Synthesis of Benzofurans via Ruthenium-Catalyzed Redox-Neutral C-H Functionalization and Reaction with Alkynes under Mild Conditions

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I. General

NMR spectra were recorded on a Varian Mercury Vx400 spectrometer in solvents as indicated. Chemical shifts (δ) are given in ppm relative to TMS. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl₃: δH = 7.26 ppm, δC = 77.16 ppm; d₆-DMSO: δH = 2.50 ppm, δC = 39.52 ppm). Infrared spectra were obtained on a Bio-Rad FTS-185 instrument. Mass spectra were provided on Agilent 5973 or Agilent 1100 instruments. All melting points were uncorrected. Alkynes were commercially available or synthesized according to known procedure. All other reagents were from commercial sources. No attempts were made to optimize yields for substrate synthesis.

II. Synthesis of substrate 1

General Procedure for the Synthesis of Substrates 1:

\[
\begin{align*}
\text{arylboronic acid} + \text{CuCl/py} &\rightarrow \text{arylboronic acid chloride} \\
\text{DCE} &\rightarrow \text{arylboronic acid chloride}
\end{align*}
\]

\[1) \text{NH}_2\text{NH}_2 \quad \text{MeOH/HCl} \quad 2) \text{R}^2\text{Cl}, \text{Na}_2\text{CO}_3 \quad \text{EtOAc/H}_2\text{O}\]

\[\begin{align*}
R^1 &= \text{H, } R^2 = \text{Piv: } 1\text{a} \\
R^1 &= \text{4-Me, } R^2 = \text{Piv: } 1\text{b} \\
R^1 &= \text{2-Me, } R^2 = \text{Piv: } 1\text{c} \\
R^1 &= \text{3-Me, } R^2 = \text{Piv: } 1\text{d} \\
R^1 &= \text{4-Bu, } R^2 = \text{Piv: } 1\text{e} \\
R^1 &= \text{4-Ph, } R^2 = \text{Piv: } 1\text{f}
\end{align*}\]

\[\begin{align*}
R^1 &= \text{H: } 4\text{a} \\
R^1 &= \text{3-CF}_3: \text{4g} \\
R^1 &= \text{4-Me: } 4\text{b} \\
R^1 &= \text{3,5-difluoro: } 4\text{h} \\
R^1 &= \text{2-Me: } 4\text{c} \\
R^1 &= \text{3,5-dimethyl: } 4\text{i} \\
R^1 &= \text{3-Me: } 4\text{d} \\
R^1 &= \text{4-Bu: } 4\text{e} \\
R^1 &= \text{4-Ph: } 4\text{f}
\end{align*}\]

\[N\text{-aryloxyphthalimides } 4\text{ were prepared following a published procedure}\text{: In a reaction flask, a mixture of } N\text{-hydroxyphthalimide (1 eq), arylboronic acid (2 eq), CuCl (1 eq), freshly activated 4-Å molecular sieves (250 }\text{mg/mmol) and pyridine (1.1 eq) in 1,2-dichloroethane (0.2 M) were stirred at room temperature. The reaction flask was open to atmosphere. After 48 h, the reaction mixture became green as the reaction proceeded. Silica gel was added to the flask and volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel to afford the desired } N\text{-aryloxyphthalimides.}

\[\text{Hydrazine monohydrate (3 eq) was added to the solution of } N\text{-aryloxyphthalimide } 4\text{ (1 eq) in 10\% MeOH in CHCl}_3 (0.1 M). The reaction was allowed to stir at room temperature overnight. The precipitate was filtered off and washed with DCM. The filtrate was concentrated and the resulting oil was passed through a plug of silica gel washing with 30\% EtOAc in Petrol ether. The solvent was then removed under reduce pressure to afford the corresponding } N\text{-aryloxyamine.}\]
*N*-Aryloxyamine (1 eq) was added to a biphasic mixture of Na₂CO₃ (1.2 eq) in a 2:1 mixture of EtOAc:H₂O (0.6 M). The resulting solution was cooled to 0 °C, followed by dropwise addition of pivaloyl chloride (1 eq). After stirring at 0 °C for 2 h, the reaction was quenched with sat. NaHCO₃ and diluted with EtOAc. The organic phase was washed twice with sat. NaHCO₃ after which it was dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude product was purified by recrystallization from EtOAc/PE to give the desired *N*-aryloxypivalamide as colorless crystals.

1a (1 eq) in DMF (0.3 M) was cooled to 0 °C, then NaH (1.5 eq) was added portion wise. After ten minutes, MeI (2.0 eq) was slowly added to the reaction mixture at 0 °C. After stirring at rt overnight, the resulting reaction mixture was quenched with sat. NaHCO₃, diluted with EtOAc, washed with water, dried over Na₂SO₄. The purification was performed by flash column chromatography on silica gel to afford the desired *N*-methyl-*N*-phenoxypivalamide (1n) in the yield of 58%.

Characterization of Compounds 5 and Substrates 1
4a, 4b, 4c, 4d, 4f, 4g, 4h, 4i, 1a, 1j, 1k, 1l are known compounds and all data were in agreement with those reported.

