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PAPER

Alkylation and silylation of α-fluorobenzyl anion intermediates

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Simple α-fluorobenzyl anions reacted with electrophiles such as non-activated alkyl halides and chlorotrimethylsilane. Upon treatment with LTMP as base, fluoromethylbenzenes took part in the formation of α-monofluorobenzyl anion without stabilizing *o*-substituents. Furthermore, the resulting α-silyl fluoromethylbenzenes reacted with electrophiles such as acetophenone and benzaldehyde in the presence of cesium fluoride to form α-fluorobenzylated alcohols.

Introduction

Fluorine-containing organic compounds have a bioactive potential which makes them drug candidate compounds.[1,2] However, the pinpoint introduction of fluorine atoms in the synthesis of designed molecules often requires the use of fluorinating reagents, which are hazardous, expensive or sometimes explosive.[1] Therefore, it is helpful that easily prepared fluorinated compounds are considered as synthetic blocks. To date, the synthesis and applications of α-fluorobenzyl compounds have attracted significant attention in organic chemistry.[3-11] In particular, several α-substituted α-fluorobenzyl compounds (Ar-CHF-R) have shown potential bioactivity.[11] To synthesize monofluorobenzyl compounds (Ar-CHF-R), the most general methods are *(a)* fluorination of the benzyl positions (Scheme 1);[3,4] *(b)* cross-coupling to introduce fluoroalkyl groups into aromatic compounds which have recently been reported;[5,6] or, *(c)* the use of α-fluorobenzyl anions which is a promising method to synthesize various α-substituted α-fluorobenzyl compounds (Ar-CHF-R) from Ar-CH_2F as common starting materials. However, the chemistry of monofluorobenzyl anions has been much less explored compared to that of trifluoromethyl anion.[7,8] In general, α-fluorocarbanions are destabilized by electronic repulsion between lone pairs of anionic carbons and non-bonded pairs in fluorine atom(s). For instance, deprotonation of fluoroform is quite difficult.[12-14] In previous reports, fluoromethylarenes possessing certain directing groups for the effective deprotonation underwent the C-C bond forming reactions with electrophiles.[7,8] As shown in Eq. 1 (Scheme 1), the *o*-sulfinyl group works as a stabilizer of the fluorobenzyl anion intermediate as well as a chiral auxiliary in diastereoselective transformations.[8] To the best of our knowledge, there has been no report on the reactions of α-fluorobenzyl anions through deprotonation starting from fluoromethylarenes without stabilization by *o*-substituents. Herein, we report the deprotonation of simple fluoromethylarenes **1** and the subsequent reactions with electrophiles such as non-activated alkyl halides (Eq. 2, Scheme 1).

Results and discussion

Methyl iodide was used as an electrophile in the coupling reaction of α-fluorobenzyl anions (Table 1). The use of an excess of methyl iodide had practically no effect on the yield of **2a** (entry 1 vs entry 2). However, the addition of 5 equivalents of LTMP led to a higher yield of the desired compound **2a** (entry 1 vs entry 3). The combination of the increased amount of both methyl iodide and LTMP was significant with regard to the chemical yield (entry 1 vs entry 4). Larger amounts of the two reagents, methyl iodide and LTMP, resulted in a higher yield of the desired compound **2a** (entry 1 vs entries 4-6). Consequently, 10 equivalents of methyl iodide and LTMP were added to generate **2a** in >95% NMR yield (entry 6).

As shown in Table 2, the substrate scope of the alkylation of the simple fluoromethylarenes **1** in question presented herein was then studied. Various alkyl iodides, such as ethyl iodide, *n*-butyl iodide, and isopropyl iodide acted as electrophiles and the corresponding products **2b**-**2d** were obtained in high yields (entries 2-4). The use of iodoalkanes is effective; for entry 3, we examined the reactions with bromobutane and chlorobutane as electrophiles, the butylated compound **2c** was formed in 36% and 0%, respectively. Other fluoromethylbenzenes, such as 1-chloro-4-(fluoromethyl)benzene (**1e**) and 1-bromo-4-(fluoromethyl)benzene (**1f**) acted as nucleophilic α-

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monofluorobenzylating reagents to afford the corresponding products **2d** and **2e** in moderate yields. It is remarkable that chloro- and bromo- functionalities were tolerable under the deprotonative generation of benzyllithium species (entries 5 and 6).[15,16] On the contrary, 1-(*tert*-butyl)-4-(fluoromethyl)benzene **1g** did not work under the standard reaction conditions (entry 7).

