Supporting Information

Copper-mediated regioselective C-H Etherification of naphthylamides with arylboronic acids using water as oxygen Source

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General Information. Cu(OAc)$_2$ (98%), Cu(OAc)$_2$•H$_2$O (98%), CuO (99.9%), CuI (99.9%), CuCl$_2$ (99.9%), CuSO$_4$ (98%) and Cs$_2$CO$_3$ (99.9%) were purchased from Aldrich and used as received. The solvents were purchased from commercial sources and dried according to standard procedure. Naphthylamides were prepared according to literature.$^1$ Purification of the reaction products was carried out on column chromatography using Merck silica gel (60-120 mesh). Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on Bruker Avance III 600 MHz and Varian 400 MHz using CDCl$_3$ as solvent and Me$_4$Si as an internal standard. Chemical shifts ($\delta$) were reported in ppm and spin-spin coupling constants ($J$) were given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Thermo Fisher Scientific spectrometer. Mass spectra were recorded on a Q-TOF ESI-MS instrument (model HAB 273). Single crystal X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXL-14 (Göttingen, Germany).

Procedure for the Synthesis of Naphthylamides.$^1$ To a stirred solution of picolinic acid (1 mmol) in 5 mL dichloromethane at 0 °C under nitrogen atmosphere, was added oxalyl chloride (1.1 mmol, 0.1 mL), followed by catalytic amount of $N,N$-dimethylformamide (10 $\mu$L). The resultant mixture was stirred at 0 °C for 0.5 h and then at room temperature for 1 h. The reaction mixture was then cooled to 0 °C and triethylamine (2 mmol, 0.28 mL) was added. Then, (i.e. 0 °C), naphthylamine (1.1 mmol) was added portion wise and the resultant mixture was allowed to warm up to room temperature and the stirring was continued for 24 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was diluted with dichloromethane (45 mL), and washed with brine (3 × 5 mL).
and water (1 x 5 mL). Drying (Na$_2$SO$_4$) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using $n$-hexane and ethyl acetate as an eluent.

**Screening of Directing Groups**

\[ \text{DG} + \text{Ph-B(OH)$_2$} \xrightarrow{\text{Cu(OAc)$_2$ (1.5 equiv)}} \text{DG-O$^\text{Ph}$} \]

\[ \begin{align*}
\text{DG} &= \begin{array}{c}
\text{A, nr} \\
\text{B, nr} \\
\text{C, nr} \\
\text{D, nr} \\
\text{E, nr}
\end{array} \\
\end{align*} \]

Reaction conditions: substrates A-E (0.1 mmol), boronic acid (0.2 mmol), Cu(OAc)$_2$ (0.15 mmol), Cs$_2$CO$_3$ (0.25 mmol), DMSO (1.0 mL), 130 °C, air, 10 h. nr = no reaction.

**General Procedure for Copper-Mediated Etherification.** $N$-Naphthalenyl picolinamide 1 (0.2 mmol), boronic acid 2 (0.4 mmol), Cs$_2$CO$_3$ (0.5 mmol, 163 mg), Cu(OAc)$_2$ (0.3 mmol, 55 mg) and DMSO (1.5 mL) were stirred in a preheated oil bath at 130 °C under air for an appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (45 mL). The mixture was washed with 3 mL of aqueous ammonia, brine (5 mL)}
and water (5 mL). Drying (Na$_2$SO$_4$) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using $n$-hexane and ethyl acetate as an eluent.

**Crystal Data and Structure Refinement for 3k**

![ORTEP diagram of [N-(1-(4-fluorophenoxy)naphthalen-8-yl)picolinamide] 3k with 50% ellipsoid. H-Atoms are omitted for clarity (CCDC 1528745).](image)

**Figure S1.** ORTEP diagram of [N-(1-(4-fluorophenoxy)naphthalen-8-yl)picolinamide] 3k with 50% ellipsoid. H-Atoms are omitted for clarity (CCDC 1528745).

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|                      | c = 11.0350(9)Å  
|                      | $\alpha$ = 64.897(5)  
|                      | $\beta$ = 78.682(5)  
<p>|                      | $\gamma$ = 89.685(5) |
| Volume, $V$/Å$^3$   | 868.09(13)  |</p>
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<td>( R ) indices (all data)</td>
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**Characterization Data**

\textit{N-(1-Phenoxynaphthalen-8-yl)picolinamide 3a}. Brown solid; yield 82% (55.8 mg); analytical TLC on silica gel \( R_f \) 0.35 in 15% ethyl acetate/hexane; mp 110-114 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 13.0 (s, 1H), 9.02 (d, \( J=7.8 \) Hz, 1H), 8.25 (d, \( J=7.2 \) Hz, 2H), 7.84-7.81 (m, 1H), 7.65-7.55 (m, 3H), 7.39 (t, \( J=7.8 \) Hz, 2H), 7.35-7.32 (m, 2H), 7.22 (d, \( J=7.8 \) Hz, 2H), 7.18-7.16 (m, 1H), 6.96 (d, \( J=7.8 \) Hz, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 162.8, 156.8, 154.4, 150.7, 148, 137.5, 136.8, 134.7, 129.9, 127.1, 126.2, 125.8, 124.4, 124.2, 124.1, 122.4, 120.3, 118.1, 117.3, 114.2; IR (KBr): 3436, 2924, 1682, 1534, 1359, 1490, 1228, 1037, 748 cm\(^{-1} \). HRMS (ESI): calcd for [M+H]\(^+\) \( C_{22}H_{16}N_2O_2 \), 341.1285; found 341.1301.
N-(1-(o-Tolyloxy)naphthalen-8-yl)picolinamide 3b. Yellow solid; yield 71% (50.3 mg); analytical TLC on silica gel Rf 0.4 in 15% ethyl acetate/hexane; mp 135-138 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 13.26 (s, 1H), 9.08-9.06 (m, 1H), 8.3 (d, \(J=8\) Hz, 1H), 8.09-8.08 (m, 1H), 7.86-7.82 (m, 1H), 7.64-7.54 (m, 3H), 7.38 (d, \(J=7.2\) Hz, 1H), 7.33-7.28 (m, 3H), 7.22-7.18 (m, 1H), 7.14 (d, \(J=8\) Hz, 1H), 6.72-6.7 (m, 1H), 2.36 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 162.9, 155.2, 153.9, 150.8, 147.8, 137.6, 137, 135.1, 131.7, 130.9, 127.6, 127.1, 126.2, 125.8, 125.2, 124, 123.5, 122.3, 121.5, 117.3, 117, 111.2, 16.87; IR (KBr): 3437, 2925, 1683, 1539, 1496, 1231, 1116, 1032, 746 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) C\(_{23}\)H\(_{18}\)N\(_2\)O\(_2\), 355.1441; found 355.1458.

