meta-Selective C-H Difluoromethylation of Various Arenes with a Versatile Ruthenium Catalyst

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- 1. **Reagents:** Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Column chromatography purifications were performed using 200–300 mesh silica gel.
- 2. Instruments: NMR spectra were recorded on Varian Inova-400 MHz, Inova-300 MHz, Bruker DRX-400 or Bruker DRX-500 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br = broad singlet, m = multiplet. HRMS analysis were carried out using a Bruker micrOTOF-Q instrument or a TOF-MS instrument.
- **3.** The procedures for preparation of 4,4-dimethyl-2-aryl-4,5-dihydrooxazole and its derivatives were according to previous reports^[1].
- 4. Table S1: Optimization for Ruthenium(II) -catalyzed meta C-H bond difluoroacetylation.

	K_2CO_3 (300 mmol %)				
	[∕] ∧ → BrC	F ₂ CO ₂ Et <u>DCE, 120 °C, 48 h</u>	, Ar R _f	N N	
	3	equiv			
MeO			MeO'		
Entry	Add.	Cat.	Silver Salt	Yilde(%)	
1 ^[a]	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	-	35	
2[^{b]}	MesCOOH	[RuCl ₂ (p-cymene)] ₂	-	32	
3	Piv-OH	[RuCl ₂ (p-cymene)] ₂	-	33	
4	Piv-Va l- OH	[RuCl ₂ (p-cymene)] ₂	-	25	
5	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	$AgBF_4$	47	
6	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	$AgSbF_6$	43	
7	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	AgNTf ₂	60	
8 ^[c]	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	AgNTf ₂	80	
9	1-Ad-OH	Cu ₂ O	AgNTf ₂	<5	
10	1-Ad-OH	Ni(acac) ₂ · 2H ₂ O	AgNTf ₂	<5	
11	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	no	21	
		/Cul/phenanthroline			
12	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	AgNTf ₂	14	
/Ni(NO ₃) ₂ 6H ₂ O /phenanthroline					
13	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	AgNTf ₂	25	
		/Pd(PPh ₃) ₄ /Xantphos			
14	1-Ad-OH	[RuCl ₂ (p-cymene)] ₂	AgNTf ₂	28	
		/Co(acac) ₂ · 2H ₂ O			

[a] 2-phenyl-4,5-dihydrooxazole instead of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole.[b] 4-methyl-2-phenyl-4,5-dihydrooxazole instead of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole.

[c] 150°C.

5. Procedures for preparation 3.



A mixture of **1** (0.2 mmol, 1.0 equiv), BrCF₂CO₂Et (80 μ L, 121.2 mg, 3 equiv), [RuCl₂(p-cymene)]₂ (6 mg, 0.05 mol %), K₂CO₃ (81.6 mg, 300 mol %), 1-Ad-OH (10.8 mg, 30 mol %), AgNTf₂ (14.4 mg, 20 mol %) and DCE (1 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 150 °C for 48 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE/EA/Et₃N = 100:10:1) on silica gel to give the product **3**.



3a

Yellow oil. Isolated yield: 50.9mg 78%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.22 (s, 1H), 8.06 (d, J = 8.6 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 4.31 (dd, J = 14.1, 7.1 Hz, 2H), 4.10 (s, 2H), 3.85 (s, 3H), 1.37 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 163.90 (t, $J_{C-F} = 33.9$ Hz), 161.32, 159.02 (t, $J_{C-F} = 4.8$ Hz), 132.78, 127.03 (t, $J_{C-F} = 7.6$ Hz), 122.14 (t, $J_{C-F} = 24.4$ Hz), 120.89, 111.96 (t, $J_{C-F} = 248.0$ Hz), 111.09, 67.79, 62.88, 56.09, 28.53, 14.07.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -103.24.

HRMS Calcd for C₁₆H₁₉F₂NO₄ [M+H⁺]: 328.1360; Found: 328.1367.



3b

Yellow oil. Isolated yield: 40.9 mg 58%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.17 (d, J = 1.9 Hz, 1H), 7.97 (dd, J = 8.5, 1.8 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 4.10 (s, 2H), 1.41 (s, 9H), 1.38 (s, 6H), 1.31 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 164.63 (t, J_{C-F} = 35.0 Hz), 161.20, 152.59, 130.95 (t, J_{C-F} = 23.8 Hz), 130.29, 129.02 (t, J_{C-F} = 12.1 Hz), 128.85, 125.88, 115.10 (t, J_{C-F} = 251.8 Hz), 79.31, 67.88, 63.41, 37.08, 32.13 (t, J_{C-F} = 4.0 Hz), 28.52, 13.93.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -90.90.

HRMS Calcd for C₁₉H₂₅F₂NO₃ [M+H⁺]: 354.1881; Found: 354.1892.



Colorless oil. Isolated yield: 38.5 mg 62%. ¹**H NMR** (400 MHz, CDCl₃) δ 8.14 (d, J = 1.5 Hz, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.27 (d, J = 6.9 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.11 (s, 3H), 2.44 (s, 3H), 1.38 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H). ¹³**C NMR** (101 MHz, CDCl₃) δ 164.03 (t, $J_{C-F} = 35.0$ Hz), 161.40, 139.90, 132.09, 131.54 (t, $J_{C-F} = 23.7$ Hz), 130.58, 126.21 (t, $J_{C-F} = 8.5$ Hz), 113.87 (t, $J_{C-F} = 252.1$ Hz), 79.35, 67.88, 63.37, 28.53, 19.88, 14.02. ¹⁹**F** NMR (376 MHz, CDCl₃) δ -103.14. HRMS Calcd for $C_{16}H_{19}F_2NO_3$ [M+H⁺]: 312.1411; Found: 312.1419.



3d

Yellow oil. Isolated yield: 33.8 mg 45%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.31 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 8.3, 1.9 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 4.14 (s, 2H), 1.39 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.66, 160.61, 131.78, 130.82, 127.48 (t, $J_{C-F} = 8.6$ Hz), 100.13, 79.62, 68.17, 63.59, 28.50, 13.96.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -102.48.