\[
\begin{align*}
\text{Yield } & 60\%; \text{ white solid; m.p. } 117-119 \degree C; \ 
^1\text{H NMR (400 MHz, CDCl}_3) : \delta 7.91-7.89 \ (m, 2H), 7.80-7.78 \ (m, 2H), 7.34 \ (d, J = 9.2 \ Hz, 2H), 7.11 \ (d, J = 9.2 \ Hz, 2H), 1.29 \ (s, 9H); \ 
^13\text{C NMR (100 MHz, CDCl}_3) : \delta 163.1, 156.7, 147.6, 134.9, 128.8, 126.6, 124.0, 114.2, 34.4, 31.5; \ 
\text{IR (neat, cm}^{-1} \text{): } \nu 2967, 2901, 1788, 1733, 1504, 1077, 704; \ 
\text{MS (m/z, EI): } 295, 280, 130, 102, 76; \ 
\text{HRMS calculated for C}_18\text{H}_{17}\text{NO}_3(M^+) : 295.1208; \ 
\text{Found: } 295.1206; \ R_f = 0.6 \ (PE: \text{EtOAc, 3:1}).
\end{align*}
\]
Yield 80%; white solid; m.p. 179-180 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.93-7.90 (m, 2H), 7.82-7.80 (m, 2H), 6.77 (s,3H), 2.28 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.1, 159.0, 139.9, 134.9, 129.0, 126.4, 124.1, 111.9, 21.5; IR (neat, cm$^{-1}$): $\nu$ 3022, 2917, 1795, 1733, 1590, 1186, 1121, 876, 837, 699; MS (m/z, ESI): 268, 163; HRMS calculated for C$_{16}$H$_{14}$NO$_3$ (M+H)$^+$: 268.0968; Found: 268.0973; $R_f$ = 0.6 (PE: EtOAc, 3:1).

\[\text{ONHPiv}\]

Yield 70% from 4b; white solid; m.p. 113-114 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.13 (s, 1H), 7.04 (d, $J$ = 8 Hz, 2H), 6.87 (d, $J$ = 8.8 Hz, 2H), 2.27 (s, 3H), 1.23 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.1, 157.7, 132.2, 129.9, 113.3, 38.4, 27.3, 20.6; IR (neat, cm$^{-1}$): $\nu$ 3161, 2966, 2923, 1658, 1499, 1478, 1189, 827, 816; MS (m/z, ESI): 208, 107; HRMS calculated for C$_{12}$H$_{18}$NO$_2$ (M+H)$^+$: 208.1332; Found: 208.1337; $R_f$ = 0.3 (PE: EtOAc, 5:1).

\[\text{ONHPiv}\]

Yield 88% from 4c; white solid; m.p. 103-104 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.05 (s, 1H), 7.11-7.08 (m, 2H), 6.93-6.90 (m, 2H), 2.27 (s, 3H), 1.24 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 176.9, 157.6, 131.1, 126.9, 124.8, 122.6, 111.6, 38.4, 27.3, 15.9; IR (neat, cm$^{-1}$): $\nu$ 3165, 2962, 1658, 1566, 1476, 1132, 771, 685; MS (m/z, ESI): 208, 102; HRMS calculated for C$_{12}$H$_{18}$NO$_2$ (M+H)$^+$: 208.1332; Found: 208.1338; $R_f$ = 0.5 (PE: EtOAc, 3:1).

\[\text{ONHPiv}\]

Yield 80% from 4d; white solid; m.p. 72-74 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.43 (s, 1H), 7.10 (t, $J$ = 8 Hz, 1H), 6.80-6.74 (m, 3H), 2.28 (s, 3H), 1.18 (s, 9H); $^{13}$C NMR
(100MHz, CDCl₃): δ 177.1, 159.7, 139.4, 129.1, 123.5, 113.9, 110.2, 38.3, 27.2, 21.5; IR (neat, cm⁻¹): ν 3165, 2962, 2928, 1658, 1586, 1241, 1207, 1133, 942, 771; MS (m/z, ESI): 208, 107; HRMS calculated for C₁₂H₁₅NO₂ (M+H)⁺: 208.1332; Found: 208.1336; Rf = 0.3 (PE: EtOAc, 5:1).

Yield 70% from 4e; white solid; m.p. 132-134 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.37 (s, 1H), 7.26 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 1.28 (s, 9H), 1.18 (s, 9H); ¹³C NMR (100MHz, CDCl₃): δ 177.1, 157.5, 145.5, 126.2, 112.8, 38.3, 34.2, 31.6, 27.2; IR (neat, cm⁻¹): ν 3139, 2963, 2905, 1664, 1502, 1478, 1164, 930, 835; MS (m/z, ESI): 250, 194; HRMS calculated for C₁₅H₂₄NO₂ (M+H)⁺: 250.1802; Found: 250.1799; Rf = 0.5 (PE: EtOAc, 3:1).

1e

Yield 92% from 4f; white solid; m.p. 129-132 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.42 (s, 1H), 7.48-7.42 (m, 4H), 7.37 (t, J = 7.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 1.22 (s, 9H); ¹³C NMR (100MHz, CDCl₃): δ 177.4, 159.3, 140.6, 136.0, 128.8, 128.2, 127.0, 126.9, 113.6, 38.4, 27.3; IR (neat, cm⁻¹): ν 3152, 2959, 1647, 1480, 1191, 1161, 830, 757, 693; MS (m/z, ESI): 270, 169, 141; HRMS calculated for C₁₇H₂₀NO₂ (M+H)⁺: 270.1489; Found: 270.1492; Rf = 0.6 (PE: EtOAc, 3:1).

1f

Yield 55% from 4g; white solid; m.p. 75-78 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.98 (s, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.13 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 1.14 (s, 9H); ¹³C NMR (100MHz, CDCl₃): δ 177.7, 159.8, 132.0, 131.6, 130.0, 125.2, 122.5, 119.5 (d, J = 3.7 Hz), 116.6, 110.2 (d, J = 3.7 Hz), 38.4, 27.0; ¹⁹F
NMR (376 MHz, CDCl$_3$): -62.9; IR (neat, cm$^{-1}$): $\nu$ 3159, 3056, 2966, 1657, 1447, 1328, 1170, 1108, 869, 815; MS (m/z, ESI): 262; HRMS calculated for C$_{12}$H$_{14}$F$_3$NO$_2$ (M+H)$^+$: 262.1049; Found: 262.1044; $R_f$ = 0.5 (PE: EtOAc, 3:1).