N-(1-(3-Chlorophenoxy)naphthalen-8-yl)picolinamide 3c. Yellow solid; yield 65% (48.7 mg); analytical TLC on silica gel Rf 0.37 in 15% ethyl acetate/hexane; mp 130-132 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 12.7 (s, 1H), 8.98 (d, \(J=7.2\) Hz, 1H), 8.36-8.35 (m, 1H), 8.25 (d, \(J=7.8\) Hz, 1H), 7.86-7.83 (m, 1H), 7.66 (d, \(J=7.8\) Hz, 2H), 7.57 (t, \(J=7.8\) Hz, 1H), 7.41-7.36 (m, 2H), 7.27-
7.24 (m, 2H), 7.11 (d, J=8.4 Hz, 1H), 7.03-7.01 (m, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 162.8, 157.9, 153.1, 150.6, 147.89, 137.71, 136.98, 135.22, 134.23, 130.65, 127.18, 126.40, 125.87, 125.41, 124.32, 124.14, 122.5, 120.5, 118.2, 117.8, 117.5, 115.3; IR (KBr): 3274, 2925, 1675, 1544, 1496, 1286, 1040, 821 cm$^{-1}$. HRMS (ESI): calcld for [M+H]$^+$ C$_{22}$H$_{15}$ClN$_2$O$_2$, 375.0895; found 375.0902.

![3d](image)

**N-(1-(3-Methoxyphenoxy)naphthalen-8-yl)picolinamide 3d.** Brown solid; yield 70% (51.9 mg); analytical TLC on silica gel $R_f$ 0.36 in 25% ethyl acetate/hexane, mp 112-115 °C; $^1$H NMR (400 MHz, CDCl$_3$): 12.94 (s, 1H), 9.0 (d, J=8 Hz, 1H), 8.32-8.25 (m, 2H), 7.86-7.83 (m, 1H), 7.65-7.54 (m, 3H), 7.38-7.27 (m, 3H), 6.99 (d, J=8 Hz, 1H), 6.79-6.70 (m, 3H), 3.77 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 162.9, 161.1, 157.9, 154.0, 150.7, 148.1, 137.5, 136.8, 134.6, 130.2, 127.0, 126.2, 125.9, 124.6, 124.1, 122.3, 118.1, 117.3, 114.4, 112.3, 109.9, 106.6, 55.6; IR (KBr): 3274, 2925, 1675, 1544, 1496, 1286, 1040, 821 cm$^{-1}$. HRMS (ESI): calcld for [M+H]$^+$ C$_{23}$H$_{18}$N$_2$O$_3$, 371.1390; found 371.1390.

![3e](image)
**N-(1-(m-Tolyloxy)naphthalen-8-yl)picolinamide 3e.** Yellow solid; yield 73% (51.7 mg); analytical TLC on silica gel $R_f$ 0.33 in 15% ethyl acetate/hexane; mp 99-103°C; $^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ 12.99 (s, 1H), 8.98 (d, $J$=7.6 Hz, 1H), 8.25-8.21 (m, 2H), 7.82-7.78 (m, 1H), 7.62-7.51 (m, 3H), 7.34-7.29 (m, 2H), 7.24-7.22 (m, 1H), 7.0-6.92 (m, 4H), 2.32 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.9, 156.8, 154.4, 150.8, 148, 140.1, 137.5, 136.8, 134.7, 129.6, 127.1, 126.2, 125.8, 125, 124.3, 124.1, 122.4, 121.2, 120.8, 118.1, 117.2, 114.2, 21.6; IR (KBr): 3437, 2924, 1684, 1536, 1431, 1341, 1229, 1032, 817 cm$^{-1}$. HRMS (ESI): calcd for [M+H]$^+$ C$_{23}$H$_{18}$N$_2$O$_2$, 355.1441; found 355.1458.

![Structure of 3e](image)

**N-(1-(3-Nitrophenoxy)naphthalen-8-yl)picolinamide 3f.** Yellow solid; yield 51% (39.3 mg); analytical TLC on silica gel $R_f$ 0.32 in 20% ethyl acetate/hexane; mp 151-153 °C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 12.43 (s, 1H), 8.95 (d, $J$=7.2 Hz, 1H), 8.47-8.46 (m, 1H), 8.24 (d, $J$=7.8 Hz, 1H), 8.15-8.14 (m, 1H), 7.94-7.93 (m, 1H), 7.86-7.83 (m, 1H), 7.75 (d, $J$=8.4 Hz, 1H), 7.7 (d, $J$=8.4 Hz, 1H), 7.6 (t, $J$=7.8 Hz, 1H), 7.46-7.41(m, 3H), 7.34-7.32 (m, 1H), 7.08 (d, $J$=7.2 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.8, 158.5, 151.9, 150.3, 149.3, 148.1, 137.7, 137.1, 134.0, 130.4, 127.5, 126.7, 126.4, 125.9, 124.6, 124.2, 122.6, 118.6, 118.5, 118.4, 116.5, 114.8; (KBr): 3429, 2924, 1673, 1524, 1498, 1351, 1240, 1032, 803 cm$^{-1}$. HRMS (ESI): calcd for [M+Na]$^+$ C$_{22}$H$_{15}$N$_3$O$_4$, 408.0955; found 408.0971.
**N-(1-(3-(Trifluoromethyl)phenoxy)naphthalen-8-yl)picolinamide 3g.** Yellow solid; yield 72% (58.8 mg); analytical TLC on silica gel R<sub>f</sub> 0.35 in 15% ethyl acetate/hexane; mp 127-130 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 12.56 (s, 1H), 8.87 (d, <i>J</i>=7.6 Hz, 1H), 8.23-8.22 (m, 1H), 8.15 (d, <i>J</i>=7.6 Hz, 1H), 7.74 (t, <i>J</i>=7.6 Hz, 1H), 7.58 (d, <i>J</i>=9.2 Hz, 2H), 7.5-7.45 (m, 2H), 7.35-7.27 (m, 4H), 7.16-7.12 (m, 1H), 6.91 (d, <i>J</i>=7.6 Hz, 1H);<sup>13</sup>C NMR (CDCl<sub>3</sub>, 150 MHz): δ 162.8, 157.5, 152.9, 150.6, 147.9, 137.6, 137, 134.2, 132.3 (<i>J</i><sub>C-F</sub>=32.5 Hz ), 130.5, 127.3, 126.4, 125.8, 125.6, 124.4, 123.8 (<i>J</i><sub>C-F</sub>=270.9 Hz ), 122.5, 122.2, 120.5 (<i>J</i><sub>C-F</sub>=3.7 Hz ), 118.4, 118, 117.07 (<i>J</i><sub>C-F</sub>=3.7 Hz ), 115.5; IR (KBr): 3293, 3071, 1673, 1547, 1327, 1169, 1287, 1093, 798 cm<sup>-1</sup>. HRMS (ESI): calcd for [M+H]<sup>+</sup> C<sub>23</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>, 409.1158; found 409.1174.