HRMS Calcd for C₁₅H₁₆BrF₂NO₃ [M+H⁺]: 376.0360; Found: 376.0363.



3e

Yellow oil. Isolated yield: 31.6 mg 48%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.31 (d, J = 2.0 Hz, 1H), 8.01 (dd, J = 8.3, 2.0 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 4.14 (s, 2H), 1.39 (s, 6H), 1.30 (t, J = 7.1 Hz, 3H). ¹³**C** NMR (101 MHz, CDCl₃) δ 162.84, 160.45, 134.79, 131.62, 131.46, 130.66, 127.76 – 126.73 (m), 111.85, 79.47, 68.02, 63.44, 28.36, 13.81. ¹⁹**F** NMR (376 MHz, CDCl₃) δ -102.50. **HRMS** Calcd for C₁₅H₁₆ClF₂NO₃ [M+H⁺]: 332.0865; Found: 332.0871.



3f

Yellow oil. Isolated yield: 29.5 mg 45%.

¹**H** NMR (400 MHz, CDCl₃) δ 7.78 (s, 1H), 7.62 (s, 1H), 7.26 – 7.23 (m, 1H), 4.32 (dd, J = 14.3, 7.1 Hz, 2H), 4.14 (s, 2H), 3.89 (s, 3H), 1.41 (s, 6H), 1.33 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 161.23, 159.82, 134.53, 130.28, 117.75 (t, $J_{C-F} = 6.4$ Hz), 116.26, 115.62, 115.45, 114.87 (t, $J_{C-F} = 6.4$ Hz), 79.44, 68.01, 63.41, 55.93, 28.50, 28.11, 14.03.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -103.24.

HRMS Calcd for C₁₆H₁₉F₂NO₄ [M+H⁺]: 328.1360; Found: 328.1366.



Colorless oil. Isolated yield: 51.8 mg 81%.

¹**H** NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 2.2 Hz, 1H), 7.69 (dd, J = 8.3, 2.0 Hz, 1H), 7.25 (d, J = 9.8 Hz, 2H), 5.50 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 164.09, 156.03, 149.15, 137.00, 133.79, 131.71, 123.82, 119.67 (t, $J_{C-F} = 9.4$ Hz), 113.93, 86.06, 63.30, 59.00, 19.33, 14.73, 14.03. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -101.49.

HRMS Calcd for C₁₆H₁₈F₂N₂O₃ [M+H⁺]: 325.1364; Found: 325.1360.



3h

Colorless oil. Isolated yield: 36.4 mg 53%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.15 (d, J = 2.6 Hz, 1H), 7.82 (dd, J = 8.7, 2.6 Hz, 1H), 7.44 (d, J= 8.7 Hz, 1H), 5.52 (s, 1H), 4.35 (d, J = 7.1 Hz, 2H), 3.95 (s, 3H), 2.27 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 162.45, 155.65, 149.22, 137.29, 131.14, 130.43, 127.76, 123.74, 119.62 (t, *J_{C-F}* = 9.0 Hz), 111.41, 85.89, 76.85, 76.53, 76.21, 62.89, 58.54, 14.09, 13.33.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -102.43.

HRMS Calcd for C₁₅H₁₅ClF₂N₂O₃ [M+H⁺]: 345.0818; Found: 345.0817.



3i

Colorless oil. Isolated yield: 41.8 mg 61%.

¹**H NMR** (400 MHz, CDCl₃) δ 7.99 (d, J = 3.0 Hz, 1H), 7.90 (s, 1H), 7.84 – 7.79 (m, 1H), 7.76 – 7.70 (m, 2H), 7.58 – 7.54 (m, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.31 (td, J = 7.1, 1.6 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 163.87, 142.41, 142.22, 130.26, 127.35 – 127.09 (m), 124.06 (t, $J_{C-F} = 6.0$ Hz), 121.41 (s), 118.86, 116.14 (t, J = 6.6 Hz), 99.58 – 93.25 (m), 63.57, 14.03. ¹⁹F NMR (376 MHz, CDCl₃) δ -103.98.





Colorless oil. Isolated yield: 32.2 mg 50%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.03 (s, 1H), 7.71 (d, J = 7.1 Hz, 2H), 7.65 – 7.52 (m, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 2.60 (s, 3H), 2.50 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 193.41, 163.59 (t, *J*_{C-F} = 34.8 Hz), 143.10, 142.27, 138.91, 134.33 (t, $J_{C-F} = 26.1$ Hz), 129.84, 127.93, 126.79 (t, $J_{C-F} = 6.2$ Hz), 125.82 (t, $J_{C-F} = 6.0$ Hz), 122.79 (t, $J_{C-F} = 6.4$ Hz), 121.43, 112.61 (t, $J_{C-F} = 253.0$ Hz), 63.50, 28.77, 13.90, 12.39.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -103.85.

HRMS Calcd for C₁₆H₁₆F₂N₂O₃ [M+H⁺]: 323.1207; Found: 323.1212.





Yellow oil. Isolated yield: 36.2 mg 58%.

¹**H NMR** (400 MHz, CDCl₃) δ 7.79 – 7.70 (m, 1H), 7.64 – 7.52 (m, 1H), 7.27 – 7.17 (m, 1H), 6.02 (s, 1H), 4.36 (dd, J = 14.3, 7.1 Hz, 2H), 2.30 (d, J = 8.4 Hz, 6H), 1.32 (t, J = 7.2 Hz, 3H). ¹³**C NMR** (101 MHz, CDCl₃) δ 168.59, 149.82, 139.73, 136.45, 129.28, 129.19, 125.68, 123.70 (dd, $J_{C-F} = 7.2$, 4.6 Hz), 117.30, 117.08, 107.69, 63.67, 13.98, 13.62, 12.49. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -102.23 (d, J = 7.5 Hz), -116.59 (dd, J = 5.3, 1.6 Hz). **HRMS** Calcd for C₁₅H₁₅F₃N₂O₂ [M+H⁺]: 312.1086; Found: 312.1091.



Yellow oil. Isolated yield: 34.6 mg 53%.