Yield 62% from 4h; white solid; m.p. 107-109 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 11.83 (br, s, 1H), 6.90-6.85 (m, 1H), 6.76-6.72 (m, 2H), 1.19 (s, 9H); $^{13}$C NMR (100MHz, DMSO-d$_6$): $\delta$ 175.6, 164.2 (d, $J$ = 15.5 Hz), 162.2, 162.1, 161.9, 161.7, 97.9, 97.7, 97.4, 97.1, 37.6, 26.9; $^{19}$F NMR (376 MHz, DMSO-d$_6$) -108.6; IR (neat, cm$^{-1}$): $\nu$ 3227, 2976, 2966, 2873, 1666, 1615, 1466, 1112, 993, 830; MS (m/z, ESI): 230, 130; HRMS calculated for C$_{11}$H$_{14}$F$_2$NO$_2$ (M+H)$^+$: 230.0979; Found: 230.0987; $R_f$ = 0.7 (PE: EtOAc, 5:1).

Yield 64% from 4i; white solid; m.p. 115-116 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.56 (br s, 1H), 6.60 (s, 1H), 6.57 (s, 2H), 2.22 (s, 6H), 1.16 (s, 9H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 177.0, 159.7, 139.0, 124.3, 110.9, 38.2, 27.1, 21.4; IR (neat, cm$^{-1}$): $\nu$ 3199, 2987, 2917, 1660, 1592, 1508, 1235, 1128, 835, 682; MS (m/z, ESI): 222, 121; HRMS calculated for C$_{13}$H$_{20}$NO$_2$ (M+H)$^+$: 222.1489; Found: 222.1491; $R_f$ = 0.6 (PE: EtOAc, 3:1).

Yield 47% from 4m; gray crystal; m.p. 114-116 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61 (s, 1H), 7.28 (t, $J$ = 8 Hz, 2H), 7.11 (d, $J$ = 8.8 Hz, 2H), 6.99 (t, $J$ = 7.2 Hz, 1H), 2.92 (s, 6H); $^{13}$C NMR (100MHz, CDCl$_3$): $\delta$ 160.2, 159.7, 129.4, 122.3, 113.4, 36.5;
IR (neat, cm⁻¹): ν 3149, 2929, 1665, 1492, 1477, 1187, 1155, 746, 689; MS (m/z, ESI): 181; HRMS calculated for C₉H₁₃N₂O₂ (M+H)+: 181.0972; Found: 181.0973; Rᵣ = 0.3 (PE: EtOAc, 3:1).

Yield 58% from 1a; colorless oil; ¹H NMR (400 MHz, CDCl₃): δ 7.36 (t, J = 8 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 6.99 (d, J = 8 Hz, 2H), 3.23 (s, 3H), 1.21 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 181.0, 157.3, 130.0, 123.1, 113.5, 39.8, 36.2, 27.3; IR (neat, cm⁻¹): ν 2979, 2965, 2923, 2852, 1644, 1480, 1336, 1153, 1073, 922, 762; MS (m/z, ESI): 208, 114; HRMS calculated for C₁₂H₁₈NO₂ (M+H)+: 208.1332; Found: 208.1323; Rᵣ = 0.7(PE: EtOAc, 5:1).

III. Synthesis of Benzofuran

General Procedure

Without any particular precautions to extrude oxygen or moisture, the aryloxypivalamide 1 (1.2eq), the alkyne 2 (1 eq), [Ru(p-cymene)Cl₂]₂ (2.5 mol%) and K₂CO₃ (25 mol%) were weighted in a 4 mL vial equipped with a stir bar. DCM (0.4 M) was then added. The reaction was stirred at room temperature and monitored by TLC. Afterwards, it was diluted with EtOAc and transferred to a round bottom flask. Silica gel was added to the flask and volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel (see below for specific eluents).

Table S1 Optimization Studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Additive (eq)</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bz</td>
<td>CsOAc (0.25)</td>
<td>DCM</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>CONMe₂</td>
<td>CsOAc (0.25)</td>
<td>DCM</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>---</td>
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<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Piv</td>
<td>NaOAc (0.25)</td>
<td>DCM</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>Piv</td>
<td>Na₂CO₃ (0.25)</td>
<td>DCM</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>Piv</td>
<td>K₃PO₄ (0.25)</td>
<td>DCM</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Piv</td>
<td>KO'Bu (0.25)</td>
<td>DCM</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Piv</td>
<td>KOAc (0.25)</td>
<td>DCM</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>Piv</td>
<td>K₂CO₃ (0.25)</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>Piv</td>
<td>K₂CO₃ (0.25), HOPiv (2)</td>
<td>DCM</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Piv</td>
<td>K₂CO₃ (0.25), PivNH₂(2)</td>
<td>DCM</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>Piv</td>
<td>K₂CO₃ (0.25), PhOH (2)</td>
<td>DCM</td>
<td>25</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1 (0.12 mmol), 2a (0.1 mmol), [Ru(p-cymene)Cl₂]₂ (2.5 mol %), and additives in solvent (0.4 M) at room temperature for 12h under air. *b ¹H NMR yield. *c Reaction was monitored by TLC, 24-48h. *d Phenol was detected.

**Characterization of products 3**

3aa, 3ab, 3ag, 3ah, 3ai, 3aj, 3al, 3an, 3ga are known compounds and all data were in agreement with those reported.³a,⁴

![](image)

Yield 99%; white solid; ¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, J = 7.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.46-7.43 (m, 1H), 7.32-7.28 (m, 1H), 3.98 (s, 3H), 2.59 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.0, 154.4, 140.7, 129.0, 127.9, 126.0, 123.2, 121.2, 112.2, 52.1, 9.4; IR (neat, cm⁻¹): ν 2924, 1710, 1439, 1366, 747; MS (m/z, ESI): 280, 248, 221, 189, 159; Rf: 0.5 in PE.