**N-(1-(4-Bromophenoxy)naphthalen-8-yl)picolinamide 3h.** Yellow solid; yield 63% (52.8 mg); analytical TLC on silica gel R<sub>f</sub> 0.35 in 15% ethyl acetate/hexane; mp 110-112 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 13.01 (s, 1H), 9.01 (d, <i>J</i>=7.6 Hz, 1H), 8.25 (d, <i>J</i>=7.2 Hz, 2H), 7.85-7.8 (m, 1H),
7.65-7.54 (m, 3H), 7.41-7.31 (m, 3H), 7.23-7.15 (m, 3H), 6.96 (d, \(J=7.6\) Hz, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 163, 156.8, 154.5, 150.8, 148.1, 137.4, 136.7, 134.7, 130.1, 127.1, 126.2, 125.8, 124.4, 124.2, 124.1, 122.4, 120.3, 118.1, 117.3, 114.2; IR (KBr): 3443, 2924, 1682, 1536, 1431, 1341, 1230, 1029, 818 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) C\(_{22}\)H\(_{15}\)BrN\(_2\)O\(_2\), 419.0390; found 419.0363.

![Diagram](image)

\(N\)-(1-(4-Chlorophenoxy)naphthalen-8-yl)picolinamide 3i. Pale yellow solid; yield 70% (52.5 mg); analytical TLC on silica gel \(R_f\) 0.34 in 15% ethyl acetate/hexane; mp 142-143 °C; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 12.81 (s, 1H), 8.99 (d, \(J= 8.4\) Hz, 1H), 8.29-8.25 (m, 2H), 7.86-7.83 (m, 1H), 7.66-7.62 (m, 2H), 7.58-7.56 (m, 1H), 7.39-7.33 (m, 4H), 7.15-7.27 (m, 2H), 6.95-6.94 (m, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 162.9, 155.5, 153.9, 150.7, 147.9, 137.5, 136.9, 134.5, 130, 129.3, 127.3, 126.3, 125.8, 125, 124.2, 122.5, 121.3, 118.1, 117.6, 114.6; IR (KBr): 3285, 2924, 1669, 1541, 1487, 1228, 1091, 848 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) C\(_{22}\)H\(_{15}\)ClN\(_2\)O\(_2\), 375.0895; found 375.0901.
**N-(1-(4-Ethylphenoxy)naphthalen-8-yl)picolinamide 3j.** Yellow solid; yield 77% (56.7 mg); analytical TLC on silica gel Rf 0.35 in 15% ethyl acetate/hexane; mp 99-104 °C; 1H NMR (400 MHz, CDCl3): δ 13.0 (s, 1H), 8.92 (d, J=7.6 Hz, 1H), 8.16 (d, J=7.2 Hz, 2H), 7.75-7.71 (m, 1H), 7.54-7.43 (m, 3H), 7.22 (t, J=8 Hz, 2H), 7.16-7.11 (m, 2H), 7.05 (d, J=8.4 Hz, 2H), 6.85 (d, J=7.6 Hz, 1H), 2.57 (q, J=7.6 Hz, 2H), 1.16 (t, J=7.6 Hz, 3H); 13C NMR (150 MHz, CDCl3): δ 162.9, 154.8, 154.5, 150.8, 148.0, 140.2, 137.5, 136.8, 134.8, 129.2, 127.1, 126.2, 125.8, 124.1, 122.3, 120.2, 117.9, 117.1, 113.7, 28.4, 15.9; IR (KBr): ν 3274, 2925, 1677, 1542, 1498, 1230, 1210, 1030, 820 cm⁻¹. HRMS (ESI): calcd for [M+H]+ C24H20N2O2, 369.1598; found 369.1603.

**N-(1-(4-Fluorophenoxy)naphthalen-8-yl)picolinamide 3k.** Pale yellow solid; yield 78% (55.9 mg); analytical TLC on silica gel Rf 0.37 in 15% ethyl acetate/hexane; mp 120-123 °C; 1H NMR (400 MHz, CDCl3): δ 13.0 (s, 1H), 9.02-8.99 (m, 1H), 8.27-8.23 (m, 2H), 7.86-7.81 (m, 1H), 7.64-7.54 (m, 3H), 7.36-7.31 (m, 2H), 7.21-7.17 (m, 2H), 7.11-7.07 (m, 2H), 6.9 (d, J=7.2 Hz,
$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.7 ($J_{C,F}$=221 Hz), 158.6, 154.6, 152.3, 150.8, 148.1, 137.6, 136.7, 134.6, 127.2, 126.2, 125.8, 124.5, 124.1, 122.4, 121.7 ($J_{C,F}$=8 Hz), 117.8, 117.4, 116.6 ($J_{C,F}$=23 Hz), 113.5; IR (KBr): $\nu$ 3438, 2924, 1671, 1540, 1432, 1223, 1030, 852 cm$^{-1}$.