¹**H NMR** (400 MHz, CDCl₃) δ 7.69 (dd, J = 6.2, 2.5 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.24 – 7.17 (m, 1H), 4.36 (dd, J = 14.3, 7.1 Hz, 2H), 2.23 (d, J = 4.5 Hz, 6H), 1.98 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H).

¹³**C** NMR (101 MHz, CDCl₃) δ 162.96, 149.01, 136.73, 136.28, 129.12, 129.03, 123.54 (t, J_{C-F} = 8.4 Hz), 117.26, 117.04, 114.07, 111.27, 63.64, 13.98, 12.02, 11.08, 8.32.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -102.21 (d, J = 7.5 Hz), -116.57 (dd, J = 5.3, 1.6 Hz).

HRMS Calcd for C₁₆H₁₇F₃N₂O₂ [M+H⁺]: 326.1212; Found: 326.1214.



3n

White solid. Isolated yield: 60.1 mg 74%.

¹**H** NMR (400 MHz, CDCl₃) δ 7.70 – 7.60 (m, 3H), 7.51 – 7.39 (m, 3H), 7.38 – 7.27 (m, 5H), 7.09 (d, J = 6.6 Hz, 2H), 5.46 (s, 2H), 4.43 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ¹³**C** NMR (101 MHz, CDCl₃) δ 164.53 (t, $J_{C\cdot F} = 33.6$ Hz), 155.10, 140.44 (t, $J_{C\cdot F} = 4.4$ Hz), 136.81, 136.13, 130.25, 129.85, 129.61, 129.29, 128.82, 128.08, 126.06, 124.25 – 123.18 (m), 122.55, 119.87 (t, $J_{C\cdot F} = 6.7$ Hz), 115.67, 113.51, 113.18, 63.15, 48.69, 14.11. ¹⁹**F** NMR (376 MHz, CDCl₃) δ -99.94.

HRMS Calcd for $C_{24}H_{20}F_2N_2O_2$ [M+Na⁺]: 429.1391; Found: 429.1391.

6. Procedures for preparation of 5



A mixture of **4** (0.2 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (80µL, 121.2 mg, 3 equiv), $[RuCl_2(p-cymene)]_2$ (6 mg, 0.05 mol %), K_2CO_3 (81.6 mg, 300 mol %), 1-Ad-OH (10.8 mg, 30 mol %) and DCE (4 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 120 °C for 48 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE/EA/Et₃N = 100:10:1) on silica gel to give the product **5**.



Yellow oil. Isolated yield: 41.1 mg 71%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.78 – 8.63 (m, 1H), 8.22 (d, *J* = 1.8 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.83 – 7.65 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.26-7.23 (m, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

¹³**C** NMR (101 MHz, CDCl₃) δ 163.64 (t, J_{C-F} = 35.1 Hz), 155.79, 149.24, 136.80, 136.72 (t, J_{C-F} = 3.1 Hz), 136.39, 131.96, 131.09 (t, J_{C-F} = 23.4 Hz), 128.56, 124.17 (t, J_{C-F} = 9.0 Hz), 121.89, 119.89, 113.65 (t, J_{C-F} = 251.9 Hz), 62.70, 19.01, 13.41.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -101.31.

HRMS Calcd for C₁₆H₁₅F₂NO₂ [M+H⁺]: 292.1149; Found: 292.1159.





Colorless oil. Isolated yield: 37.9 mg 62%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.76 – 8.60 (m, 1H), 8.28 (d, *J* = 2.2 Hz, 1H), 8.15 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.82 – 7.61 (m, 2H), 7.23-7.20 (m, *J* = 6.6, 4.8, 1.6 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 164.12 (t, J_{C-F} = 33.9 Hz), 157.53, 156.28, 149.79, 137.00, 132.27, 131.02, 125.22 (t, J_{C-F} = 7.6 Hz), 122.37, 122.09, 120.13, 112.32, 111.72, 62.86, 56.08, 14.11. ¹⁹F NMR (376 MHz, CDCl₃) δ -102.78.

HRMS Calcd for C₁₆H₁₅F₂NO₃ [M+H⁺]: 308.1098; Found: 308.1105.



5c

Yellow oil. Isolated yield: 39.9 mg 60%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.69 (d, J = 4.8 Hz, 1H), 8.26 (d, J = 1.9 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.78-7.70 (m, 2H), 7.25 – 7.20 (m, 1H), 4.33 (q, J = 7.1 Hz, 2H), 1.45 (s, 9H), 1.31 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 164.86 (t, J_{C-F} = 35.0 Hz), 156.22, 150.07, 149.90, 136.92, 136.85, 131.11 (d, J_{C-F} = 47.0 Hz), 129.26, 128.80, 127.73 (t, J_{C-F} = 11.7 Hz), 122.48, 120.46, 115.48 (t, J_{C-F} = 250.0 Hz), 63.36, 36.79, 32.26 (t, J_{C-F} = 4.1 Hz), 13.97. ¹⁹F NMR (376 MHz, CDCl₃) δ -90.74.

HRMS Calcd for C₁₉H₂₁F₂NO₂ [M+H⁺]: 334.1619; Found: 334.1621.



5d

Yellow oil. Isolated yield: 31.2 mg 44%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.72 (d, *J* = 4.5 Hz, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 8.01 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.83 – 7.72 (m, 3H), 7.31-7.28 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 163.13, 155.40, 150.08, 139.01, 139.01, 137.21, 134.64, 133.37, 130.48, 126.29 (t, J_{C-F} = 9.0 Hz), 123.09, 121.19, 120.60, 63.58, 13.98.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -101.72.

HRMS Calcd for C₁₅H₁₂BrF₂NO₂ [M+H⁺]: 356.0098; Found: 356.0101.





Colorless oil. Isolated yield: 32.2 mg 52%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.74 – 8.64 (m, 1H), 8.38 (d, *J* = 2.1 Hz, 1H), 8.10 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.31-7.26 (m, 1.6 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 163.21 (t, J_{C-F} = 35.0 Hz), 155.32, 150.05, 138.50, 137.19, 132.68 (t, J_{C-F} = 4.3 Hz), 131.68 (t, J_{C-F} = 24.2 Hz), 131.16, 130.39, 125.95 (t, J_{C-F} = 8.6 Hz), 123.03, 120.61, 112.31 (t, J_{C-F} = 249.0 Hz), 63.54, 13.97.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -102.32.

