DDQ-promoted Direct C5-alkylation of Oxazole with Alkylboronic Acids via Palladium-catalyzed C-H Bond Activation

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General Remarks

All commercially available compounds were purchased from Sigma-Aldrich, Alfa-Aesar, Acros, J&K Chemicals, Adamas and Aladdin Chemicals. Palladium(II) diacetate were purchased from Acros (99.9% purity, CAS No. 3375-31-3). Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Oxazole-4-carboxylic derivatives 1a-1p were prepared from corresponding nitriles by our previous reported methods\[1\]. 2,4-Diphenyloxazole 1q was prepared using the method in literature.\[2\] Products were purified by flash chromatography on silica gel using petroleum ether and ethyl acetate as the effluent. Melting point (m.p.) was measured on a microscopic melting point apparatus. $^1$H-NMR spectra were recorded on Bruker AVANCE III-400 spectrometers. Chemical shifts (in ppm) were referenced with TMS in CDCl$_3$ (0 ppm). $^{13}$C-NMR spectra were obtained by using the same NMR spectrometers and were calibrated with CDCl$_3$ ($\delta = 77.00$ ppm). High resolution mass spectra were obtained from an Agilent QTOF 6520 mass spectrometer with electron spray ionization (ESI) as the ion source.

References


Experimental Procedure and Characterization Data

Typical Procedure: To a reaction tube charged with Pd(OAc)$_2$ (6.7 mg, 0.03 mmol, 10 mol%), AgOAc (200 mg, 1.2 mmol, 4 eq), DDQ (34 mg, 0.15 mmol, 0.5 eq), alkylboronic acid (1.2 mmol, 4 eq) was added a solution of oxazole (0.3 mmol, 1 equiv) in ethylbenzene (1 mL) and acetic acid (1 mL). The reaction mixture was then stirred at 120 °C for 24 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give dark residue, which was purified by flash chromatography (using petroleum ether and ethyl acetate as the effluent) on silica gel to afford the C5-alkylated oxazole 3a – 3y.

Methyl 5-n-Butyl-2-phenyloxazole-4-carboxylate (3a):

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of n-butylboronic acid (2a) afforded 80% of 3a after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.09-8.07 (m, 2H), 7.46-7.44 (m, 3H), 3.95 (s, 3H), 3.12 (t, 2H, $J = 7.6$ Hz), 1.75 (p, 2H, $J = 7.6$ Hz), 1.43 (h, 2H, $J = 7.6$ Hz), 0.97 (t, 3H, $J = 7.6$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 162.8, 160.3, 159.6, 130.7, 128.7, 128.0, 126.6, 126.5, 51.9, 29.8, 25.7, 22.2, 13.6 ppm; HRMS m/z (ESI) calcd for [C$_{15}$H$_{17}$NO$_3$+H]$^+$ 260.1287, found 260.1282.

Methyl 5-n-Butyl-2-(4-methylphenyl)oxazole-4-carboxylate (3b):

The reaction of 0.3 mmol of methyl 2-(4-methylphenyl)oxazole-4-carboxylate (1b) and 1.2 mmol of n-butylboronic acid (2a) afforded 81% of 3b after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1 to 15:1, v/v) as the effluent. Offwhite solid, m.p. 63-65 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 7.96 (d, 2H, $J = 8.4$ Hz), 7.26 (d, 2H, $J = 8.4$ Hz), 3.94 (s, 3H), 3.11 (t, 2H, $J = 7.2$ Hz), 2.40 (s, 3H), 1.74 (p, 2H, $J = 7.2$ Hz), 1.43 (h, 2H, $J = 7.2$ Hz), 0.96 (t, 3H, $J = 7.2$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 162.8, 160.0, 159.8, 141.0, 129.3, 127.9, 126.5, 123.9, 51.8, 29.8, 25.7, 22.2, 21.4, 13.6 ppm; HRMS m/z (ESI) calcd for [C$_{16}$H$_{19}$NO$_3$+H]$^+$ 274.1443, found 274.1439.
Methyl 5-\textit{n}-Butyl-2-(2-methylphenyl)oxazole-4-carboxylate (3c):