HRMS (ESI): calcd for [M+H]$^+$ C$_{22}$H$_{15}$FN$_2$O$_2$, 359.1190; found 359.1204.

*N-(1-(p-Tolyloxy)naphthalen-8-yl)picolinamide 3l*. Yellow solid; yield 71% (50.3 mg); analytical TLC on silica gel $R_f$ 0.32 in 10% ethyl acetate/hexane; mp 157-160 °C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 13.11 (s, 1H), 9.05-9.03 (m, 1H), 8.29-8.27 (m, 2H), 7.87-7.84 (m, 1H), 7.66-7.64 (m, 1H), 7.6-7.57 (m, 2H), 7.38-7.37 (m, 1H), 7.35-7.32 (m, 1H), 7.22 (d, $J$=8.4 Hz, 2H), 7.15-7.14 (m, 2H), 6.96-6.94 (m, 1H), 2.39 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 162.9, 154.8, 154.3, 150.8, 148, 137.5, 136.8, 134.8, 133.8, 130.4, 127.1, 126.2, 125.8, 124.1, 122.4, 120.3, 117.9, 117.1, 113.5, 21; IR (KBr): $\nu$ 3538, 2925, 1682, 1537, 1430, 1378, 1031, 750 cm$^{-1}$. HRMS (ESI): calcd for [M+H]$^+$ C$_{23}$H$_{18}$N$_2$O$_2$, 355.1441; found 355.1457.
**N-(1-(4-Methoxyphenoxy)naphthalen-8-yl)picolinamide 3m.** Yellow solid; yield 82% (60.7 mg); analytical TLC on silica gel Rf 0.35 in 25% ethyl acetate/hexane; mp 115-118 °C; 

1H NMR (600 MHz, CDCl$_3$): δ 13.16 (s, 1H), 9.033-9.02 (m, 1H), 8.27-8.24 (m, 2H), 7.85-7.82 (m, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.57-7.54 (m, 2H), 7.35-7.34 (m, 1H), 7.3 (t, J=7.8 Hz, 1H), 7.19-7.17 (m, 2H), 6.96-6.94 (m, 2H), 6.88 (d, J=7.8 Hz, 1H), 3.84(s, 3H);

13C NMR (150 MHz, CDCl$_3$): δ 163, 156.6, 155.5, 150.8, 149.8, 148.0, 137.5, 136.8, 134.9, 127.2, 126.2, 125.8, 124.0, 123.8, 122.4, 121.8, 117.6, 117.0, 115.0, 112.6, 56.3; IR (KBr): 3265, 3054, 1686, 1540, 1429, 1343, 1285, 1033, 850 cm$^{-1}$. HRMS (ESI): calcd for [M+H]$^+$ C$_{23}$H$_{18}$N$_2$O$_3$, 371.1390; found 371.1405.

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**N-(1-(4-Vinylphenoxy)naphthalen-8-yl)picolinamide 3n.** Yellow solid; yield 79 % (57.9 mg); analytical TLC on silica gel Rf 0.32 in 10% ethyl acetate/hexane; mp 128-131°C; 

1H NMR (600 MHz, CDCl$_3$): δ 12.95 (s, 1H), 9.02-9.00 (m, 1H), 8.29-8.25 (m, 2H), 7.85-7.82 (m, 1H), 7.65-7.55 (m, 3H), 7.44 (d, J=8.4 Hz, 2H), 7.37-7.32 (m, 2H), 7.18-7.17 (m, 2H), 6.98-6.96 (m, 1H), 6.74-6.69 (m, 1H), 5.70 (d, J=17.4 Hz, 1H), 5.23 (d, J=10.8 Hz, 1H); 

13C NMR (150 MHz, CDCl$_3$) δ 163, 156.5, 154.3, 150.7, 148.0, 137.5, 136.8, 136.1, 134.7, 133.8, 127.7, 127.2, 126.2, 125.8, 124.6, 124.2, 122.4, 120.3, 118.1, 117.3, 114.3, 113.5; IR (KBr): 3432, 2924, 1677, 1543,
1429, 1287, 1114, 853 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\)C\(_{24}\)H\(_{18}\)N\(_2\)O\(_2\), 367.1441; found 367.1438.

\[N-(1-(2,4-Dimethylphenoxy)naphthalen-8-yl)picolinamide\] 3o. Thick oil, yield 55\% (40.5 mg); analytical TLC on silica gel R\(_f\) 0.4 in 10\% ethyl acetate/hexane; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 13.3 (s, 1H), 9.05 (d, \(J=7.8\) Hz, 1H), 8.29-8.28 (m, 1H), 8.12-8.11 (m, 1H), 7.85-7.82 (m, 1H), 7.62 (m, 1H), 7.58-7.55 (m, 1H), 7.33-7.31 (m, 1H), 7.27-7.25 (m, 1H), 7.17 (s, 1H), 7.07-7.06 (m, 1H), 7.02-7.01 (m, 1H), 6.68-6.66 (m, 1H), 2.39 (s, 3H), 2.29 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 162.9, 155.4, 151.5, 150.9, 147.9, 137.4, 136.8, 135.2, 134.6, 132.4, 130.6, 128.2, 127.1, 126.2, 125.9, 123.9, 123.2, 122.4, 121.5, 117.2, 116.8, 110.8, 21.1, 16.5; IR (KBr, cm\(^{-1}\)): \(\nu\) 3283, 2923, 1684, 1538, 1497, 1342, 1205, 1032, 816 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\)C\(_{24}\)H\(_{20}\)N\(_2\)O\(_2\), 369.1598; found 369.1606.
**N-(1-(Pyridin-3-yloxy)naphthalen-8-yl)picolinamide 3p.** Colorless solid; yield 59% (40.3 mg); analytical TLC on silica gel R_f 0.34 in 35% ethyl acetate/hexane; mp 108-110 °C; ^1H NMR (400 MHz, CDCl_3): δ 12.65 (s, 1H), 8.92 (d, J=7.6 Hz, 1H), 8.65 (s, 1H), 8.35 (s, 1H), 8.3-8.29 (m, 1H), 8.18 (d, J=7.2 Hz, 1H), 7.77-7.75 (m, 1H), 7.61-7.59 (m, 2H), 7.53-7.5 (m, 1H), 7.2-7.19 (m, 4H), 6.92 (d, J=7.2 Hz, 1H); ^13C NMR (150 MHz, CDCl_3): δ 162.8, 153.1, 150.5, 148.0, 144.9, 142.4, 137.7, 136.9, 134.3, 127.4, 126.1, 126.5, 125.8, 125.6, 124.4, 122.5, 118.3, 117.9, 115; IR (KBr): 3269, 2915, 1667, 1535, 1486, 1238, 1036, 829 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]^+ C_{21}H_{16}N_{3}O_{2}, 342.1237; found 342.1244.

