). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.55−7.28 (m, 7H), 7.28−7.15 (m, 1H), 6.31 (dd, 1H, J = 56.3, 5.1 Hz), 6.06 (dd, 1H, J = 56.9, 4.7 Hz) 3.84 (s, 3H), 3.80 (s, 3H), 3.73−3.05 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.2 (d, J = 5.9 Hz), 170.5 (d, J = 3.7 Hz), 156.6 (s), 143.9 (d, J = 5.1 Hz), 141.5 (t, J = 5.9 Hz), 138.8 (d, J = 19.0 Hz), 138.0 (d, J = 16.1 Hz), 130.7 (d, J = 4.4 Hz), 130.0 (d, J = 2.9 Hz), 127.3 (dd, J = 18.3, 2.9 Hz), 126.0 (d, J = 2.9 Hz), 125.1 (dd, J = 41.7, 1.5 Hz), 125.2 (d, J = 2.9 Hz), 124.3 (s), 98.1 (d, J = 180.8 Hz), 95.5 (d, J = 178.6 Hz), 52.3 (d, J = 19.0 Hz), 50.9 (d, J = 21.9 Hz), 49.7 (d, J = 23.4 Hz), 43.5 (s), 36.2 (s), 32.9 (dd, J = 144.9, 1.5 Hz); ^{19}F NMR ($CDCl_3$) δ −163.9 (dd, 1F, J = 58.8, 24.7 Hz), −167.0 (dd, 1F, J = 55.7, 30.9 Hz); IR (CH_2Cl_2) 1740 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{11}H_{11}FO_2Na^+$ 217.0641, found 217.0637. Yield: (34.5 mg, 71%).

Methyl 3-Fluoro-2,3-diphenylpropanoate (12). Clear oil; ^{1}H NMR ($CDCl_3$) δ 7.50−7.08 (m, 20H), 6.11−5.90 (m, 2H), 4.18−4.06 (m, 2H), 3.83 (s, 4H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 171.9 (s), 170.9 (s), 137.9 (s), 137.7 (s), 136.9 (s), 136.6 (s), 134.6 (s), 133.4 (s), 133.3 (s), 128.9 (d, J = 23.0 Hz), 128.7 (d, J = 24.2 Hz), 128.3 (s), 128.1 (s), 126.7 (m), 92.8 (d, J = 178.4 Hz), 92.3 (d, J = 177.8 Hz), 58.7 (d, J = 26.9 Hz), 52.5 (s), 52.3 (s); ^{19}F NMR: −167.6 (dd, 1F, J = 45.4, 8.3 Hz), −178.2 (dd, 1F, J = 46.4, 13.4 Hz); IR (CH_2Cl_2) 1737 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{16}H_{15}FO_2Na^+$ 281.0954, found 281.0959. Yield: (48.4 mg, 75%).

Ethyl-3-(4-chlorophenyl)-3-fluoropropanoate (13). Spectral and analytical data were in agreement with previous reports.[25] Yield: (21.9 mg, 38%).

Ethyl-3-(3-methoxyphenyl)-3-fluoropropanoate (14). Spectral and analytical data were in agreement with previous reports.[25] Yield: (24.3 mg, 43%).

Ethyl-3-(4-bromophenyl)-3-fluoropropanoate (15). Spectral and analytical data were in agreement with previous reports.[25] Yield: (27.5 mg, 40%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization data for new compounds. 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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