The C-C bond forming reactions of fluoromethylbenzene **1a** with carbonyl compounds were explored under the basic conditions of LTMP (Scheme 2). Benzophenone acted as an electrophile to yield **2h** in 88% yield. However, under the same conditions, fluoromethylbenzene **1a** did not form a C-C bond with acetophenone or benzaldehyde, added as electrophile, not resulting in the desired products **2i** or **2j** of the α-monofluorobenzylation with recovery of the starting material **1a**.

Instead of the direct functionalization of fluoromethylbenzenes **1** with carbonyl compounds, we next synthesized α-fluorobenzyl trimethylsilanes **3** [17,18] using 2.0 equivalents of chlorotrimethylsilane (Scheme 3). Subsequently, α-fluorobenzyl trimethylsilanes **3** were treated with benzaldehyde using cesium fluoride (1.0 equiv) to obtain **4a-c** in good yields. Similarly, α-fluorobenzyl trimethylsilane **2k** reacted with acetophenone in the presence of cesium fluoride (1.0 equiv) to provide **4d** in 65% (dr = 57:43).

Conclusions

In conclusion, the alkylation of *o*-substituent-free fluoromethylarenes (**1**) with alkyl halides or benzophenone was achieved using LTMP, and alkylated fluorobenzyl compounds (**2a**-**g**) were obtained in moderate to high yields. In a similar way, the benzylic position of the fluoromethylbenzene derivative **1a** was functionalized by chlorotrimethylsilane. Other α-fluorobenzyl alcohols, which could not be directly obtained by the studied synthesis of α-fluorobenzyl compounds with ketones and aldehydes, were synthesized from the trimethylsilylated fluoromethylbenzene **2k** with cesium fluoride in good yields.

Experimental section

General information

All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. Most commercially supplied chemicals were purchased from commercial suppliers and used without further purification. THF was dried by reflux over Na chips in the presence of benzophenone as indicator. Analytical TLC was performed on aluminum silica gel 60 F_{254} (Merck) sheets, which were visualized by the quenching of UV fluorescence (254 nm). Column chromatography was conducted on silica gel (Cica, 60–210 mesh, spherical, neutral). NMR spectra were acquired on a JEOL JNMECS 400 and JNMECS 300 (400 MHz for ^{1}H, 75 MHz for ^{13}C, and 376 MHz for ^{19}F, respectively) spectrometers. ^{1}H NMR spectra were recorded using TMS (Me_4Si) as internal standard (δ = 0). ^{13}C NMR spectra were recorded considering the residual solvent peak (δ = 77.0). ^{19}F NMR spectra were recorded using hexafluorobenzene (C_6F_6) as internal standard (δ = 0). GC-MS spectra were recorded on a Thermo TRACE DSQ.

General procedure for 2: Synthesis of 2a

2,2,6,6-Tetramethylpiperidine (424 mg, 3.0 mmol) and THF (3 mL) were placed in a 20 mL two-necked round bottom flask equipped with a stirrer bar, under an argon atmosphere and stirred at -78 °C for 10 min. *n*-BuLi (1.6 M in hexane, 1.9 mL, 3.0 mmol) was added dropwise to the solution and the temperature was increased from -78 °C to 0 °C for 15 min. After that, the reaction mixture was once again kept at -78 °C and THF (2.0 mL) solution of 4-(1-fluoromethyl)biphenyl **1a** (55.9 mg, 0.3 mmol) and methyl iodide (426 mg, 3.0 mmol) was added in a dropwise manner. After stirring at -78 °C for 2 hours, the reaction was quenched with methanol. The ^{19}F NMR yield was determined using 1,3-bis(trifluoromethyl)benzene as internal standard. The reaction residue was extracted with ethyl acetate, washed with water, and dried over Na_2SO_4. The filtered mixture was concentrated using an evaporator and purified with column chlomatography (hexane : ethyl acetate = 50 : 1) to afford 4-(1-fluoroethyl)biphenyl **2a** (54.2 mg, 90%).