![](image)

Yield 96%; white solid; ¹H NMR (400 MHz, CDCl₃): δ 7.61 (d, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 1H), 7.43 (t, J = 7.2 Hz, 1H), 7.29 (t, J = 7.2 Hz, 1H), 4.45 (q, J = 7.2 Hz, 2H), 2.59 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 160.6, 154.4, 141.0, 129.2, 127.8, 125.7, 123.2, 121.1, 112.3, 61.2, 14.5, 9.5; IR (neat, cm⁻¹): ν 2984, 1708, 1400, 1294, 1143, 745; MS (m/z, ESI): 204, 176, 159, 131, 103, 77; Rf:
Yield 93%; yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.67 (d, \(J = 8\) Hz, 1H), 7.52-7.44 (m, 2H), 7.29 (t, \(J = 8\) Hz, 1H), 3.10 (t, \(J = 7.6\) Hz, 2H), 2.62 (s, 3H), 1.70-1.63 (m, 2H), 1.46-1.37 (m, 2H), 0.94 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 191.3, 154.1, 148.0, 129.2, 129.0, 128.1, 123.3, 121.9, 112.3, 31.9, 28.0, 23.9, 22.9, 14.1; IR (neat, cm\(^{-1}\)): \(\nu\) 2957, 2928, 2859, 1679, 1568, 1287, 1262, 1134, 745, 649; MS (m/z, EI): 216, 201, 187, 174, 159, 131; HRMS calculated for C\(_{14}\)H\(_{16}\)O\(_2\) (M\(^+\)): 216.1150; Found: 216.1148; \(R_f = 0.8\) (PE: EtOAc, 15:1).

Yield 99%; yellow solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.28 (d, \(J = 8.8\) Hz, 2H), 7.92 (d, \(J = 8.8\) Hz, 2H), 7.59 (d, \(J = 7.6\) Hz, 1H), 7.49 (d, \(J = 8\) Hz, 1H), 7.35 (t, \(J = 7.2\) Hz, 1H), 7.27 (t, \(J = 7.2\) Hz, 1H), 2.95 (t, \(J = 8\) Hz, 2H), 1.77-1.70 (m, 2H), 1.54-1.44 (m, 2H), 0.98 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 154.3, 147.9, 146.7, 137.5, 130.3, 126.7, 125.9, 124.1, 123.0, 120.7, 120.3, 111.4, 31.9, 24.3, 23.0, 14.0; IR (neat, cm\(^{-1}\)): \(\nu\) 2960, 2918, 2853, 1593, 1515, 1334, 1311, 1106, 852, 742; MS (m/z, EI): 295, 252, 206, 176, 152; HRMS calculated for C\(_{18}\)H\(_{17}\)NO\(_3\) (M\(^+\)): 295.1208; Found: 295.1207; \(R_f = 0.3\) in PE.

Yield 61%; colorless liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.14 (d, \(J = 8.4\) Hz, 2H), 7.87 (d, \(J = 8.4\) Hz, 2H), 7.59 (d, \(J = 7.6\) Hz, 1H), 7.50 (d, \(J = 8\) Hz, 1H), 7.33 (t, \(J = 8\) Hz, 1H), 7.26 (t, \(J = 7.2\) Hz, 1H), 4.41 (q, \(J = 7.2\) Hz, 2H), 2.96 (t, \(J = 8\) Hz, 2H), 2.01 (t, \(J = 7.2\) Hz, 2H), 1.23 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 202.9, 163.7, 149.0, 141.1, 130.3, 129.0, 128.1, 126.2, 125.9, 124.1, 123.3, 121.9, 30.9, 28.0, 23.9, 22.9, 14.0; IR (neat, cm\(^{-1}\)): \(\nu\) 2960, 2918, 2853, 1593, 1515, 1334, 1311, 1106, 852, 742; MS (m/z, EI): 295, 252, 206, 176, 152; HRMS calculated for C\(_{18}\)H\(_{17}\)NO\(_3\) (M\(^+\)): 295.1208; Found: 295.1207; \(R_f = 0.3\) in PE.
1.79-1.71 (m, 2H), 1.53-1.45 (m, 2H), 1.43 (t, $J = 7.2$ Hz, 3H), 0.98 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 166.5, 154.2, 149.4, 135.7, 130.6, 130.0, 129.5, 126.4, 125.1, 122.7, 120.0, 118.8, 111.3, 61.2, 32.0, 24.3, 23.1, 14.5, 14.1; IR (neat, cm$^{-1}$): ν 2957, 2926, 2857, 1717, 1609, 1454, 1272, 1108, 744; MS (m/z, EI): 322, 279, 251, 206, 178, 152; HRMS calculated for C$_{21}$H$_{22}$O$_3$ (M$^+$): 322.1569; Found: 322.1567; $R_f$ = 0.5 (PE: EtOAc, 30:1)

Yield 43%; colorless liquid; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.06 (d, $J = 8.0$ Hz, 2H), 7.90 (d, $J = 8$ Hz, 2H), 7.59 (d, $J = 7.2$ Hz, 1H), 7.51 (d, $J = 8$ Hz, 1H), 7.33 (t, $J = 8$ Hz, 1H), 7.26 (t, $J = 8$ Hz, 1H), 2.96 (t, $J = 8$ Hz, 2H), 2.65 (s, 3H), 1.79-1.71 (m, 2H), 1.54-1.44 (m, 2H), 0.98 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 197.6, 154.2, 149.2, 136.0, 135.9, 130.6, 128.9, 126.5, 125.2, 122.7, 120.1, 119.2, 111.3, 32.0, 26.8, 24.3, 23.1, 14.1; IR (neat, cm$^{-1}$): ν 2957, 2927, 2858, 1682, 1601, 1356, 1260, 838, 745; MS (m/z, EI): 292, 277, 249, 207, 178; HRMS calculated for C$_{20}$H$_{20}$O$_2$ (M$^+$): 292.1463; Found: 292.1466; $R_f$ = 0.5 (PE: EtOAc, 15:1).