HRMS Calcd for C₁₅H₁₂ClF₂NO₂ [M+H⁺]: 312.0603; Found: 312.0612.



5f

Yellow oil. Isolated yield: 31.6 mg 56%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.76 (dd, *J* = 3.5, 1.3 Hz, 1H), 8.48 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.83 (dd, *J* = 4.9, 1.4 Hz, 2H), 7.34 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 163.27 (t, $J_{C-F} = 140.5$ Hz), 154.80, 150.25, 143.02, 137.29, 129.24, 128.36 (dd, $J_{C-F} = 11.3$, 5.7 Hz), 126.58 (t, $J_{C-F} = 10.3$ Hz), 123.65, 121.12, 112.97 (t, $J_{C-F} = 253.0$ Hz), 63.58, 13.92.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -58.25 (t, J = 11.0 Hz), -98.62 (q, J = 10.9 Hz). HRMS Calcd for C₁₆H₁₂F₅NO₂ [M+H⁺]: 346.0866; Found: 346.0877.



5g

Yellow oil. Isolated yield: 26.1 mg 41%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.77 – 8.72 (m, 1H), 8.50 (d, *J* = 1.6 Hz, 1H), 8.29 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.87 – 7.79 (m, 2H), 7.35-7.26 (m, 1H), 4.38 (dd, *J* = 14.3, 7.1 Hz, 2H), 2.65 (s,3H), 1.35 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 199.54, 176.43, 176.01, 155.19, 150.22, 143.11, 137.24, 130.75, 129.02, 125.89, 125.79, 123.52, 121.22, 100.13, 62.87, 29.85, 28.40, 14.08.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -99.46.

HRMS Calcd for C₁₇H₁₅F₂NO₂ [M+H⁺]: 320.1098; Found: 320.1101.



5h

Colorless oil. Isolated yield: 43.6 mg 75%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.53 (s, 1H), 8.20 (s, 1H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 8.8 Hz, 2H), 7.59-7.53 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 164.33 (t, $J_{C-F} = 35.1$ Hz), 153.63, 150.39, 140.15, 137.58, 133.46 (t, $J_{C-F} = 25.5$ Hz), 132.46, 132.46, 129.38, 129.24, 127.02, 125.69 (t, $J_{C-F} = 6.1$ Hz), 123.81 (t, $J_{C-F} = 6.3$ Hz), 120.26, 113.54 (t, $J_{C-F} = 252.3$ Hz), 63.32, 18.34, 14.03.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -103.69.

HRMS Calcd for C₁₆H₁₅F₂NO₂ [M+H⁺]: 292.1149; Found: 292.1162.



5i

Colorless oil. Isolated yield: 39.5 mg 68%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.56 (d, J = 5.0 Hz, 1H), 8.20 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.57-7.54 (m, 1H), 7.10 (d, J = 4.3 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 164.20 (t, J_{C-F} = 35.2 Hz), 156.07, 149.57, 148.04, 140.15, 133.31 (t, J_{C-F} = 25.6 Hz), 129.53, 129.10, 127.16, 125.77 (t, J_{C-F} = 6.1 Hz), 123.68, 121.64, 113.40 (t, J_{C-F} = 252.3 Hz), 63.20, 21.23, 13.90.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -103.75.

HRMS Calcd for C₁₆H₁₅F₂NO₂ [M+H⁺]: 292.1149; Found: 292.1158.



5j

Colorless oil. Isolated yield: 45.6 mg 82%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.83 (d, J = 4.8 Hz, 2H), 8.74 (s, 1H), 8.59 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 4.8 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 164.29 (t, J_{C-F} = 35.3 Hz), 163.76, 157.49, 138.35, 133.54 (t, J_{C-F} = 25.7 Hz), 130.73, 129.15, 128.54, 127.80 (t, J_{C-F} = 6.0 Hz), 125.51 (t, J_{C-F} = 6.3 Hz), 119.74, 113.50 (t, J_{C-F} = 252.3 Hz), 63.33, 14.04.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -103.60.

HRMS Calcd for C₁₄H₁₂F₂N₂O₂ [M+H⁺]: 279.0945; Found: 279.0948.



White solid. Isolated yield: 46.7 mg 80%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.80 (d, J = 4.8 Hz, 2H), 8.70 (d, J = 1.6 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 4.8 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 164.19 – 163.17 (m), 156.80, 138.76, 135.13, 131.84, 131.10 (t, $J_{C-F} = 23.5$ Hz), 129.74, 125.63 (t, $J_{C-F} = 9.1$ Hz), 118.81, 113.65 (t, $J_{C-F} = 251.9$ Hz), 62.69, 19.22, 13.42.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -101.14.

HRMS Calcd for C₁₅H₁₄F₂N₂O₂ [M+H⁺]: 293.1102; Found: 293.1156.



Colorless oil. Isolated yield: 43.1 mg 70%.

¹**H** NMR (400 MHz, \dot{CDCl}_3) δ 8.89 – 8.74 (m, 3H), 8.64 (d, J = 8.6 Hz, 1H), 7.21 (s, 1H), 7.06 (d, J = 8.6 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 164.05 (t, $J_{C-F} = 34.0$ Hz), 163.34, 159.21, 157.42, 132.75, 129.73, 127.15 (t, $J_{C-F} = 7.8$ Hz), 122.47 (t, $J_{C-F} = 24.2$ Hz), 119.04, 112.21 (t, $J_{C-F} = 247.0$ Hz)), 111.49, 62.87, 56.15, 14.10.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -102.92.

HRMS Calcd for C₁₅H₁₄F₂N₂O₃ [M+H⁺]: 309.1051; Found: 309.1044.