4-(1-Fluoroethyl)biphenyl (2a). Colorless solid. Yield 54.2 mg, 90%; Mp = 43.6–44.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.57 (4H, m), 7.46-7.42 (4H, m), 7.37-7.33 (1H, m), 5.67 (1H, dq, *J* = 47.9, 6.4), 1.68 (3H, dd, *J* = 24.2, 6.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3 (d, *J* = 1.4 Hz), 140.8, 140.5 (d, *J* = 19.4 Hz), 128.9, 127.6, 127.4, 127.3, 125.9 (d, *J* = 6.5 Hz), 90.9 (d, *J* = 165.7 Hz), 23.0 (d, *J* = 25.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -4.91(1F, dq, *J* = 47.9, 24.2). IR (KBr): 3033, 2988, 2933 cm^{-1}. Mass m/e: (m/z) (%) 200 (M^+, 37), 185 (100), 180 (40). Anal. Calcd for $C_{14}H_{13}F$: C, 83.97; H, 6.54. Found: C, 83.70; H, 6.66.

4-(1-Fluoropropyl)biphenyl (2b). Colorless oil. Yield 55.5 mg, 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (4H, m), 7.46-7.32 (5H, m), 5.41 (1H, ddd, *J* = 47.9, 7.4, 5.2), 2.10-1.82 (2H, m), 1.01 (3H, t, *J* = 7.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2 (d, *J* = 1.4 Hz), 140.8, 139.4 (d, *J* = 20.0 Hz), 128.9, 127.5, 127.27, 127.25, 126.2 (d, *J* = 7.1 Hz), 95.7 (d, *J* = 169.2 Hz), 30.3 (d, *J* = 24.4 Hz), 9.6 (d, *J* = 5.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -13.4 (1F, ddd, *J* = 47.9, 25.9, 17.6). IR (neat): 3059, 3033, 2974, 2940, 2884 cm^{-1}. Mass m/e: (m/z) (%) 214 (M^+, 30), 194 (8), 185 (100), 165 (12), 152 (5). Anal. Calcd for $C_{15}H_{15}F$: C, 84.08; H, 7.06. Found: C, 83.80; H, 7.11.

4-(1-Fluoropentyl)biphenyl (2c). Colorless solids. Yield 64.1 mg, 88%; Mp = 36.4–37.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.56 (4H, m), 7.46-7.39 (4H, m), 7.35 (1H, t, *J* = 7.2), 5.46 (1H, ddd, *J* = 48.0, 8.0, 5.2), 2.08-1.77 (2H, m), 1.54-1.35 (4H, m), 0.92 (3H, t, *J* =7.0). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 140.8, 139.7 (d, *J* = 20.2 Hz), 128.9, 127.5, 127.30, 127.26, 126.2 (d, *J* = 6.5 Hz), 94.7 (d, *J* = 170.0 Hz), 37.0 (d, *J* = 23.9 Hz), 27.4 (d, *J* = 4.4 Hz), 22.6, 14.1.^{19}F NMR (376 MHz, $CDCl_3$) δ -12.0 (1F, ddd, *J* = 47.8, 30.4, 17.2). IR (KBr): 3059, 3033, 2959, 2866 cm^{-1}. Mass m/e: (m/z) (%) 242 (M^+), 222 (66), 193 (100), 178 (92), 165 (42). Anal. Calcd for $C_{17}H_{19}F$: C, 84.26; H, 7.90. Found: C, 84.29; H, 7.75.