![N-(1-(Pyridin-3-yloxy)naphthalen-8-yl)picolinamide 3p](image)

**N-(1-Phenoxynaphthalen-8-yl)quinoline-2-carboxamide 3s.** Yellow solid; yield 61% (47.63 mg); analytical TLC on silica gel R_f 0.32 in 10% ethyl acetate/hexane; mp 140-142 °C, ^1H NMR (600 MHz, CDCl_3): δ 13.21 (s, 1H), 9.11-9.10 (m, 1H), 8.4 (d, J=8.4 Hz, 1H), 8.29 (d, J=9 Hz, 1H), 7.82 (d, J=8.4 Hz, 1H), 7.66-7.65 (m, 1H), 7.61-7.56 (m, 2H), 7.53-7.5 (m, 4H), 7.35-7.31 (m, 4H), 7.01 (d, J=8.4 Hz, 1H), 6.82-6.81 (m, 1H); ^13C NMR (150 MHz, CDCl_3): δ 163.1, 155.9, 150.7, 146.7, 137.7, 136.8, 135, 130.5, 129.9, 129.8, 129.4, 127.9, 127.7, 127.2, 125.8, 125.3, 124.2, 123.8, 122.2, 119.0, 117.4, 117.3, 112.2; IR (KBr): 3232, 2915, 1674, 1535, 1486, 1238, 1036, 829 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]^+ C_{26}H_{18}N_{2}O_{2}, 391.1441, found 391.1451.
N-(1-Phenoxynaphthalen-8-yl)isoquinoline-1-carboxamide 3t. Yellow solid; yield 67% (52.3 mg); analytical TLC on silica gel Rf 0.36 in 15% ethyl acetate/hexane; mp 145-148 °C; 1H NMR (400 MHz, CDCl3): δ 13.17 (s, 1H), 9.73 (d, J=10 Hz, 1H), 9.05 (d, J=6.8 Hz, 1H), 8.11 (d, J=5.6 Hz, 1H), 7.84-7.81 (m, 1H), 7.71-7.6 (m, 6H), 7.4-7.34 (m, 3H), 7.22-7.16 (m, 3H), 6.95 (d, J=8 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ 164.5, 157.6, 156.8, 154.5, 148.5, 141.4, 140.1, 137.7, 136.9, 134.9, 130.5, 130.0, 128.8, 128, 127.4, 127.1, 127.1, 125.8, 124.6, 124.5, 124.3, 124.1, 120.3, 118.3, 117.2, 114.2; IR (KBr): 3436, 2924, 1669, 1533, 1434, 1233, 1140, 1033, 815 cm⁻¹. HRMS (ESI): calcd for [M+H]+ C26H18N2O2, 391.1441; found 391.1450.

N-(1-Phenoxynaphthalen-8-yl)pyrazine-2-carboxamide 3u. Yellow solid, yield 71% (48.5 mg); analytical TLC on silica gel Rf 0.36 in 25% ethyl acetate/hexane; mp 149-152 °C ; 1H NMR (600 MHz, CDCl3): δ 12.79 (s, 1H), 9.5 (s, 1H), 8.97 (d, J=7.8 Hz, 1H), 8.66-8.65 (m, 1H), 8.22 (s, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.61(d, J=8.4 Hz, 1H), 7.58-7.56 (m, 1H), 7.41-7.38 (m, 2H), 7.35-7.33 (m, 1H), 7.2-7.17 (m, 3H), 6.95 (d, J=7.8 Hz, 1H); 13C NMR (150 MHz, CDCl3): δ 161.3, 156.6, 154.2, 147.2, 145.4, 144.6, 142.4, 136.8, 134.2, 130.0, 127.1, 126, 124.7,
124.6, 124.4, 120.1, 117.9, 117.5, 114.4; IR (KBr): 3467, 2900, 1641, 1541, 1491, 1342, 1031, 822 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) \(\text{C}_{21}\text{H}_{15}\text{N}_{3}\text{O}_2\), 342.1237; found 342.1243.

\(\text{N-(4-Phenoxyisoquinolin-5-yl)picolinamide 3v.}\) Thick liquid, yield 65% (44.4 mg); analytical TLC on silica gel \(R_f\) 0.35 in 35% ethyl acetate/hexane; \(^1\text{H NMR (600 MHz, CDCl}_3\text{)}\): \(\delta\) 12.86 (s, 1H), 9.24-9.22 (m, 1H), 9.0 (s, 1H), 8.31-8.27 (m, 2H), 8.14 (s, 1H), 7.88-7.86 (m, 1H), 7.79 (d, \(J=7.8\) Hz, 1H), 7.75-7.72 (m, 1H), 7.46-7.43 (m, 2H), 7.41-7.39 (m, 1H), 7.29-7.28 (m, 2H), 7.25-7.22 (m, 1H); \(^13\text{C NMR (150 MHz, CDCl}_3\text{)}\): \(\delta\) 163.1, 156.4, 150.2, 149.6, 148.3, 148.1, 137.6, 134.1, 132.3, 131.1, 130.1, 128.9, 126.5, 124.8, 123.0, 122.5, 120.7, 120.6, 119.8; IR (KBr): 3433, 2925, 1634, 1534, 1463, 1284, 1014, 745 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) \(\text{C}_{21}\text{H}_{15}\text{N}_{3}\text{O}_2\), 342.1237; found 342.1252.