Yellow oil. Isolated yield: 40.0 mg 58%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.97 (s, 1H), 8.87 (d, J = 4.8 Hz, 2H), 8.72 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 7.30 (t, J = 4.8 Hz, 1H), 4.34 (q, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 162.53, 157.64, 141.23, 130.50, 128.22 (q, J_{C-F} = 17.0 Hz), 127.93 (t, J_{C-F} = 10.4 Hz), 124.89, 120.42, 112.97, 102.27, 100.13, 63.56, 13.92.

¹⁹**F** NMR (376 MHz, CDCl₃) δ -58.40 (t, J = 11.1 Hz), -98.55 (q, J = 11.1 Hz).

HRMS Calcd for C₁₅H₁₁F₅N₂O₂ [M+H⁺]: 347.0819; Found: 347.0830.



5n

White solid. Isolated yield: 35.9 mg 55%.

¹**H** NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 8.7 Hz, 1H), 8.21 (dd, J = 5.3, 3.3 Hz, 2H), 8.14 (d, J = 7.2 Hz, 1H), 7.98 (t, J = 9.0 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.56 – 7.50 (m, 1H), 7.49-7.45 (m, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 156.77, 138.52, 136.98, 130.62, 130.08, 128.97, 127.80, 127.44 – 127.23 (m), 127.17, 125.64, 119.07, 100.13, 62.76, 13.87.

¹⁹F NMR (376 MHz, CDCl₃) δ -101.91. HRMS Calcd for $C_{19}H_{15}F_2NO_2$ [M+H⁺]: 328.1149; Found: 328.1148.

7. X-ray of 5k.

X–Ray Data for Complex 5k: Intensity data were collected with a Rigaku Mercury CCD area detector in ω scan mode using Mo Karadiation ($\lambda = 0.71070$ Å). The diffracted intensities were corrected for Lorentz polarization effects and empirical absorption corrections. Details of the intensity data collection and crystal data are given in Table 2. The structures were solved by direct methods and refined by fullmatrix least–squares procedures based on |F|2. All the non–hydrogen atoms were refined anisotropically. All the H atoms were held stationaryand included in the structure factor calculation in the final stage of full–matrix least–squares refinement. The structures were solved and refinedusing OLEX-2 programs.



Empirical formula	C15 H14 F2 N2 O2		
	202 28		
	292.28		
Temperature	296(2) K		
Wavelength	0.71073 A		
Crystal system, space group	monoclinic		
Unit cell dimensions	a = 11.8627(7) A alpha = 90 deg		
	b = 7.5770(4) A beta = 104.622(2) deg		
	c = 16.1929(9) A gamma = 90 deg		
Volume	1408.34(14) A^3		
Z, Calculated density	4 Mg/m^3		
Absorption coefficient	0.110 mm^-1		
F(000)	608		
Crystal size	0.30 x 0.20 x 0.10 mm		
Thata range for data collection	2.45 to 27.36 deg		
Limiting indices	-15<=h<=15, -9<=k<=9, -20<=l<=21		
Reflections collected / unique	3227 / 2339		
Completeness to theta $= 25.00$	99.4 %		
Absorption correction	Semi-empirical from equivalents		
Max. and min. transmission	0.989 and 0.974		
Refinement method	Full-matrix least-squares on F ²		
Data / restraints / parameters	3227 / 0 / 190		
Goodness-of-fit on F^2	1.454		
Final R indices [I>2sigma(I)]	R1 = 0.0779, wR2 = 0.2025		
R indices (all data)	R2 = 0.0558, wR2 = 0.1898		
Largest diff. peak and hole	0.257 and -0.257 e.A^-3		

8. Secondary C-H functionalizations.

8.1 Preparation of 6a.^[2]



A mixture of **51** (0.2 mmol, 1.0 equiv), $PhI(OAc)_2$ (96.6 mg, 1.5 equiv), $Pd(OAc)_2$ (2 mg, 0.05 mol %), AcOH (0.5 mL) and AcO₂ (0.5mL) in a 15 mL glass vial sealed was heated at 120 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE:EA / 5:1) on silica gel to give the product **7a**.



7a

Colorless oil. Isolated yield: 52.5 mg 75%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.85 – 8.74 (m, 3H), 7.24 – 7.21 (m, 1H), 7.11 (d, *J* = 1.1 Hz, 1H), 4.50 – 4.44 (m, 2H), 2.67 (d, *J* = 1.6 Hz, 3H), 2.35 (d, *J* = 2.2 Hz, 3H), 1.44 (td, *J* = 7.1, 2.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 187.63, 169.61, 164.26, 162.55, 157.15, 153.08, 145.63, 136.65, 129.63, 128.29, 128.13, 119.49, 62.56, 21.51, 21.31, 14.24, 1.17.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -100.72.

HRMS Calcd for C₁₇H₁₆F₂N₂O₄ [M+H⁺]: 351.1156; Found: 356.1151.

8.2 Preparation of 7b.^[3]



A mixture of **3g** (0.2 mmol, 1.0 equiv), $[Cp*RhCl_2]_2$ (1.0 mg, 1 mol %), $Cu(NO_3)_2$ H2O (144 mg, 3 equiv) and DMF (0.5 mL) in a 15 mL glass vial sealed was heated at 60 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE:EA / 5:1) on silica gel to give the product **7b**.



7b

Colorless oil. Isolated yield: 65.0 mg 77%.

¹**H** NMR (400 MHz, CDCl₃) δ 7.62 (s, 1H), 7.53 (s, 1H), 7.48 (d, J = 16.1 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 5.50 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.45 (s, 3H), 2.27 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H).

¹³**C NMR** (101 MHz, CDCl₃) δ 166.53, 163.63 (t, J_{C-F} = 30.9 Hz), 156.77, 149.91, 139.43, 135.20 (t, J_{C-F} = 156.5 Hz), 133.17 (t, J_{C-F} = 24.0 Hz), 130.42, 126.33 (t, J_{C-F} = 9.1 Hz), 121.36, 113.40, 85.26, 63.51, 60.72, 58.90, 19.62, 14.75, 14.38, 14.00.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -101.75.