4-(1-Fluoro-2-methylpropyl)biphenyl (2d). Colorless solids. Yield 53.6 mg, 78%; Mp = 53.8–54.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.58 (4H, m), 7.46-7.42 (2H, m), 7.37-7.33 (3H, m), 5.15

(1H, dd, *J* = 46.8, 6.8), 2.20-2.08 (1H, m), 1.05 (3H, d, *J* = 6.8), 0.89 (3H, dd, *J* = 6.8, 0.8). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1 (d, *J* = 1.4 Hz), 140.8, 138.5 (d, *J* = 20.9 Hz), 128.9, 127.5, 127.2, 127.1, 126.7 (d, *J* = 7.2 Hz), 99.2 (d, *J* = 174.0 Hz), 34.5 (d, *J* = 23.1 Hz), 18.5 (d, *J* = 5.8 Hz), 17.7 (d, *J* = 5.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -17.9 (1F, dd, *J* = 46.8, 17.2). IR (KBr): 2966, 2933, 2910, 2880 cm^{-1}. Mass m/e: (m/z) (%) 228 (M^+, 23), 208 (4), 185 (100), 165 (11). Anal. Calcd for $C_{16}H_{17}F$: C, 84.17; H, 7.51. Found: C, 84.16; H, 7.49.

1-Chloro-4-(1-fluoroethyl)benzene (2e). Colorless oil. Yield 27.4 mg, 57%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.34 (2H, m), 7.29-7.27 (2H, m), 5.60 (1H, dq, *J* = 47.7, 6.4), 1.62 (3H, dd, *J* = 23.0, 6.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0 (d, *J* = 19.6 Hz), 134.1, 128.8, 126.8 (d, *J* = 7.2 Hz), 90.4 (d, *J* = 167.1 Hz), 23.0 (d, *J* = 24.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -5.83 (1F, dq, *J* = 47.7, 23.0). IR (neat): 2989, 2959, 2933, 2858 cm^{-1}. Mass m/e: (m/z) (%) 160 (M^+2, 12), 158 (M^+, 41), 142 (100), 123 (58). Anal. Calcd for C_8H_8ClF: C, 60.58; H, 5.08. Found: C, 60.46; H, 5.01.

1-Bromo-4-(1-fluoroethyl)benzene (2f). Colorless oil. Yield 37.0 mg, 57% from 1f (59.6 mg, 0.32 mmol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (2H, dd, *J* = 8.0, 0.8), 7.22 (2H, dd, *J* = 8.0, 0.8), 5.58 (1H, dq, *J* = 47.9, 6.4), 1.61 (3H, dd, *J* = 24.3, 6.4). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6 (d, *J* = 19.6 Hz), 131.7, 127.0 (d, *J* = 7.2 Hz), 122.2, 90.4 (d, *J* = 167.1 Hz), 23.0 (d, *J* = 25.1 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -6.38 (1F, dq, *J* = 47.9, 24.3). IR (neat): 2989, 2933, 2858 cm^{-1}. Mass m/e: (m/z) (%) 204 (M^{++}2, 46), 202 (M^+,49), 189 (95), 187 (100), 123 (99), 108 (40). Anal. Calcd for C_8H_8BrF: C, 47.32; H, 3.97. Found: C, 47.51; H, 4.29.

2-(4-Biphenyl)-2-fluoro-1,1-diphenylethan-1-ol (2h). Colorless solids. Yield 74.8 mg, 70%; Mp = 218.7–219.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (4H, m), 7.43-7.29 (8H, m), 7.21-7.17 (5H, m), 7.06-7.03 (2H, m), 6.36 (1H, d, *J* = 44.8), 2.72 (1H, s). ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.3, 144.3 (d, *J* = 3.6 Hz), 139.5 (d, *J* = 19.4 Hz), 135.7, 135.4, 128.9, 127.6, 127.5, 127.0, 126.7, 126.6, 126.3, 125.1, 94.3 (d, *J* = 176.3 Hz), 78.7 (d, *J* = 23.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -18.3 (1F, d, *J* = 44.8). IR (KBr): 3569, 3555 cm^{-1}. Mass m/e: (m/z) (%) 243 (100), 181 (20), 165 (27), 105 (73). Anal. Calcd for $C_{26}H_{21}FO$: C, 84.76; H, 5.74. Found: C, 84.40; H, 6.01.