Yield 57%; white solid; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.65 (d, $J = 7.2$ Hz, 2H), 7.56-7.38 (m, 7H), 7.32-7.20 (m, 5H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 154.1, 150.6, 132.9, 130.8, 130.4, 129.9, 129.1, 128.6, 128.5, 127.8, 127.2, 124.8, 123.0, 120.2, 117.6, 111.2; IR (neat, cm$^{-1}$): ν 3062, 1602, 1498, 748, 694; MS (m/z, EI): 270, 255, 239, 165, 134; $R_f$: 0.7 in PE.
Yield 54%; white solid; \( ^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.60 (d, \( J = 8.8 \) Hz, 2H), 7.51 (d, \( J = 8.4 \) Hz, 1H), 7.46 (d, \( J = 7.6 \) Hz, 1H), 7.41 (d, \( J = 8.8 \) Hz, 2H), 7.28 (dt, \( J_1 = 7.2 \) Hz, \( J_2 = 1.2 \) Hz, 1H), 7.21 (t, \( J = 7.2 \) Hz, 1H), 6.99 (d, \( J = 8.8 \) Hz, 2H), 6.84 (d, \( J = 8.8 \) Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 159.7, 159.1, 153.9, 150.6, 131.0, 130.7, 128.5, 125.3, 124.3, 123.6, 122.9, 119.8, 115.7, 114.5, 114.0, 111.0, 55.39, 55.38; IR (neat, cm\(^{-1}\)): \( \nu \) 2963, 2923, 2851, 1726, 1606, 1500, 1451, 1247, 1024; MS (m/z, EI): 330, 315, 255, 243, 215, 165; Rf: 0.5 in PE.

Yield 59%; white solid; \( ^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.15 (d, \( J = 8.4 \) Hz, 2H), 7.97 (d, \( J = 9.2 \) Hz, 2H), 7.68 (d, \( J = 8.8 \) Hz, 2H), 7.57 (d, \( J = 8.4 \) Hz, 3H), 7.48 (d, \( J = 8.0 \) Hz, 1H), 7.38 (dt, \( J = 7.2 \), 1.6 Hz, 1H), 7.27 (dt, \( J = 7.6 \), 0.8 Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 166.9, 166.7, 154.4, 149.9, 137.5, 134.5, 130.5, 129.9, 129.82, 129.78, 129.6, 126.9, 125.8, 123.6, 120.2, 118.6, 111.5, 52.4, 52.3 (one signal missing due to overlap); IR (neat, cm\(^{-1}\)): \( \nu \) 2923, 2852, 1716, 1607, 1451, 1432, 1412, 1286, 1118, 1066; MS (m/z, EI): 386, 355, 268, 239, 162, 119; Rf: 0.5 in PE.

Yield 71%; white solid; \( ^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.58-7.53 (m, 3H), 7.46-7.39
(m, 5H), 7.35 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 8.9 Hz, 2H), 7.25 (t, J = 8.0 Hz, 1H);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.1, 149.7, 134.6, 133.9, 131.1, 129.8, 129.5, 129.0, 128.3, 125.3, 123.4, 120.0, 116.9, 111.4 (two signals missing due to overlap);

IR (neat, cm$^{-1}$): v 3060, 1582, 1497, 834, 751; MS (m/z, EI): 338, 302, 268, 239, 134; R$_f$: 0.7 in PE.

Yield 89%; 3ak and 3ak’ were inseparable yellow solid, 3ak:3ak’ = 10:1; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.32 (d, J = 8.4 Hz, 0.2H), 8.14 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.4 Hz, 0.2H), 7.60-7.49 (m, 7.7H), 7.44-7.38 (m, 1.2H), 7.31-7.27 (m, 1.2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.4, 147.9, 147.0, 136.8, 132.0, 130.6, 130.0, 129.7, 129.5, 129.3, 128.9, 128.6, 127.5, 127.1, 126.2, 125.4, 124.4, 123.9, 123.6, 121.4, 120.8, 111.5; IR (neat, cm$^{-1}$): v 3060, 2956, 2919, 2849, 1593, 1509, 1338, 854, 743, 697; MS (m/z, EI): 315, 268, 239, 189, 134, 119; HRMS calculated for C$_{20}$H$_{13}$NO$_3$ (M$^+$): 315.0895; Found: 315.0899; R$_f$ = 0.6 (PE: EtOAc, 15:1).

Yield 36%; white solid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.80 (d, J= 8.3 Hz, 2H), 7.53-7.45 (m, 4H), 7.35 (t, J= 7.4 Hz, 1H), 7.31-7.22 (m,2H), 2.48 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 153.9, 150.8, 131.6, 131.3, 128.8, 128.0, 126.8, 124.4, 122.5, 119.4, 111.4, 111.1, 9.6; IR (neat, cm$^{-1}$): v 3059, 2924, 1457, 1362, 743, 693; MS (m/z, EI): 208, 178, 152, 131; R$_f$: 0.7 in PE.
Yield 60%; white solid; m.p. 131-133°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.62 (d, $J$ = 7.6 Hz, 1H), 7.47-7.41 (m, 2H), 7.30 (t, $J$ = 7.2 Hz, 1H), 6.57 (br s, 1H), 6.27 (br s, 1H), 2.64 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.5, 153.5, 142.4, 129.8, 127.4, 123.6, 123.2, 121.2, 111.7, 9.1; IR (neat, cm$^{-1}$): v 3401, 3349, 3168, 2922, 2852, 1693, 1659, 1622, 1607, 1412, 1375, 1163, 1125, 742; MS (m/z, EI): 175, 159, 131, 102, 77; HRMS calculated for C$_{10}$H$_9$NO$_2$(M$^+$): 175.0633; Found: 175.0629; $R_f$ = 0.4 (PE: EtOAc, 2:1).