\(\text{N-(1-Cyano-5-phenoxynaphthalen-4-yl)picolinamide 3w.}\) Yellow oil; yield 65% (47.5 mg); analytical TLC on silica gel \(R_f\) 0.35 in 30% ethyl acetate/hexane; \(^1\text{H NMR (600 MHz, CDCl}_3\text{)}\): \(\delta\) 13.44 (s, 1H), 9.16 (d, \(J=8.4\) Hz, 1H), 8.28 (d, \(J=7.8\) Hz, 1H), 8.21 (m, 1H), 8.05-8.1 (m, 2H),
7.9-7.87 (m, 1H), 7.57-7.54 (m, 1H), 7.54-7.48 (m, 2H), 7.41-7.39 (m, 1H), 7.29-7.28 (m, 3H),
7.07-7.06 (m, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 163.5, 155.8, 155.5, 150.0, 148.1, 139.9,
137.8, 135.9, 134.7, 130.3, 128.6, 126.8, 125.1, 122.7, 121.2, 120.7, 118.6, 117.2, 115.3, 114.6,
104.9; IR (KBr): 3435, 2924, 1745, 1636, 1526, 1460, 1241, 1050, 740. HRMS (ESI): calcd for
$[M+H]^+$ C$_{23}$H$_{15}$N$_3$O$_2$, 366.1237; found 366.1249.

N-(1-Nitro-5-phenoxy-4-yl)picolinamide 3x. Yellow solid; yield 68% (52.4 mg); analytical TLC on silica gel R$_f$ 0.35 in 35% ethyl acetate/hexane; mp 218-220 °C; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 13.57 (s, 1H), 9.18 (d, $J$=9 Hz, 1H), 8.41-8.45 (m, 2H), 8.28 (d, $J$=7.8 Hz, 1H), 8.21-8.19 (m, 2H), 7.59-7.56 (m, 1H), 7.51-7.48 (m, 2H), 7.42-7.4 (m, 1H), 7.3-7.28 (m, 3H), 7.09-7.04 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.5, 155.8, 155.4, 150, 148.1, 142.2,
140.9, 137.8, 130.3, 129.2, 128.9, 126.8, 126.7, 125.2, 122.7, 120.8, 118.8, 117.9, 114.7, 114.2;
IR (KBr): 3447, 2924, 2854, 1636, 1537, 1499, 1499, 1117, 742 cm$^{-1}$. HRMS (ESI): calcd for
$[M+H]^+$ C$_{22}$H$_{13}$N$_3$O$_4$, 386.1135; found 386.1148.
**N-(4-Phenoxypyren-3-yl)picolinamide 3y.** Yellow solid; yield 70% (58.1 mg); analytical TLC on silica gel R<sub>f</sub> 0.39 in 15% ethyl acetate/hexane; mp 174-177 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 13.2 (s, 1H), 9.45 (d, <i>J</i>=8.4 Hz, 1H), 8.16-8.12 (m, 3H), 7.89-7.86 (m, 2H), 7.81(d, <i>J</i>=9 Hz, 1H), 7.74-7.68 (m, 3H), 7.32-7.21(m, 6H), 7.12-7.1(m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 162.8, 156.3, 154.0, 150.8, 148, 137.6, 133.8, 131.9, 131.5, 130.1, 128.0, 127.8, 127.5, 127.4, 126.6, 126.37, 126.3, 124.6, 124.1, 123.4, 122.7, 122.4, 120.8, 119.2, 114.8, 112.33; IR (KBr): 3430, 2924, 1689, 1522, 1490, 1327, 1257, 1045, 847 cm<sup>-1</sup>. HRMS (ESI): calcd for [M+H]<sup>+</sup> C<sub>28</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>, 415.1441; found 415.1456.

**N-(8-Phenoxy-1,2,3,4-tetrahydronaphthalen-1-yl)picolinamide 3z.** Yellow solid; yield 50% (34.5 mg) analytical TLC on silica gel R<sub>f</sub> 0.3 in 25% ethyl acetate/hexane; mp 139-141 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.36 (s, 1H), 7.7 (d, <i>J</i>=7.8 Hz, 1H), 7.53 (t, <i>J</i>=7.2 Hz, 1H), 7.37 (d, <i>J</i>=7.2 Hz, 1H), 7.29-7.27 (m, 1H), 7.20-7.18 (m, 1H), 7.09-7.01 (m, 4H), 6.81 (d, <i>J</i>=6.6 Hz, 2H), 6.33-6.31 (m, 1H), 2.68-2.64 (m, 2H), 2.09-2.08 (m, 1H), 1.76-1.71 (m, 3H), 1.29-1.25 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>): δ 169.7, 155.2, 148.87, 140.8, 138.3, 136.4, 136.1, 129.5, 129.4, 128.6, 128.1, 127.2, 127.0, 126.5, 123.7, 54.98, 29.63, 28.20, 22.04; IR (KBr): 3437, 3062, 2925, 2859, 1650, 1595, 1494, 1386, 1340, 1146, 1112, 913, 744 cm<sup>-1</sup>. HRMS (ESI): calcd for [M+H]<sup>+</sup> C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>, 345.1598; found 345.1601.
8-Phenoxy naphtalen-1-amine 4a. Thick oil, yield 91% (21.4 mg); analytical TLC on silica gel
R_f 0.43 in 3% ethyl acetate/hexane; ^1H NMR (400 MHz, CDCl_3): δ 7.49 (d, J = 8 Hz, 1H), 7.38
(t, J = 8.0 Hz, 2H), 7.29-7.14 (m, 4H), 7.09 (d, J = 7.6 Hz, 2H), 6.69 (d, J = 7.6 Hz, 1H), 6.64 (d,
J = 6.8 Hz, 1H), 5.19 (s, 2H); ^13C NMR (150 MHz, CDCl_3): δ 157.1, 155.4, 144.1, 137.6, 130.2,
127.5, 125.7, 124.2, 124.1, 119.8, 117.4, 116.5, 113, 110.2; IR (KBr): 3399, 2924, 2854, 1592,
1487, 1393, 1229, 1029, 819, 756 cm^{-1}. HRMS (ESI): calcd for [M+H]^+ C_{16}H_{13}NO, 236.1070;
found 236.1074.

