Oxidative Cross-Coupling of β,β -Difluoroenol Silyl Ethers with Nucleophiles; A Dipole Inversion Method to Difluoroketones

Kenji Uneyama,* Hiroaki Tanaka, Satoru Kobayashi, Manabu Shioyama and Hideki Amii

*Department of Applied Chemistry, Faculty of Engineering,
Okayama University, Okayama 700-8530, Japan
uneyamak@cc.okayama-u.ac.jp*

General Procedures

Unless otherwise noted, all manipulations were carried out under an inert atmosphere (nitrogen or argon) in a flame-dried glassware and by using syringe-cannula/septa technique. THF was distilled from sodium/benzophenone ketyl. DMSO, DMF, hexane (for reaction use), MeCN, and *i*-PrCN were freshly distilled from CaH₂. MeOH was stored over MS4A. All other reagents and solvents were employed without further purification. E. Merck silica gel (Kieselgel 60, 230-400 mesh) was employed for the chromatography.

¹H NMR (200MHz) and ¹⁹F NMR (188MHz) spectra were recorded on a Varian VXR-200 spectrometer using CDCl₃ as a solvent. The chemical shifts are reported in δ (ppm) value relative to tetramethylsilane (δ 0 ppm) for ¹H NMR spectra and to C₆F₆ (δ 0 ppm) for ¹⁹F NMR spectra. Coupling constants *J* are reported in hertz (Hz). Infrared spectra were recorded on a Hitachi 270-30 spectrometer (cm⁻¹). Melting points were determined on a Yanako MP-S3 melting point measurement apparatus. GC/MS analyses were performed on a Hewlett-Packard HP5971A. Perkin-Elmer Series II CHNS/O Analyzer 2400 was employed for elemental analysis. Yields obtained by NMR were estimated by using 1,4-bis(trifluoromethyl)benzene as an internal standard.

Typical procedure for the preparation of difluoroenol silyl

ether (10)

To a mixture of chlorotrimethylsilane (1.30 g, 12 mmol) and Mg (0.29 g, 12 mmol) in THF (12 mL) cooled down to 0 °C under an argon atmosphere, trifluoroacetophenone (0.52 g, 3.0 mmol) was added dropwise and then the reaction mixture was stirred for additional 20 min. After evaporation of solvent, hexane (20 mL) was added to the residue, and the resulting salt was filtered and the filtrate was concentrated to give crude **10a** (0.59 g, 2.6 mmol, the purity of this crude product of **10a** was found on the basis of ^{19}F NMR analysis to be >95%). The crude difluoroenol silyl ethers **10** were used for later cross-coupling reactions without further purification.

Typical procedure for the synthesis of tetrafluorobutan-1,4-diketones (11).

To a mixture of $\text{Cu}(\text{OTf})_2$ (868 mg, 2.4 mmol) in MeCN (2 mL) was added difluoroenol silyl ethers **10** (2.0 mmol) at -30 °C under an argon atmosphere. After 5 min, the mixture was allowed to warm to ambient temperature. After stirring for additional 15 min, the reaction was quenched with water. The reaction mixture was extracted with Et_2O , and the organic phase was washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The crude products were distilled (130 °C/0.2 mmHg) to remove the volatile impurities. Recrystallization of the residue from Et_2O at -10 °C gave **11**.

2,2,3,3-Tetrafluoro-1,4-diphenylbutan-1,4-dione (11a).¹¹ Colorless crystals (220 mg, 71 %); mp 59-60 °C; IR (KBr) 1702, 1595, 1449 cm^{-1} ; ^1H NMR δ 7.50-7.58 (m, 4 H), 7.66-7.74 (m, 2 H), 8.12 (d, J = 7.8 Hz, 4 H); ^{19}F NMR δ 48.7 (s, 4F); MS m/z (%) 311 ($\text{M}^+ + 1$, 1), 105 (100), 77 (65). Anal. Calcd for $\text{C}_{16}\text{H}_{10}\text{F}_4\text{O}_2$: C, 61.94; H, 3.25. Found: C, 61.87; H, 3.30.

1,4-Bis(4-chlorophenyl)-2,2,3,3-tetrafluorobutan-1,4-dione (11b). Colorless crystals (273 mg, 72%); mp 89-90 °C; IR (KBr) 1698, 1587 cm^{-1} ; ^1H NMR δ 7.49-7.56 (m, 4 H), 8.05 (d, J = 8.8 Hz, 4 H); ^{19}F NMR δ 48.5 (s, 4F); MS m/z (%) 378 ($\text{M}^+ - 1$, 1), 141 (53), 139 (100), 113 (17), 111 (46). Anal. Calcd for $\text{C}_{16}\text{H}_8\text{Cl}_2\text{F}_4\text{O}_2$: C, 50.69; H, 2.13. Found: C, 50.75; H, 2.32.