General procedure for 3: Synthesis of 3a

2,2,6,6-Tetramethylpiperidine and THF (6 mL) were placed in a 20 mL two-necked round bottom flask equipped with a stirrer bar, under argon atmosphere and stirred at -78 °C for 10 min. n-BuLi (1.6 M hexane solution, 3.74 mL, 6.0 mmol) was added dropwise to the solution and the temperature was increased up from -78 °C to 0 °C for 15 min. Thereafter, the reaction mixture was once again kept at -78 °C and THF (2.0 mL) solution of 4-(1-fluoromethyl)biphenyl **1a** (558.7 mg, 3.0 mmol) and chlorotrimethylsilane (651.8 mg, 6.0 mmol) was added in a dropwise manner. After stirring at -78 °C for 2 hours, the reaction was quenched with methanol. The reaction residue was extracted with ethyl acetate, washed with water, and dried over Na_2SO_4. The filtered mixture was concentrated using an evaporator and purified by recrystallization from hexane to afford **3a** (597.0 mg, 77%).

{[(1,1'-Biphenyl)-4-yl]fluoromethyl}trimethylsilane (3a). Colorless solid. Yield 597.0 mg, 77%; Mp = 79.2–80.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.56 (4H, m), 7.43 (2H, t, *J* =7.6), 7.33 (1H, t, *J* =7.2), 7.21 (2H, d, *J* = 7.6), 5.51 (1H, d, *J* = 44.0), 0.09 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 139.4, 139.2, 128.9, 127.3, 127.1, 127.0, 124.7 (d, *J* = 7.8 Hz), 94.3 (d, *J* = 169.3 Hz), -4.1 (d, *J* = 2.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.1 (1F, d, *J* = 44.0). IR (KBr): 2966, 2903, 2873 cm^{-1}. Mass m/e: (m/z) (%) 258 (M^+, 7), 215 (9), 185 (8), 164 (100). Anal. Calcd for C16H19FSi: C, 74.37; H, 7.41. Found: C, 74.20; H, 7.38.

[(3-Chlorophenyl)fluoromethyl]trimethylsilane (3b). Pale yellow oil. Yield 453.9 mg, 63%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (1H, m), 7.19-7.14 (2H, m), 7.00 (1H, d, *J* = 7.1), 5.44 (1H, d, *J* = 44.7), 0.07 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3 (d, *J* = 16.5), 134.2, 129.4, 126.3 (d, *J* = 1.5), 123.8 (d, *J* = 8.6), 121.9 (d, *J* = 7.9), 93.1 (d, *J* = 171.9), -4.5. ^{19}F NMR (376 MHz, CDCl3) δ -56.9 (1F, d, *J* = 44.7). IR (neat): 2959, 2895 cm^{-1}. Mass m/e: (m/z) (%) 218 (M^+2, 1), 216 (M^+, 3), 203 (1), 201 (3), 175 (7), 173 (19), 143 (12), 126 (23), 124 (71), 89 (39), 73 (100). Anal. Calcd for $C_{10}H_{14}ClFSi$: C, 55.41; H, 6.51. Found: C, 55.40; H, 6.42.

[(4-(*tert*-butyl)phenyl)fluoromethyl)]trimethylsilane (3c). Colorless oil. Yield 207.4 mg, 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 7.8), 7.08 (2H, d, *J* = 7.8), 5.44 (1H, d, *J* = 44.4), 1.31 (9H, s), 0.06 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 136.9 (d, *J* = 17.3), 125.0, 124.0 (d, *J* = 8.6), 94.3 (d, *J* = 168.0), 34.4, 31.4, -4.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.0 (1F, d, *J* = 44.4). IR (neat): 2966, 2907 cm^{-1}. Mass m/e: (m/z) (%) 238 (M^+, 5), 223 (5), 146 (37), 131 (100), 91 (24), 73 (52). Anal. Calcd for $C_{14}H_{23}FSi$: C, 70.53; H, 9.72. Found: C, 70.44; H, 9.81. General

General procedure for 4: Synthesis of 4a

A flask was filled with CsF (45.5 mg, 0.30 mmol), flame-dried under vacuum and then backfilled with nitrogen. After flame drying benzaldehyde (159.1 mg, 1.5 mmol) and anhydrous DMF (1 mL) were added to the flask. Next, **3a** (77.5 mg, 0.30 mmol) was transferred using a syringe and the reaction mixture was stirred at room temperature for 8 hours. The reaction residue was extracted with ethyl acetate, washed with water, and dried over Na_2SO_4. The filtered mixture was concentrated using an evaporator and purified by recrystallization from hexane to afford **4a** (64.1 mg, 72%).