3-Phenoxy pyren-4-amine 4b. Thick liquid; yield 87% (26.9 mg); analytical TLC on silica gel
R_f 0.46 in 5% ethyl acetate/hexane; ^1H NMR (400 MHz, CDCl_3): δ 7.98-7.68 (m, 6H), 7.46-7.24
(m, 2H), 7.25-7.23 (m, 4H), 7.08 (s, 1H); ^13C NMR (150 MHz, CDCl_3): δ 155.6, 154.9, 132.2,
132.1, 130.2, 130.1, 128.0, 127.5, 127.5, 126.4, 125.1, 124.6, 124.4, 122.9, 122.3, 120.0, 117.1,
112.2, 112.2, 110.3; IR (KBr): 3443, 2924, 2850, 1638, 1460, 1382, 1111, 760, 622 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) \(\text{C}_{22}\text{H}_{15}\text{NO}\), 310.1226; found 310.1234.

5-Phenoxy-4-(picolinamido)naphthalen-1-yl acetate 5a. Thick liquid; yield 60% (23.9 mg); analytical TLC on silica gel \(R_f\) 0.34 in 35% ethyl acetate/hexane; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 13.04 (s, 1H), 9.03 (d, \(J=6\) Hz, 1H), 8.25-8.21 (m, 2H), 7.84-7.82 (m, 1H), 7.64-7.55 (m, 2H), 7.44-7.39 (m, 2H), 7.38-7.33 (m, 2H), 7.24-7.13 (m, 3H), 7.04-6.98 (m, 1H), 2.48 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 169.9, 162.8, 156.4, 154.8, 150.6, 148, 142.4, 137.6, 136.4, 133.1, 130.0, 126.5, 126.3, 124.5, 122.4, 120.8, 120.5, 119.5, 118.9, 117.7, 117.1, 116.5, 114.53, 21.18; IR (KBr): 3453, 2921, 1730, 1638, 1384, 1263, 1189, 1115, 620 cm\(^{-1}\). HRMS (ESI): calcd for [M+H]\(^+\) \(\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_4\) 399.1339; found 399.1355.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{5a.png}
\caption{5a}
\end{figure}

\(N\)-(1-Phenoxy-5-tosynaphthalen-8-yl)picolinamide 5b. Colorless solid; yield 61% (30.2 mg); analytical TLC on silica gel \(R_f\) 0.37 in 35% ethyl acetate/hexane; mp 201-203 °C; \(^1\)H NMR

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{5b.png}
\caption{5b}
\end{figure}
(400 MHz, CDCl₃): δ 13.44 (s, 1H), 9.2 (d, J=8.8 Hz, 1H), 8.61 (d, J=8.4 Hz, 1H), 8.42 (d, J=8.4 Hz, 1H), 8.26 (d, J=8 Hz, 1H), 8.17-8.16 (m, 1H), 7.85 (d, J=8.4 Hz, 3H), 7.44-7.35 (m, 4H), 7.28-7.24 (m, 2H), 7.22-7.19 (m, 3H), 6.97 (d, J=8 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 163.5, 155.9, 155.4, 150.0, 148.0, 144.140., 139.2, 137.8, 137.4, 132.3, 132.0, 130.2, 129.9, 128.2, 127.6, 125, 122.7, 120.7, 120.2, 118.2, 114.5, 114.5, 21.83; IR (KBr): 3451, 2924, 2854, 1639, 1382, 1114, 767, 620 cm⁻¹. HRMS (ESI): calcd for [M+H]⁺ C₂₉H₂₂N₂O₄S, 495.1373; found 495.1379.

![Diagram](image)

**N-(7-Morpholino-1-phenoxynaphthalen-8-yl)picolinamide 5c.** Yellow oil; yield 43% (18.3 mg); analytical TLC on silica gel Rₚ 0.3 in 35% ethyl acetate/hexane; ¹H NMR (400 MHz, CDCl₃): δ 10.13 (s, 1H), 8.51-8.5 (m, 1H), 8.13 (d, J=7.6 Hz, 1H), 7.84-7.80 (m, 2H), 7.64 (d, J=8 Hz, 1H), 7.44-7.40 (m, 2H), 7.32 (t, J=8 Hz, 1H), 7.06-7.02 (m, 3H), 6.88-6.84 (m, 1H), 6.58 (d, J=8 Hz, 2H), 3.73-3.71 (m, 4H), 3.04-3.02 (m, 4H); ¹³C NMR (150 MHz, CDCl₃): δ 163.3, 158.8, 151.6, 150.6, 148.1, 146.4, 137.4, 133.7, 129.4, 128.5, 126.2, 125.2, 125.1, 124.9, 124.1, 122.6, 122.2, 120.5, 118.6, 117.4, 67.74, 51.97; IR (KBr): 3449, 2964, 2923, 2852, 1637, 1464, 1384, 1220, 1111, 772 cm⁻¹. HRMS (ESI): calcd for [M+H]⁺ C₂₂H₁₅NO, 426.1812; found 426.1818.
Preparation of \(N\)-(Naphthalen-1-yl-8-d)picolinamide 1a-d (Scheme S1)\(^{,2a}\)

\[
\begin{align*}
\text{ Compound } 1a \quad (0.25 \text{ mmol, 62 mg}) , \quad \text{D}_2\text{O} \quad (10 \text{ mmol, 200 mg}), \quad \text{Pd(OAc)}_2 \quad (15 \text{ mol }\% , \quad 0.0375 \text{ mmol, 9 mg}) \quad \text{and} \quad m\text{-xylene} \quad (5 \text{ mL}) \quad \text{were stirred at 130 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate} \quad (20 \text{ mL}), \quad \text{washed with brine} \quad (2 \times 5 \text{ mL}) \quad \text{and water} \quad (1 \times 5 \text{ mL}). \quad \text{Drying} \quad (\text{Na}_2\text{SO}_4) \quad \text{and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using} \quad n\text{-hexane and ethyl acetate} \quad (96/4 \text{ v/v}) \quad \text{as an eluent. The deuterium incorporation was determined using 400 MHz} \quad ^1\text{H NMR as 90\%}. \\
\end{align*}
\]