2,2,3,3-Tetrafluoro-1,4-bis(4-methylphenyl)butan-1,4-dione (11c). Colorless crystals (238 mg, 70%); mp 63-65 °C; IR (KBr) 1695, 1607 cm^{-1} ; ^1H NMR δ 2.46 (s, 6 H), 7.33 (d, J = 8.3 Hz, 4

H), 8.02 (d, $J = 8.3$ Hz, 4 H); ^{19}F NMR δ 48.8 (s, 4F); MS m/z (%) 338 (M^+ , 1), 119 (100), 91 (28). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{F}_4\text{O}_2$: C, 63.91; H, 4.17. Found: C, 64.15; H, 4.28.

2,2,3,3-Tetrafluoro-1,4-bis(4-methoxyphenyl)butan-1,4-dione (11d).

(Recrystallized from hexane/AcOEt) Colorless crystals (318 mg, 86%); mp 104-105 °C; IR (KBr) 1683, 1599 cm^{-1} ; ^1H NMR δ 3.91 (s, 6 H), 6.96-7.03 (m, 4 H), 8.11 (d, $J = 8.8$ Hz, 4 H); ^{19}F NMR δ 49.2 (s); MS m/z (%) 370 (M^+ , 1), 135 (100), 92 (13), 77 (15). Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{F}_4\text{O}_4$: C, 58.38; H, 3.81. Found: C, 58.52; H, 4.00.

2,2,3,3-Tetrafluoro-1,4-bis(2-furyl)butan-1,4-dione (11e).

Pale yellow crystals (160 mg, 58%); mp 75-76 °C; IR (KBr) 1692, 1464 cm^{-1} ; ^1H NMR δ 6.68 (dd, $J = 3.8$ Hz, 1.6 Hz, 2 H), 7.57 (d, $J = 3.2$ Hz, 2 H), 7.81 (d, $J = 1.2$ Hz, 2 H); ^{19}F NMR δ 45.2 (s, 4F); MS m/z (%) 290 (M^+ , 6), 95 (100), 67 (5). Anal. Calcd for $\text{C}_{12}\text{H}_6\text{F}_4\text{O}_4$: C, 49.67; H, 2.08. Found: C, 49.39; H, 2.38.

Typical procedure for the $\text{Cu}(\text{OTf})_2$ promoted cross-coupling of 10 with heteroaromatics 12

To a mixture of $\text{Cu}(\text{OTf})_2$ (398 mg, 1.1 mmol) in MeCN (10 mL) and H_2O (0.2 mL) was added heteroaromatics (10 mmol). Then difluoroenol silyl ether **10** (1.0 mmol) in MeCN (10 mL) was added dropwise to the solution by using syringe-cannula/septa technique at 0 °C under an argon atmosphere for 3 h. After filtration through a short column of silica-gel and evaporation of solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane : diethyl ether = 9 : 1) to give **13**, **14**, **15** and **16**.

2,2-Difluoro-2-(2-furyl)-1-phenylethan-1-one (13a).

(189 mg, 88% based on **9a**) Colorless oil: IR (neat) 1706 cm^{-1} ; ^1H NMR δ 6.47-6.48 (m, 1H), 6.77-6.78 (m, 1H), 7.45-7.52 (m, 3H), 7.60-7.68 (m, 1H), 8.08 (d, $J = 7.6$ Hz, 2H); ^{19}F NMR δ 63.8 (s); MS m/z (%) 222 (M^+ , 2), 117 (27), 105 (100), 77 (83); Anal. Calcd for $\text{C}_{12}\text{H}_8\text{F}_2\text{O}_2$: C, 64.87; H, 3.63; Found: C, 64.99; H, 3.52.

1-(4-Chlorophenyl)-2,2-difluoro-2-(2-furyl)ethan-1-one (13b).

(184 mg, 72% based on **10b**) Colorless oil: IR (neat) 1712 cm^{-1} ; ^1H NMR δ 6.47-6.50 (m, 1H), 6.78-6.80 (m, 1H), 7.44-7.52 (m,

3H), 8.03 (d, J = 8.0 Hz, 2H); ^{19}F NMR δ 63.9 (s, 2F); MS m/z (%) 256 (M^+ , 1), 141 (49), 139 (100), 111 (50); Anal. Calcd for $\text{C}_{12}\text{H}_7\text{ClF}_2\text{O}_2$: C, 56.16; H, 2.75. Found: C, 56.51; H, 3.07.