2-[(1,1'-Biphenyl)-4-yl]-2-fluoro-1-phenylethan-1-ol (4a). Colorless solids. Yield 64.1 mg, 72%; Mp = 126.3-127.4 °C. A diastereomer ratio of 51:49 was determined by comparing the intensities of the indicated NMR peaks. ^{1}H NMR (400 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ 7.60-7.15 (14H, m), **5.56 (1H, dd, *J* = 44.6, 6.0), *5.48 (1H, dd, *J* = 47.5, 7.4), **5.05 (1H, ddd, *J* = 12.4, 6.0, 4.0), *4.98 (1H, ddd, *J* = 13.0, 7.4, 2.4), *2.89 (1H, s), **2.14 (1H, d, *J* = 4.0). ^{13}C NMR (75 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ **141.7 (d, *J* = 1.4 Hz), *141.6 (d, *J* = 1.4 Hz), *140.6, **140.5, **139.0 (d, *J* = 3.6 Hz), *137.9 (d, *J* = 5.8 Hz), **135.1 (d, *J* = 20.2 Hz), *134.9 (d, *J* = 20.2 Hz), 128.9, 128.43, 128.38, 127.66, 127.46, 127.42, 127.28, 127.23, 127.16, 127.0, 126.9, *97.8 (d, *J* = 175.2 Hz), **96.2 (d, *J* = 176.4 Hz), *77.7 (d, *J* = 23.6 Hz), **76.4 (d, *J* = 27.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ *-19.0 (1F, dd, *J* = 47.5, 13.0), **-20.7 (1F, dd, *J* = 44.6, 12.4). IR (KBr): 3387 cm^{-1}. Mass m/e: (m/z) (%) 272 (11), 243 (23), 165 (22), 105 (100). Anal. Calcd for $C_{20}H_{17}FO$: C, 82.17; H, 5.86. Found: C, 81.89; H, 5.91.

2-(3-Chlorophenyl)-2-fluoro-1-phenylethan-1-ol (4b). Colorless solids. Yield 58.8 mg, 87%; Mp = 47.7-48.8 °C. A diastereomer ratio of 51:49 was determined by comparing the intensities of the indicated NMR peaks. ^{1}H NMR (400 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ 7.35-6.87 (9H, m), **5.49 (1H, dd, *J* = 45.7, 5.3), *5.41 (1H, dd, *J* = 47.6, 6.9), *5.01 (1H, ddd, *J* = 12.6, 5.5, 3.9), **4.90 (1H, ddd, *J* = 12.6, 7.4, 2.4), *2.76 (1H, dd, *J* = 3.3, 2.4), **2.19 (1H, d, *J* = 3.9). ^{13}C NMR (75 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ *138.4 (d, *J* = 2.9), **138.1 (d, *J* = 8.6), *137.8 (d, *J* = 9.3), **132.5 (d, *J* = 5.8), 134.1, **129.3 (d, *J* = 3.6), **128.8, *128.6 (d, *J* = 8.0), *128.3, 128.3, *127.2, 127.0, **126.9, *126.9, **126.6 (d, *J* = 7.2), *124.9 (d, *J* = 6.5), **124.8 (d, *J* = 7.2), *96.9 (d, *J* = 177.8), **95.3 (d, *J* = 177.8), *77.5 (d, *J* = 23.7), **76.1 (d, *J* = 26.5). ^{19}F NMR (376 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ *-20.8 (1F, dd, *J* =45.7, 12.6), *-22.3 (1F, dd, *J* =47.6, 12.6). IR (KBr): 3447, 3033, 3067, 2936 cm^{-1}. Mass m/e: (m/z) (%) *203 (3), **203 (4), *201 (9), **201 (15), *165 (12), **165 (19), *107 (100), **107 (100), *79 (46), **79 (48), *77 (27), **77 (25). Anal. Calcd for $C_{14}H_{12}ClFO$: C, 67.07; H, 4.82. Found: C, 67.19; H, 4.81.