Yield 82%; white solid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.98 (d, $J$ = 7.3 Hz, 2H), 7.67-7.45 (m, 6H), 7.32 (t, $J$ = 7.5 Hz, 1H), 5.65 (s, 2H), 2.65 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 191.7, 159.8, 154.8, 140.2, 134.2, 134.1, 129.1, 129.0, 128.2, 128.0, 127.4, 123.4, 121.4, 112.4, 66.5, 9.6; IR (neat, cm$^{-1}$): v 3058, 2939, 1724, 1697, 1448, 743, 687; MS (m/z, EI): 294, 175, 159, 105, 77; $R_f$ = 0.6 (EtOAc: PE, 1:4).

Yield 39%; yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.52 (d, $J$ = 8.4 Hz, 1H), 7.36 (d, $J$ = 7.6 Hz, 1H), 7.30-7.20 (m, 2H), 4.56 (t, $J$ = 8 Hz, 2H), 4.05 (t, $J$ = 8 Hz, 2H), 2.65 (t, $J$ = 7.6 Hz, 2H), 1.70-1.62 (m, 2H), 1.43-1.34 (m, 2H), 0.93 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.7, 152.0, 141.7, 129.0, 124.8, 122.7, 120.1, 113.7, 111.2, 63.0, 46.6, 31.1, 23.1, 22.9, 14.0; IR (neat, cm$^{-1}$): v 2956, 2926, 2858, 1762, 1646, 1454, 1210, 1102, 1038, 1013, 745; MS (m/z, EI): 259, 216, 172, 157, 103, 77; $R_f$ = 0.6 (PE: EtOAc, 5:1).
NOESY (400 MHz, CDCl$_3$). The copy of NOESY spectra is shown in page 52.

Yield 25%; yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44-7.40 (m, 2H), 7.26-7.23 (m, 2H), 4.59 (t, $J = 8$ Hz, 2H), 3.99 (t, $J = 8$ Hz, 2H), 2.77 (t, $J = 7.6$ Hz, 2H), 1.78-1.71 (m, 2H), 1.46-1.37 (m, 2H), 0.95 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.9, 155.6, 153.4, 125.2, 124.2, 123.1, 118.2, 114.3, 111.7, 62.7, 47.5, 29.6, 26.3, 22.6, 13.9; IR (neat, cm$^{-1}$): v 2959, 2926, 2859, 1751, 1454, 1424, 1236, 1117, 1101, 1036, 800, 745; MS (m/z, EI): 259, 216, 172, 157, 103, 77; HRMS calculated for C$_{15}$H$_{17}$NO$_3$ (M$^+$): 259.1208; Found: 259.1212; $R_f$ = 0.4 (PE: EtOAc, 5:1).

Yield 91%; yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.42-7.39 (m, 2H), 7.25 (d, $J = 8.0$ Hz, 1H), 3.97 (s, 3H), 2.56 (s, 3H), 2.46 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 161.1, 153.0, 140.8, 132.9, 129.5, 129.1, 125.9, 120.8, 111.8, 52.1, 21.5, 9.5; IR (neat, cm$^{-1}$): v 3024, 1713, 1588, 1436, 1292, 1146, 1089, 800, 771; MS (m/z, EI): 204, 189, 173, 144, 115, 91; HRMS calculated for C$_{12}$H$_{12}$O$_3$ (M$^+$): 204.0786; Found: 204.0787; $R_f$ = 0.7(PE: EtOAc, 15:1).

Yield 96%; yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43 (d, $J = 8.0$ Hz, 1H),
7.24-7.17 (m, 2H), 3.97 (s, 3H), 2.57 (s, 3H), 2.56 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.2, 153.6, 140.6, 128.6, 126.3, 123.3, 122.6, 118.5, 52.0, 15.2, 9.6 (one signal missing due to overlap); IR (neat, cm\(^{-1}\)): \(\nu\) 3029, 1713, 1597, 1438, 1291, 1148, 1085, 1057, 781, 745; MS (m/z, EI): 204, 189, 173, 145, 115, 91; HRMS calculated for C\(_{12}\)H\(_{12}\)O\(_3\)(M\(^+\)): 204.0786; Found: 204.0783; \(R_f = 0.7\) (PE: EtOAc, 15:1).

![3da and 3da']

Yield 99%; 3da and 3da’ were inseparable colorless liquid, 3da:3da’ = 5:1; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.48 (d, \(J = 8.0\) Hz, 1H), 7.35 (d, \(J = 8.0\) Hz, 1\(\times\)0.2 = 0.2H), 7.31 (s, 1H), 7.28 (s, 1\(\times\)0.2 = 0.2H), 7.11 (d, \(J = 8.0\) Hz, 1H), 6.98 (d, \(J = 7.2\) Hz, 1\(\times\)0.2 = 0.2H), 3.97 (s, 3\(+\)3\(\times\)0.2 = 3.6H), 2.77 (s, 3\(\times\)0.2 = 0.6H), 2.67 (s, 3\(\times\)0.2 = 0.6H), 2.56 (s, 3H), 2.48 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.1, 154.9, 140.3, 138.7, 134.1, 127.8, 126.7, 126.2, 124.9, 124.8, 120.7, 112.2, 110.0, 52.0, 22.1, 19.7, 11.7, 9.5; IR (neat, cm\(^{-1}\)): \(\nu\) 3031, 1712, 1621, 1436, 1137, 1096, 803, 769; MS (m/z, EI): 204, 189, 173, 146, 115, 91; HRMS calculated for C\(_{12}\)H\(_{12}\)O\(_3\)(M\(^+\)): 204.0786; Found: 204.0790; \(R_f = 0.6\) (PE: EtOAc, 15:1).