2,2-Difluoro-2-(2-furyl)-1-(4-methylphenyl)ethan-1-one (13c).

(177 mg, 75% based on **10c**) Colorless oil: IR (neat) 1706 cm^{-1} ; ^1H NMR δ 2.45 (s, 3H), 6.48-6.50 (m, 1H), 6.78-6.80 (m, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.53-7.54 (m, 1H), 8.01 (d, J = 8.2 Hz, 2H); ^{19}F NMR δ 64.2 (s, 2F); MS m/z (%) 236 (M^+ , 1), 189 (1), 119 (100), 91 (86), 65 (44); Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{F}_2\text{O}_2$: C, 66.10; H, 4.27; Found: C, 65.78; H, 4.42.

2,2-Difluoro-2-(2-furyl)-1-(4-methoxyphenyl)ethan-1-one (13d).

(207 mg, 82% based on **10d**) Colorless oil: IR (neat) 1692 cm^{-1} ; ^1H NMR δ 3.89 (s, 3H), 6.45-6.47 (m, 1H), 6.75-6.77 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 7.50-7.51 (m, 1H), 8.08 (d, J = 8.8 Hz, 2H); ^{19}F NMR δ 64.3 (s, 2F); MS m/z (%) 252 (M^+ , 1), 205 (1), 135 (100), 117 (10), 107 (3), 92 (12); Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{F}_2\text{O}_3$: C, 61.91; H, 4.00; Found: C, 61.92; H, 4.18.

2,2-Difluoro-1,2-bis(2-furyl)ethan-1-one (13e).

(189 mg, 63% based on **10e**) Colorless oil: IR (neat) 1698 cm^{-1} ; ^1H NMR δ 6.44-6.47 (m, 1H), 6.60-6.66 (m, 1H), 6.77-6.80 (m, 1H), 7.48-7.51 (m, 2H), 7.75-7.77 (m, 1H); ^{19}F NMR δ 61.0 (s, 2F); MS m/z (%) 212 (M^+ , 16), 165 (2), 117 (50), 95 (100), 75 (2), 67 (11); Anal. Calcd for $\text{C}_{10}\text{H}_6\text{F}_2\text{O}_3$: C, 56.61; H, 2.85; Found: C, 56.81; H, 3.10.

Methyl 5-(1,1-Difluoro-2-oxo-2-phenylethyl)furan-2-carboxylate (13f).

(189 mg, 61% based on **10d**) Colorless liquid: IR (neat) $1736, 1700\text{ cm}^{-1}$; ^1H NMR δ 3.89 (s, 6H), 6.83-6.85 (m, 1H), 6.96 (d, J = 9.0 Hz, 2H), 7.19-7.21 (m, 1H), 8.11 (d, J = 9.0 Hz, 2H); ^{19}F NMR δ 63.5 (s, 2F); MS m/z , 310 (M^+ , 1), 135 (100), 107 (9), 92 (11), 77 (21); Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}_5$: C, 58.07; H, 3.90; Found: C, 57.74; H, 4.02.

2,2-Difluoro-1-(4-methoxyphenyl)-2-[*N*-(toluene-4-sulfonyl)-2-pyrrolyl]ethan-1-one (14).

(271 mg, 67% based on **10d**) Colorless oil: IR (neat) 1698 cm^{-1} ; ^1H NMR δ 2.39 (s, 3H), 3.88 (s, 3H), 6.32 (t, J = 3.8, 1H), 6.67-6.70 (m, 1H), 6.92-6.99 (m, 2H), 7.26-7.30 (m, 2H), 7.35-7.39 (m, 1H), 7.72 (d, J = 8.4, 2H), 8.05-8.09 (m, 2H); ^{19}F NMR δ

71.6 (s); Anal. Calcd for $C_{20}H_{17}F_2NO_4S$: C, 59.25; H, 4.23; N, 3.45; Found: C, 58.91; H, 4.33; N, 3.48.

2,2-Difluoro-1-(4-methoxyphenyl)-2-thienylethan-1-one (15).

(212 mg, 84% based on **10d**) Colorless oil: IR (neat) 1696 cm^{-1} ; ^1H NMR δ 3.86 (s, 3H), 6.89-6.96 (m, 2H), 7.00-7.06 (m, 1H), 7.28-7.38 (m, 1H), 7.48-7.51 (m, 1H), 8.07 (d, $J = 9.0\text{ Hz}$, 2H); ^{19}F NMR δ 75.7 (s, 2F); Anal. Calcd for $C_{15}H_{10}F_2O_2S$: C, 58.20; H, 3.76; Found: C, 57.91; H, 3.93.