HRMS Calcd for C₂₁H₂₄F₂N₂O₆ [M+H⁺]: 423.1732; Found: 423.1738.

9. Removal directing group of 3c.^[4]



The procedure of removal the directing group was according to a known article^[2]. A mixture of **3c** (0.2 mmol, 1.0 equiv), HCl (6M, 1mL) in a 15 mL glass vial sealed was heated at 100 °C for 12 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE:EA / 5:1) on silica gel to give the product **8** (36.6 mg 71%).



Yellow oil. Isolated yield: 36.6 mg 71%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.26 (d, *J* = 1.6 Hz, 1H), 8.05 (t, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 3H), 3.86 (s, 3H), 2.46 (t, *J* = 1.9 Hz, 3H).

¹³**C NMR** (101 MHz, CDCl₃) δ 167.85, 166.33, 164.39, 142.03 (t, J_{C-F} = 3.0 Hz), 132.32, 131.98, 128.41, 127.68 (t, J_{C-F} = 9.1 Hz), 113.82 (t, J_{C-F} = 252.9 Hz), 53.88, 52.41, 20.01 (d, J_{C-F} = 2.8 Hz).

¹⁹**F NMR** (376 MHz, CDCl₃) δ -101.46.

HRMS Calcd for C₁₂H₁₂F₂O₄ [M+H⁺]: 259.0782; Found: 259.0788.

10. Transformations of α-aryl-α,α difluoroacetates.

10.1 Preparation of 9a.^[5]



In a 15 mL glass vial, a mixture of **5a** (0.2 mmol, 1 equiv), MeOH (30 mL) and 1 M K_2CO_3 aq. (30 mL) and stirred for 6h at 60 °C. The reaction was then poured into 1 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (100 mL), washed with water (100 mL), dried over Na_2SO_4 and concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=2/1 as the eluent.



White solid. Isolated yield: 43.8 mg, 88%.

¹**H NMR** (400 MHz, DMSO) δ 8.74 (d, *J* = 4.2 Hz, 1H), 8.28 – 8.21 (m, 2H), 8.13 – 8.07 (m, 2H), 7.76 – 7.66 (m, 2H), 7.61 – 7.51 (m, 1H).

¹³**C NMR** (101 MHz, DMSO) δ 153.50, 148.05, 139.67, 137.43, 133.47 (t, J_{C-F} = 25.5 Hz), 129.77, 127.58, 126.28 (t, J_{C-F} = 5.5 Hz), 125.75 (t, J_{C-F} = 6.1 Hz), 123.93, 123.44 (t, J_{C-F} = 6.2 Hz), 121.81, 113.41.

HRMS Calcd for C₁₃H₉F₂NO₂ [M+H⁺]: 250.0680; Found: 250.0686.

10.2 Preparation of 9b.^[5]



In a 15 mL glass vial, a mixture of **8a** (0.2 mmol, 1 equiv), AgNO₃ (6.8mg, 20 mol %), Selectflour (140 mg, 2 equiv), aceton (1 mL) and H₂O (1 mL) stirred for 1h at 55 °C. The reaction was concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=10/1 as the eluent.



-S16-

Colorless oil. Isolated yield: 23.6 mg, 53%. ¹H NMR (400 MHz, CDCl₃) δ 8.77 – 8.65 (m, 1H), 8.29 (s, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.66 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.8 Hz, 1H), 7.30 – 7.25 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 155.93, 150.01, 140.24, 137.11, 131.31 (q, J_{C-F} = 32.3 Hz), 130.16 (d, J_{C-F} = 0.8 Hz), 129.33, 125.64 (q, J_{C-F} = 3.8 Hz), 123.91 (q, J_{C-F} = 3.8 Hz), 122.94, 120.69. ¹⁹F NMR (376 MHz, CDCl₃) δ -62.58. HRMS Calcd for C₁₂H₈F₃N [M+H⁺]: 224.0687; Found: 224.0695.

10.3 Preparation of 8c.^[6]



In a 15 mL glass vial, a mixture of **5a** (0.2 mmol, 1 equiv), NaBH₄ (15 equiv), EtOH (2 mL) and stirred for 3h at room temperature. The reaction was then poured into 1 M HCl aq. to acidify to pH 1, and the aqueous phase was extracted with EtOAc (100 mL), washed with water (100 mL), dried over Na₂SO₄ and concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=2/1 as the eluent.



9c

Colorless oil. Isolated yield: 34.7 mg, 74%.

¹**H NMR** (400 MHz, CDCl₃) δ 8.82 – 8.58 (m, 1H), 8.14 (s, 1H), 8.09 – 7.99 (m, 1H), 7.81 – 7.73 (m, 2H), 7.69 – 7.48 (m, 2H), 7.34 – 7.25 (m, 1H), 4.02 (t, J = 13.3 Hz, 2H), 2.71 (s, 1H). ¹³**C NMR** (101 MHz, CDCl₃) δ 156.64, 149.86, 139.90, 137.18, 135.27 (t, $J_{C-F} = 25.8$ Hz),

129.17, 128.87, 127.22, 126.16 (t, $J_{C-F} = 6.1$ Hz), 124.38 (t, $J_{C-F} = 6.2$ Hz), 122.77, 120.99, 120.78 (t, $J_{C-F} = 242.0$ Hz), 66.02 (t, $J_{C-F} = 32.6$ Hz).

¹⁹**F NMR** (376 MHz, CDCl₃) δ -106.67.

HRMS Calcd for C₁₃H₁₁F₂NO [M+H⁺]: 236.0887; Found: 236.0896.

10.4 Preparation of 9d.^[7]



In a 15 mL glass vial, a mixture of **5a** (0.2 mmol, 1 equiv) and NH₃ (2M in MeOH, 2 mL) stirred for 3h at 60 °C. The reaction was then extracted with EtOAc (100mL), washed with water (100 mL), dried over Na₂SO₄ and concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=2/1 as the eluent.