2-(4-(tert-Butyl)phenyl)-2-fluoro-1-phenylethan-1-ol (4c). Colorless oil. Yield 69.5 mg, 74%; A diastereomer ratio of 52:48 was determined by comparing the intensities of the indicated NMR peaks. ^{1}H NMR (300 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ 7.42-7.02 (9H, m), **5.43 (1H, dd, *J* = 48.9, 5.4), *5.41 (1H, dd, *J* = 47.4, 5.4), 5.02-4.88 (1H, m), *2.78 (1H, brs), **2.09 (1H, brs), *1.32 (9H, s), **1.28 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ *152.0, **151.8, *139.3, **138.1 (d, *J* = 5.7), *133.1 (d, *J* = 20.1), **132.8 (d, *J* = 20.1), *128.3, **128.2, *128.1, **128.1, *127.3, **127.0, **126.6 (d, *J* = 5.9), *126.4 (d, *J* = 5.7), *125.2, **125.1, *97.7 (d, *J* = 175.2), **96.1 (d, *J* = 175.2), **77.5 (d, *J* = 24.5), *76.1 (d, *J* = 27.3), 34.6, 31.3. ^{19}F NMR (282 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ *-18.9 (1F, dd, *J* = 47.4, 4.9), **-19.0 (1F, dd, *J* = 48.9, 13.0). IR (neat): 3447, 3033, 3067, 2936 cm^{-1}. Mass m/e: (m/z) (%) *223 (87), **223 (56), *166 (55), *166 (53), *107 (100), **107 (100), *79 (39), **79 (40), *77 (20), **77 (26). Anal. Calcd for $C_{18}H_{21}FO$: C, 79.38; H, 7.77. Found: C, 79.49; H, 7.58.

1-[(1,1'-Biphenyl)-4-yl]-1-fluoro-2-phenylpropan-2-ol (4d). Colorless solids. Yield 63.7 mg, 65%; Mp = 93.8–94.8 °C. A diastereomer ratio of 57:43 was determined by comparing the intensities of the indicated NMR peaks. ^{1}H NMR (400 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ 7.58-7.53 (2H, m), 7.48-7.40 (4H, m), 7.38-7.26 (6H, m), 7.12-7.07 (2H, m), **5.56 (1H, d, *J* = 45.2), *5.53 (1H, d, *J* = 45.2), *2.52, **2.25, **1.73 (3H, d, *J* = 2.0), *1.59 (3H, d, *J* = 1.2). ^{13}C NMR (75 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ **143.2 (d, *J* = 2.9 Hz), *142.8 (d, *J* = 3.6 Hz), **141.8, *141.3, 140.5, *134.7 (d, *J* = 21.5 Hz), **134.6 (d, *J* = 20.9 Hz), 128.9, 128.1, *127.74, **127.69, *127.64, **127.59, *127.55, **127.49, 127.2, 126.4, *126.3, **125.9, *99.3 (d, *J* = 179.3 Hz), **98.6 (d, *J* = 180.7 Hz), *76.4 (d, *J* = 23.0 Hz), **76.0 (d, *J* = 23.7 Hz), **25.4 (d, *J* = 3.5 Hz), *24.2 (d, *J* = 2.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) (* = major isomer; ** = minor isomer) δ -22.9 (1F, d, *J* = 45.2), **-24.4 (1F, d, *J* = 45.2). IR (KBr): 3569, 3465, 3063, 3033, 2988 2936 cm^{-1}. Mass m/e: (m/z) (%) 286, 257 (9), 243 (100), 165 (58). Anal. Calcd for $C_{21}H_{19}FO$: C, 82.33; H, 6.25. Found: C, 82.11; H, 6.39.

Conflicts of interest

There are no conflicts to declare.