**Intermolecular Kinetic Isotope Study.**\(^{,2b}\) \(N\)-(Naphthalen-1-yl)picolinamide \(1a\) \((0.2 \text{ mmol, 49.6 mg}), \quad N\)-(naphthalen-1-yl-8-d)picolinamide \(1a\)-d \((0.2 \text{ mmol, 49.8 mg}), \quad \text{phenylboronic acid} \quad 2a \quad (0.4 \text{ mmol, 48.8 mg}), \quad \text{Cs}_2\text{CO}_3 \quad (0.5 \text{ mmol, 163 mg}), \quad \text{Cu(OAc)}_2 \quad (0.3 \text{ mmol, 55 mg}) \quad \text{and} \quad \text{DMSO} \quad (1.5 \text{ mL}) \quad \text{were stirred at 130 °C under air for 2 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate} \quad (45 \text{ mL}) \quad \text{and washed with 3 ml of aqueous ammonia, brine} \quad (5 \text{ mL}) \quad \text{and water} \quad (5\text{mL}). \quad \text{Drying} \quad (\text{Na}_2\text{SO}_4) \quad \text{and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using} \quad n\text{-hexane and ethyl acetate as an eluent to give} \quad 3a \quad \text{and a mixture of unreacted} \quad 1a \quad \text{and} \quad 1a\text{-d. The intermolecular} \quad k_{\text{H}}/k_{\text{D}} \quad \text{was found to be 1.94, based on 600 MHz} \quad ^1\text{H NMR analysis of the recovered substrates} \quad 1a \quad \text{and} \quad 1a\text{-d.}
\]
**H₂O¹⁸ Labeling Experiment.**³ Compound 1a (0.1 mmol, 25 mg) was mixed with 2a (0.2 mmol, 24.5 mg), Cs₂CO₃ (0.25 mmol, 81.5 mg), Cu(OAc)₂ (0.15 mmol, 49 mg), DMSO (1 mL) and H₂O¹⁸ (0.1 mmol, 2 mg) were stirred at 130 °C for 3 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (45 mL). The solution was washed with aqueous ammonia (3 mL), brine (2 × 5 ml) and water (5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to provide a 1:2 mixtures of ethers O¹⁶ (3a) and O¹⁸ (3a') as determined by ESI-MS analysis.

![Figure S3](image)

**Figure S3.** ESI-MS analysis of labelling experiment (3a and 3a') after 3 h.

**Removal of Directing Group.**⁴ To a stirred solution of NaOH (0.7 mmol, 28 mg) in EtOH (1.5 mL), compound 3a or 3y (0.1 mmol) was added. The reaction mixture was then stirred at room temperature for 2 min and heated at 80 °C for 3 h. The progress of the reaction was monitored by
TLC using ethyl acetate and hexane as an eluent. After completion, the reaction mixture was
allowed to cool to room temperature, diluted with ethyl acetate (40 mL). The solution was
washed with 0.5 N HCl (4 × 5 mL), brine (5 mL) and water (5 mL). Drying (Na₂SO₄) and
evaporation of the solvent gave a residue that was purified on silica gel column chromatography
using n-hexane and ethyl acetate (96/4 v/v) as an eluent.

Procedure for C-4 Tosylation of 3a.⁵ᵃ Compound 3a (0.1 mmol, 34.1 mg), K₂CO₃ (28 mg, 0.2
mmol), Cu(OAc)₂•H₂O (4.0 mg, 0.02 mmol) and TsCl (0.3 mmol, 58 mg) were stirred in 1,2-
dichloroethane (1 mL) at 80 °C under air for 16 h. Progress of the reaction was monitored by
TLC using ethyl acetate and hexane. After completion, the reaction mixture was cooled to room
temperature, diluted with ethyl acetate (50 mL). The organic solution was washed with brine (10
mL) and water (5 mL). Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was
purified on silica gel column chromatography using ethyl acetate/hexane as an eluent.

Procedure for C-4 Acetoxylation of 3a.⁵ᵃ Compound 3a (0.1 mmol, 34.1 mg), Cu(OAc)₂•H₂O
(0.02 mmol, 4.0 mg) and PhI(OAc)₂ (0.2 mmol, 64.4 mg) were stirred in AcOH (1 mL) at 80 °C
under air for 6 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane.
After completion, the reaction mixture was cooled to room temperature, diluted with ethyl
acetate (50 mL), washed with saturated Na₂S₂O₅ (2 × 10 mL), brine (10 mL) and water (5 mL).
Drying (Na₂SO₄) and evaporation of the solvent gave a residue that was purified on silica gel
column chromatography using ethyl acetate/hexane as eluent.

Procedure for C-2 Amination of 3a.⁵ᵇ Compound 3a (0.1 mmol, 34.1 mg), morpholine (0.2
mmol, 175 mg), Cu(OAc)₂•H₂O (0.01 mmol, 2.0 mg), PhI(OAc)₂ (64.4 mg, 0.2 mmol) and
MgCl₂ (20 mol %, 0.02 mmol, 2 mg) were stirred in 2 mL 1,4-dioxane at room temperature
under nitrogen atmosphere for 8 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (45 mL), washed with saturated Na$_2$S$_2$O$_3$ (2 x 10 mL), brine (2 x 10 mL) and water (1 x 5 mL). Drying (Na$_2$SO$_4$) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate/hexane as eluent.

References


NMR (\(^1\)H and \(^{13}\)C) Spectra
SR-4-MePB-PA-13C

$\text{Me}$

$\text{O}$

$\text{N}$

$\text{O}$_3

$\text{H}$

$\text{O}$

$\text{N}$