White solid. Isolated yield: 46.1 mg, 93%. ¹**H** NMR (400 MHz, CDCl₃) δ 8.94 – 8.62 (m, 1H), 8.25 (s, 1H), 8.08 (t, J = 8.4 Hz, 1H), 7.84 – 7.63 (m, 3H), 7.55 (t, J = 7.3 Hz, 1H), 7.26 (s, 1H), 6.74 – 6.41 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 166.40 (t, $J_{C-F} = 36.6$ Hz), 156.30, 149.90, 140.05, 137.12, 129.53, 129.30, 127.27, 126.11 (t, $J_{C-F} = 5.4$ Hz), 124.16 (t, $J_{C-F} = 6.7$ Hz), 122.84, 120.90, 114.73 (t, $J_{C-F} = 234.50$ Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -102.92. HRMS Calcd for C₁₃H₁₀F₂N₂O [M+H⁺]: 249.0839; Found: 249.0848.

10.5 Preparation of 9e.



In a 15 mL glass vial, a mixture of **5a** (0.2 mmol, 1 equiv) and morphpline (1 mL) stirred for 6h at 60 °C. The reaction was then poured into saturated NH₄Cl solution, and the aqueous phase was extracted with EtOAc (100 mL), washed with water (100 mL), dried over Na₂SO₄ and concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=2/1 as the eluent.



9e

Colorless oil. Isolated yield: 48.9 mg, 77%. ¹**H NMR** (400 MHz, CDCl₃) δ 8.74 – 8.63 (m, 1H), 8.22 (d, J = 0.7 Hz, 1H), 8.17 – 8.10 (m, 1H), 7.84 – 7.69 (m, 2H), 7.58 (d, J = 5.1 Hz, 2H), 7.28 – 7.25 (m, 1H), 3.71 (s, 4H), 3.51 (s, 4H). ¹³**C NMR** (101 MHz, CDCl₃) δ 162.17 (t, $J_{C-F} = 30.2$ Hz), 156.08, 149.97, 140.30, 137.05, 130 (m, 14), 140 (m, 14), 140 (m, 14), 150 (m

134.17 (t, J_{C-F} = 24.9 Hz), 129.41, 127.46, 125.70 (t, J_{C-F} = 5.6 Hz), 123.82 (t, J_{C-F} = 5.8 Hz), 122.86, 120.73, 115.72 (t, J_{C-F} = 251.1 Hz), 66.80, 66.48, 46.81, 43.63. ¹⁹**F NMR** (376 MHz, CDCl₃) δ -94.50.

HRMS Calcd for C₁₇H₁₆F₂N₂O₂ [M+H⁺]: 319.1258; Found: 319.1263.

10.6 Preparation of 9f.^[8]



In a 15 mL glass vial, a mixture of **5a** (0.2 mmol, 1 equiv), benzyl alcohol (62.6 μ L, 3 equiv) and BF₃.Et₂O (2.5 μ L, 10 mol %) stirred for 12h at 75 °C under nitrogen atmosphere. The reaction was then quenched with saturated aqueous NaHCO₃, and then diluted with EtOAc (100 mL). The organic phase was washed with water (100 mL), dried over Na₂SO₄ and concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=5/1 as the eluent.



Yellow oil. Isolated yield: 57.6 mg, 85%. ¹H NMR (400 MHz, CDCl₃) δ 8.79 – 8.58 (m, 1H), 8.20 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.80 – 7.73 (m, 1H), 7.70 (dd, J = 8.1, 4.6 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.40 – 7.26 (m, 6H), 5.28 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 164.10 (t, J_{C-F} = 35.7 Hz), 156.23, 149.91, 140.08, 137.12, 134.38, 129.70, 129.34, 128.80, 128.35, 127.32, 126.07 (t, J_{C-F} = 6.2 Hz), 124.18 (t, J_{C-F} = 6.2 Hz), 122.84, 120.84, 113.54, 68.62. ¹⁹F NMR (376 MHz, CDCl₃) δ -103.65. HRMS Calcd for C₂₀H₁₅F₂NO₂ [M+H⁺]: 339.1071; Found: 339.1075.

11. Preparation of 6a and 6b.



In a 50 mL round-bottomed flask, a mixture of (1mmol, 1 equiv), (chloromethyl)benzene (0.315 g, 2.5 equiv) and dry DMF (10 mL) stirred for 12h at room temperature. The reaction was then quenched with saturated aqueous NH₄Cl, and then diluted with EtOAc (100 mL). The organic phase was washed with water (100 mL), dried over Na_2SO_4 and concentrated in vacuo. Products were purified by flash chromatography on silica gel with PE/EA=1/8 as the eluent.



6a

White solid. Isolated yield: 325.9 mg, 51%.

¹**H** NMR (400 MHz, CDCl₃) δ 7.50 – 7.20 (m, 16H), 7.03 – 6.67 (m, 2H), 5.10 (s, 2H), 4.70 (s, 2H), 4.12 (t, *J* = 6.7 Hz, 2H), 3.78 (s, 3H), 3.68 – 3.49 (m, 2H), 3.34 (t, *J* = 6.7 Hz, 2H), 2.55 (dd, *J* = 7.9, 3.2 Hz, 2H), 2.03 – 1.81 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 170.22, 163.64, 159.63, 157.53, 142.30, 141.42, 140.15, 137.48, 137.08, 132.71, 132.37, 128.76, 128.74, 128.49, 127.78, 127.64, 127.57, 126.85, 126.62, 126.26, 113.67, 55.59, 51.71, 51.28, 51.22, 48.26, 32.96, 23.63, 21.83, 21.53. **HRMS** Calcd for $C_{39}H_{37}N_5O_4$ [M+H⁺]: 640.2924; Found: 640.2929.



A mixture of **64** (0.05 mmol, 1.0 equiv), BrCF₂CO₂Et (20 μ L, 30.3 mg, 3 equiv), [RuCl₂(p-cymene)]₂ (3 mg, 0.10 mol %), K₂CO₃ (20.4 mg, 300 mol %), 1-Ad-OH (2.7 mg, 30 mol %), AgNTf₂ (3.6 mg, 20 mol %)and DCE (0.5 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 150 °C for 96 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (PE/EA = 8/1) on silica gel to give the product **6b**.