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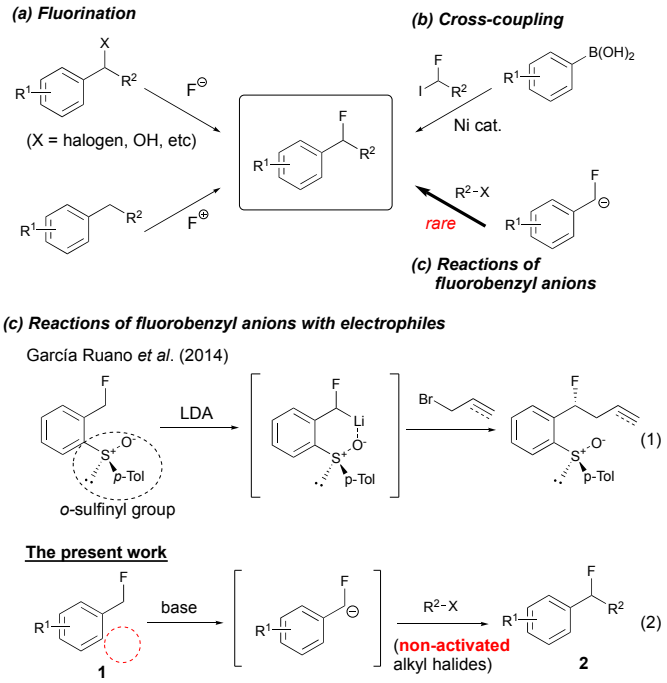
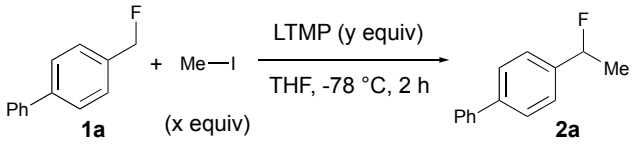


Scheme 1. Synthesis of α-substituted α-fluorobenzyl compounds

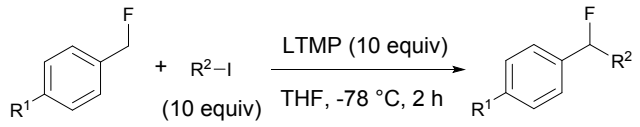
Table 1. Optimization of the reaction conditions



entry	x	y	Yield of **2a** (%)[a]	Recovery of **1a** (%)[a]
1	1.0	1.0	4	56
2	5.0	1.0	5	64
3	1.0	5.0	31	0
4	3.0	3.0	33	47
5	5.0	5.0	54	0
6	10.0	10.0	>95	0

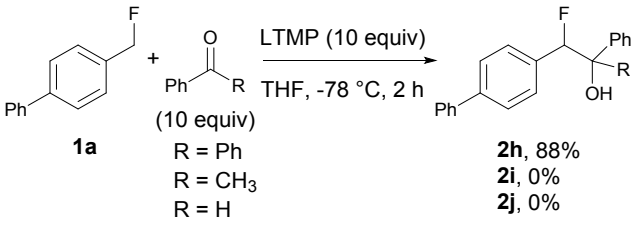
[a]The yield was determined by ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene as an internal standard.

Table 2. Alkylation of fluoromethylarenes

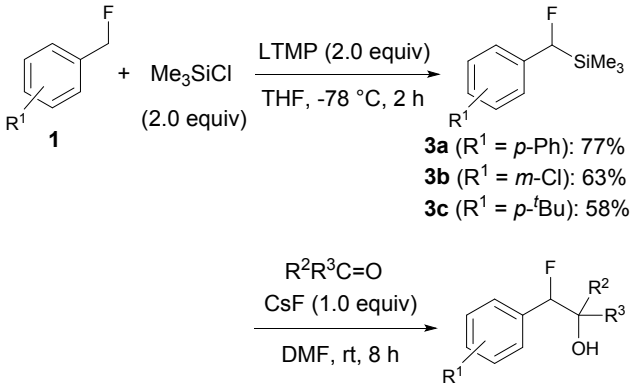


entry	1		2	Yield of **2** (%)[a]
	R^1	R^2		
1[b]	Ph	Me	**2a**	90
2	Ph	Et	**2b**	87
3	Ph	^{n}Bu	**2c**	88
4	Ph	^{i}Pr	**2d**	78
5	Cl	Me	**2e**	57
6[c]	Br	Me	**2f**	57
7	^{t}Bu	Me	**2g**	0

[a] Isolated yield. [b] 20.0 equiv of methyl iodide and LTMP were required for the isolation of **2a**. [c] 5.0 equiv of methyl iodide and LTMP were also required.



Scheme 2. Synthesis of α-fluorobenzyl alcohols from fluroomethylbenzene **1a**



Scheme 3. Synthesis of α-fluorobenzylated alcohols with α-fluorobenzyltrimethylsilanes **3**

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