3ea

Yield 65%; yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.58 (s, 1H), 7.53 (d, \(J = 8.8\) Hz, 1H), 7.46 (d, \(J = 8.8\) Hz, 1H), 3.98 (s, 3H), 2.60 (s, 3H), 1.39 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 161.1, 152.8, 146.5, 140.9, 128.7, 126.4, 126.3, 116.9, 111.7, 52.1, 35.0, 31.9, 9.5; IR (neat, cm\(^{-1}\)): \(\nu\) 2957, 1716, 1600, 1507, 1463, 1438, 1148, 1114, 1018, 809; MS (m/z, EI): 246, 231, 215, 203, 172, 128, 115, 86; HRMS calculated for C\(_{15}\)H\(_{18}\)O\(_3\)(M\(^+\)): 246.1256; Found: 246.1257; \(R_f = 0.7\) (PE: EtOAc, 15:1).
Yield 88%; white solid; m.p. 88-90 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.76 (d, \(J = 1.2\) Hz, 1H), 7.67-7.56 (m, 4H), 7.45 (t, \(J = 8\) Hz, 2H), 7.35 (t, \(J = 7.6\) Hz, 1H), 3.98 (s, 3H), 2.61 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 160.9, 154.0, 141.3, 141.1, 137.1, 129.6, 128.9, 127.7, 127.5, 126.2, 119.5, 112.4, 52.1, 9.5; IR (neat, cm\(^{-1}\)): v 2947, 2920, 2849, 1713, 1601, 1585, 1436, 1298, 1142, 1096, 760, 696; MS (m/z, EI): 266, 235, 207, 178, 152, 117, 89; HRMS calculated for C\(_{17}\)H\(_{14}\)O\(_3\) (M\(^+\)): 266.0943; Found: 266.0938; \(R_f\) = 0.6 (PE: EtOAc, 15:1).

Yield 23%; white solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.80 (s, 1H), 7.73 (d, \(J = 8.3\) Hz, 1H), 7.55 (d, \(J = 8.3\) Hz, 1H), 4.00 (s, 3H), 2.61 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 160.5, 153.4, 143.0, 131.9, 130.1, 129.8, 125.5, 125.4, 122.8, 122.3, 121.9, 120.2, 120.1, 110.0, 109.9, 52.4, 9.4; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) -61.6; IR (neat, cm\(^{-1}\)): v 3075, 2964, 1716, 1673, 1432, 1361, 850, 820; MS (m/z, EI): 258, 243, 227, 199, 151; \(R_f\) 0.7 with 10% EtOAc in PE.

Yield 13%; white solid; m.p. 69-71 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.06 (dd, \(J = 8.4, 0.8\) Hz, 1H), 6.76 (td, \(J = 10.0, 2.0\) Hz, 1H), 3.98 (s, 3H), 2.70 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 164.0 (d, \(J = 12.1\) Hz), 161.5 (d, \(J = 12.1\) Hz), 160.2, 158.9 (d, \(J = 15.1\) Hz), 156.2 (d, \(J = 15.1\) Hz), 155.4 (dd, \(J = 15.2, 12.1\) Hz), 141.4, 124.6, 114.8 (d, \(J = 19.0\) Hz), 99.6 (dd, \(J = 27.7, 23.9\) Hz), 96.2 (dd, \(J = 26.6, 4.6\) Hz), 52.2, 10.7; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) -108.9, -117.8; IR (neat, cm\(^{-1}\)): v 3079, 2961,
2919, 2850, 1716, 1597, 853, 835; **MS (m/z, EI):** 226, 211, 195, 167, 138, 127, 119, 99; **HRMS** calculated for C_{11}H_{8}F_{2}O_{3} (M^{+}): 226.0442; Found: 226.0438; **R_{f} = 0.6** (PE: EtOAc, 15:1).

![结构式](image)

3la

Yield 83%; white solid; m.p. 97-99 °C; **^1H NMR (400 MHz, CDCl_{3}):** δ 7.13 (s, 1H), 6.82 (s, 1H), 3.96 (s, 3H), 2.74 (s, 3H), 2.62 (s, 3H), 2.41 (s, 3H); **^13C NMR (100 MHz, CDCl_{3}):** δ 161.2, 155.3, 139.9, 138.5, 133.5, 127.4, 126.6, 125.0, 110.0, 52.0, 21.8, 19.6, 11.7; **IR (neat, cm^{-1}):** ν 2955, 2923, 2851, 1703, 1619, 1586, 1431, 1389, 1264, 1148, 844, 772; **MS (m/z, EI):** 218, 203, 187, 160, 128, 115, 91; **HRMS** calculated for C_{13}H_{14}O_{3} (M^{+}): 218.0943; Found: 218.0941; **R_{f} = 0.6** (PE: EtOAc, 15:1).

**Gram Scale Synthesis of Ethyl 3-methylbenzofuran-2-carboxylate (3ab)**

Without any particular precautions to extrude oxygen or moisture, phenoxy-pivalamide (1a) (1.158 g, 6 mmol, 1.2 eq), ethyl 2-butynoate (2b) (0.58 ml, 5 mmol, 1 eq), [Ru(p-cymene)Cl_{2}]_2 (30.6 mg, 0.05 mmol, 2.5 mol%) and K_{2}CO_{3} (0.1725 g, 1.25 mmol, 0.25 eq) were weighted in a 25 mL vial equipped with a stir bar. DCM (12.5 ml, 0.4M) was then added. The reaction mixture was stirred at room temperature and monitored by TLC. Afterwards, it was diluted with EtOAc and transferred to a round bottom flask. Silica gel was added to the flask and volatiles were evaporated under reduced pressure. The purification was performed by flash column chromatography on silica gel.