White solid. Isolated yield: 16.3 mg, 43%.

¹**H** NMR (400 MHz, CDCl₃) δ 7.71 (d, J = 2.5 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.40 – 7.24 (m, 14H), 6.88 (d, J = 9.0 Hz, 1H), 5.07 (s, 2H), 4.73 (s, 2H), 4.29 (dd, J = 14.2, 7.0 Hz, 2H), 4.12 (t, J = 6.5 Hz, 2H), 3.79 (s, 3H), 3.68 – 3.55 (m, 2H), 3.34 (t, J = 6.6 Hz, 2H), 2.56 (t, J = 5.4 Hz, 2H), 1.99 – 1.89 (m, 4H), 0.88 (t, J = 6.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ 170.26, 163.54, 157.44, 140.10, 137.35, 137.06, 132.67, 129.55, 128.89, 128.83, 128.81, 128.54, 127.96, 127.64, 127.57, 126.96, 126.34, 110.96, 62.89, 56.20, 51.74, 51.34, 48.57, 33.01, 32.08, 23.68, 22.85, 21.58, 14.09.

¹⁹**F NMR** (376 MHz, CDCl₃) δ -102.69.

HRMS Calcd for C₃₉H₃₇N₅O₄ [M+H⁺]: 761.3025; Found: 761.3030.

12. Preparation of complex I.^[9]

To an oven-dried, purged with argon Schlenk tube (screw type) was added under argon $[RuCl(\mu-Cl)(pcymene)]_2$ (305 mg, 0.5 mmol) to CH_3CN (5 mL) followed by 2-phenylpyridine (143 μ L, 0.98 mmol) and KOAc (147 mg, 1.5 mmol). The Schlenk tube was then screwed closed. The reaction mixture was stirred at room temperature for 24h. The reaction mixture was purified through neutral alumina and eluted with EtOAc (100 %).



Orange solid. Isolated yield: 186.6 mg, 40%.

¹**H** NMR (400 MHz, DMSO) δ 9.40 – 9.32 (m, 1H), 8.19 – 8.07 (m, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.78 (m, 1H), 7.72 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.08 – 7.04 (m, 1H), 7.01 – 6.88 (m, 1H), 5.75 (d, *J* = 5.8 Hz, 1H), 5.68 (d, *J* = 5.7 Hz, 1H), 5.42 (d, *J* = 5.8 Hz, 1H), 5.16 (d, *J* = 5.8 Hz, 1H), 2.27 (q, *J* = 6.5 Hz, 1H), 1.93 (s, 2H), 0.85 (d, *J* = 6.9 Hz, 2H), 0.77 (d, *J* = 6.9 Hz, 2H).

¹³C NMR (101 MHz, DMSO) δ 182.37, 164.99, 155.94, 144.21, 140.39, 137.53, 128.64, 123.96, 122.19, 122.08, 118.98, 101.00, 99.23, 91.30, 89.57, 85.02, 82.34, 30.75, 22.61, 21.80, 18.77.

13. Non-reactive substrates

We tried the following substrates. The results are not satisfactory.



Scheme 1S: Non-reactive substrates.

14. Kinetic isotope effect studies.



Scheme 2S: Kinetic isotope effect studies.

To a stirred solution of substrate 1a or [D5]-1a (0.2 mmol) BrCF₂CO₂Et (80 μ L, 121.2 mg, 3 equiv), [RuCl₂(p-cymene)]₂ (6 mg, 0.05 mol %), K₂CO₃ (81.6 mg, 300 mol %), 1-Ad-OH (10.8 mg, 30 mol %) and DCE (4 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 150 °C. GC analysis using *n*-Tridecane as an internal standard to provide the following conversions.



15. Proposed reaction mechanism.

15.1 The probable active ruthenium species



Complex **I** was prepared and characterized according to the reports of Jutand et al.²⁰ Interestingly, when complex **I** was directly treated with 2 under the standard reaction conditions, **9** was obtained in only 12% yield. These results indicated that the complex **I** might be not the catalyst active species in the reaction. When complex **I** was used instead of $[RuCl_2(p-cymene)]_2$, the difluoromethylated product **5a** was obtained in 56% yield. This result suggests that the heteroaromatic substrates might also act as an internal ligand during the catalytic cycle to generate the active catalyst species (Scheme 5, b, (2)).

Inspired by the previous work of Zhang et al.¹⁸ and the preliminary experiment results, we may can speculat that complex A may have been an active species in the catalytic cycle (Scheme 5, b). However when we tried to isolated this ruthenium intermediate, we failed to isolate this complex.



Complex A





References.

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NMR spectra



¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3a.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3b.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3c.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3d.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3e.





0ct22-2016-h400-y-1883 -1.18 -1.18 -1.18 -1.28 -1.28 -1.28 -1.28 -1.28 141 -12000 -11000 EtO₂C 0 -10000 N -9000 1) 1 MeÓ 3f -8000 -7000 -6000 -5000 -4000 -3000 -2000 -1000 ليا -0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 f1 (ppm) 00.00 7.5 **5** 1.0 0.5 0.0 -0.5 -1.0 --1000 10.5 10.0 9.5 9.0 8.5 8.0 7.0

¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3f.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3g.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3h.






¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3i.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3j.



-S40-



¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 31.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3m.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 3n.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5a.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5b.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5c.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5d.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5e.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5f.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5g.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5h.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5i.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5j.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5k.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 51.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5m.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 5n.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 7a.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 7b.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 8.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 9a.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 9b.








¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 9c.





¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 9d.









¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 9e.





Jan19-2017-h400-c2345 -28000 -26000 -24000 Ň -22000 -20000 II. F O -18000 F 0 -16000 9f -14000 -12000 -10000 -8000 -6000 -4000 -2000 MI ł I -0 000 0 8.5 8.0 7.5 7.0 2.10 ---2000 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 fl (ppm) 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 6.5

¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 9f.





¹H NMR and ¹³C NMR of compound 6a.







¹H NMR, ¹³C NMR and ¹⁹F NMR of compound 6b.





¹H NMR and ¹³C NMR of compound I.