2-(3-Benzo[b]furyl)-2,2-difluoro-1-(4-methoxyphenyl)ethan-1-one (16).

(151 mg, 50% based on **10d**) Colorless oil: IR (neat) 1698 cm^{-1} ; ^1H NMR δ 3.86 (s, 3H), 6.90-6.95 (m, 2H), 7.11-7.13 (m, 1H), 7.24-7.29 (m, 1H), 7.33-7.38 (m, 1H), 7.61 (d, $J = 8.6\text{ Hz}$, 1H), 8.12 (d, $J = 9.0\text{ Hz}$, 2H); ^{19}F NMR δ 63.0 (s, 2F); MS m/z (%) 302 (M^+ , 1), 167 (4), 135 (100), 119 (1), 107 (13), 92 (15), 77 (23); Anal. Calcd for $C_{17}H_{12}F_2O_3$: C, 67.55; H, 4.00; Found: C, 67.55; H, 3.78.

Typical procedure for the cross-coupling of 10d with alcohols

Difluoroenol silyl ether **10d** (1.0 mmol) in MeCN (10 mL) was added dropwise to the solution of a mixture of $\text{Cu}(\text{OTf})_2$ (773 mg, 2.1 mmol) in MeCN (10 mL) and alcohol (2 mL) for 3 h under an argon atmosphere. After evaporation of solvent, the residue was purified by silica gel column chromatography (hexane : diethyl ether = 9 : 1) to give **17a** and **17b**.

2,2-Difluoro-2-methoxy-1-(4-methoxyphenyl)ethan-1-one (17a).

(173 mg, 80% based on **10d**) Colorless oil: IR (neat) 1706 cm^{-1} ; ^1H NMR δ 3.77 (s, 3H), 3.89 (s, 3H), 6.96 (d, $J = 8.6\text{ Hz}$, 2H), 8.08 (d, $J = 8.6\text{ Hz}$, 2H); ^{19}F NMR δ 82.1 (s, 2F); MS m/z (%) 216 (M^+ , 1), 135 (100), 107 (12), 92 (14), 77 (22); Anal. Calcd for $C_{10}H_{10}F_2O_3$: C, 55.56; H, 4.66; Found: C, 55.68; H, 4.44.

2,2-Difluoro-2-isopropoxy-1-(4-methoxyphenyl)ethan-1-one (17b).

(173 mg, 73% based on **10d**) Colorless oil: IR (neat) 1700 cm^{-1} ; ^1H NMR δ 1.41 (d, $J = 6.3\text{ Hz}$, 6H), 3.90 (s, 3H), 4.81 (sept, $J = 6.3\text{ Hz}$, 1H), 6.96 (d, $J = 7.5\text{ Hz}$, 2H), 8.10 (d, $J = 7.5\text{ Hz}$, 2H); ^{19}F NMR δ 86.0 (s, 2F); MS m/z (%) 244 (M^+ , 1), 135 (100), 107 (6), 92 (7), 77 (12); Anal. Calcd for $C_{12}H_{14}F_2O_3$: C, 59.01; H, 5.78; Found: C, 58.68; H, 5.79.

2,2-Difluoro-2-(trifluoromethanesulfonyloxy)-1-phenylethan-1-one (17c). To a mixture of Cu(OTf)₂ (868 mg, 2.4 mmol) in *i*-PrCN (1 mL) was added difluoroenol silyl ether **10a** (456 mg, 2.0 mmol) at 0 °C under an argon atmosphere. After stirring for additional 15 min, the reaction was quenched with water. The reaction mixture was extracted with Et₂O, and the organic phase was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. Bulb-to-bulb distillation (130 °C/0.2 mmHg) gave **17c** (401 mg, 1.32 mmol, 66%) as a colorless oil: IR (neat) 1728, 1602, 1446, 1228 cm⁻¹; ¹H NMR δ 7.54-7.62 (m, 2 H), 7.71-7.80 (m, 1 H), 8.08 (d, *J* = 7.4 Hz, 2 H); ¹⁹F NMR δ 87.7 (s, 3 F), 92.5 (s, 2 F); MS *m/z* (%) 304 (M⁺, 1), 235 (1), 154 (1), 133 (1), 105 (100), 77 (69). Anal. Calcd for C₉H₅F₅O₄S: C, 35.54; H, 1.66. Found: C, 35.74; H, 1.87.