5 was prepared following a published procedure. To an ice-cold, stirred solution of 3ab (0.935 g, 4.6 mmol, 1 eq) in methanol (5 ml) was slowly added a solution of potassium hydroxide (0.308 g, 5.5 mmol, 2 eq) in methanol (10 ml). The resulting solution was stirred without further cooling until completion. Afterwards, MeOH was evaporated. The residue was dissolved in water and ether and the separated aqueous layer was acidified with 2 M hydrochloric acid. The liberated acid was extracted into
ether (3 x 30 ml); the combined extracts were dried and evaporated. Recrystallization of the residue from ether-petrol gave the acid 5 (0.749 g, 93%) as a colourless solid. 5 is a known compound and all data were in agreement with those reported.5 m.p. 185-187 °C; 1H NMR (400 MHz, CDCl3): δ 11.15 (br s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 2.65 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 166.0, 155.0, 140.1, 129.1, 128.7, 128.6, 123.5, 121.5, 112.5, 9.8; IR (neat, cm⁻¹): ν 2848, 1671, 1591, 1436, 1300, 918, 741; MS (m/z, EI): 176, 131, 102, 77.

IV Mechanism Studies

Ortho Deuteration Experiments

Without any particular precautions to extrude oxygen or moisture, the phenoxypivalamide (1a) (19.3 mg, 0.1 mmol, 1.0 eq), [Ru(p-cymene)Cl₂]₂ (1.5 mg, 0.0025 mmol, 2.5 mol%) and K₂CO₃ (3.5 mg, 0.025 mmol, 25 mol%) were weighted in a 4 mL vial equipped with a stir bar. DCM (0.25 ml, 0.4M), HOAc-d₄ (56 μL, 10 eq) or D₂O (20 μL, 10 eq) was then added, and the mixture was stirred at room temperature for 3 hours. Crude NMR indicated no deuterium incorporation at the ortho position of the substrate.

Without any particular precautions to extrude oxygen or moisture, the phenoxypivalamide (1a) (23.2 mg, 0.12 mmol, 1.2 eq), [Ru(p-cymene)Cl₂]₂ (1.5 mg, 0.0025 mmol, 2.5 mol%), alkyne 2a (10.0 μL, 0.1 mmol, 1.0 eq) and K₂CO₃ (3.5 mg, 0.025 mmol, 25 mol%) were weighted in a 4 mL vial equipped with a stir bar. DCM (0.25 ml) and D₂O (20 μL, 10 eq) were then added, and the mixture was stirred at room temperature for 12 hours. Afterwards, it was diluted with EtOAc and transferred to a round bottom flask. Silica gel was added to the flask and volatiles were evaporated under reduced pressure. After purification by flash column chromatography, 3a (19 mg, 99% yield) was isolated and no deuterium incorporation was found.

KIE experiments
Synthesis of deuterated substrate 1a-d5

(D5-phenyl)boronic acid was prepared according to the known procedure.6

Following the general procedure for the synthesis of substrate, deuterated substrate 1a-d5 was obtained in 63% yield (two steps) from (D5-phenyl)boronic acid.

1H NMR (400 MHz, CDCl3): δ 9.09 (s, 1H), 1.24 (s, 9H); 13C NMR (100 MHz, CDCl3): δ 177.3, 159.6, 129.0 (t, J = 24.0 Hz), 122.3 (t, J = 23.2 Hz), 112.9 (t, J = 24.6 Hz), 38.4, 27.3; IR (neat, cm-1): v3136, 2964, 2930, 1658, 1363, 1142, 928, 667; MS (m/z, ESI): 199; HRMS calculated for C9H11D5NO2 (M+H)+: 199.1489; Found: 199.1497; Rf = 0.5 (PE: EtOAc, 3:1).

Without any particular precautions to extrude oxygen or moisture, 1a (23.2 mg, 0.12 mmol, 1.2 eq) or 1a-d5 (23.8 mg, 0.12 mmol, 1.2 eq), [Ru(p-cymene)Cl2]2 (1.5 mg, 0.0025 mmol, 2.5 mol%), K2CO3 (3.5 mg, 0.025 mmol, 25 mol%) were mixed with 0.25 mL DCM. After addition of 2a (10 μl, 0.10 mmol, 1.0 eq.), the mixture was stirred at rt and timing was started. After 100 min, two reaction mixtures were filtered separately through silica column, washed with 10 mL of DCM. The solvent was then removed under reduced pressure and 1H NMR was taken for these two samples separately using trimethoxybenzene (5.6 mg) as the internal standard. 3aa was obtained in 83% yield and 3aa-d5 was obtained in 52% yield. Thus the KIE was found to be 1.6.
Crude $^1$H NMR of the reaction of 1a and 2a under standard condition for 100 min

Crude $^1$H NMR of the reaction of 1a-$d_3$ and 2a under standard condition for 100 min
Another intermolecular KIE experiment was performed by treating 1.2 equiv of 1a, 1.2 equiv of 1a-d5, and 1.0 equiv of 2a under the standard conditions in one pot for 100 min. The KIE was also determined to be $k_{H/D} = 1.6$.

V References


$^{19}$F Spectra of 1g

\[ \text{F}_3\text{C} - \text{ONHPIv} \]
$^{19}$F Spectra of 1h
On Bu

3ac

On Bu

3ac
On Bu

3ad

On Bu

3ad
and

3ak

and

3ak’
3da and 3da'

and

3da and 3da'
$^{19}$F Spectra of 3ga
$^{19}$F Spectra of 3ha

3ha