\begin{center}
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\end{center}

The reaction of 0.3 mmol of methyl 2-(2-methylphenyl)oxazole-4-carboxylate (1c) and 1.2 mmol of \textit{n}-butylboronic acid (2a) afforded 75% of 3c after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1 to 15:1, \textit{v}/\textit{v}) as the effluent. Colorless oil. \textit{^1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta = 8.00-7.97 \) (m, 1H), 7.37-7.33 (m, 1H), 7.29-7.27 (m, 2H), 3.94 (s, 3H), 3.13 (t, 2H, \( \textit{J} = 7.2 \) Hz), 2.67 (s, 3H), 1.75 (p, 2H, \( \textit{J} = 7.2 \) Hz), 1.43 (h, 2H, \( \textit{J} = 7.2 \) Hz), 0.96 (t, 3H, \( \textit{J} = 7.2 \) Hz) ppm; \textit{^{13}C} NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta = 162.9, 160.1, 160.0, 137.4, 131.5, 130.3, 129.2, 127.8, 125.9, 125.8, 51.8, 29.8, 25.6, 22.2, 21.7, 13.6 \) ppm; HRMS m/z (ESI) calcd for [C\textsubscript{16}H\textsubscript{19}NO\textsubscript{3}+Na]\textsuperscript{+} 296.1263, found 296.1265.

Methyl 5-\textit{n}-Butyl-2-(4-methoxylphenyl)oxazole-4-carboxylate (3d):

\begin{center}
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\end{center}

The reaction of 0.3 mmol of methyl 2-(4-methoxylphenyl)oxazole-4-carboxylate (1d) and 1.2 mmol of \textit{n}-butylboronic acid (2a) afforded 71% of 3c after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1 to 15:1, \textit{v}/\textit{v}) as the effluent. Light yellow solid, m.p. 66-68 °C. \textit{^1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta = 8.01 \) (d, 2H, \( \textit{J} = 8.4 \) Hz), 6.96 (d, 2H, \( \textit{J} = 8.4 \) Hz), 3.94 (s, 3H), 3.85 (s, 3H), 3.10 (t, 2H, \( \textit{J} = 7.2 \) Hz), 1.73 (p, 2H, \( \textit{J} = 7.2 \) Hz), 1.43 (h, 2H, \( \textit{J} = 7.2 \) Hz), 0.96 (t, 3H, \( \textit{J} = 7.2 \) Hz) ppm; \textit{^{13}C} NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta = 162.9, 161.6, 159.8, 159.7, 128.2, 127.8, 119.3, 114.0, 55.3, 51.8, 29.8, 25.6, 22.2, 13.6 \) ppm; HRMS m/z (ESI) calcd for [C\textsubscript{16}H\textsubscript{19}NO\textsubscript{4}+H]\textsuperscript{+} 290.1392, found 290.1385.

Methyl 5-\textit{n}-Butyl-2-(3-methoxylphenyl)oxazole-4-carboxylate (3e):

\begin{center}
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\end{center}

The reaction of 0.3 mmol of methyl 2-(3-methoxylphenyl)oxazole-4-carboxylate (1e) and 1.2 mmol of \textit{n}-butylboronic acid (2a) afforded 74% of 3d after flash chromatography on silica gel using petroleum ether and ethyl acetate (12:1 to 10:1, \textit{v}/\textit{v}) as the effluent. Light yellow solid, m.p. 53-55 °C. \textit{^1}H NMR (CDCl\textsubscript{3}, 400 MHz): \( \delta = 7.66-7.60 \) (m, 2H), 7.36 (t, 1H, \( \textit{J} = 8.0 \) Hz), 7.02-7.00 (m, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.12 (t, 2H, \( \textit{J} = 7.6 \) Hz), 1.75 (p, 2H, \( \textit{J} = 7.6 \) Hz), 1.43 (h, 2H, \( \textit{J} = 7.6 \) Hz), 0.97 (t, 3H, \( \textit{J} = 7.6 \) Hz) ppm; \textit{^{13}C} NMR (CDCl\textsubscript{3}, 100 MHz): \( \delta = 162.7, 160.4, 159.8, 159.5, 129.7, 128.0, 127.7, 119.0, 117.3, 111.0, 55.4, 51.9, 29.8, 25.7, 22.2, 13.6 \) ppm; HRMS m/z (ESI) calcd for [C\textsubscript{16}H\textsubscript{19}NO\textsubscript{4}+H]\textsuperscript{+} 290.1404, found 290.1392.
Methyl 5-n-Butyl-2-(4-trifluoromethylphenyl)oxazole-4-carboxylate (3f):

The reaction of 0.3 mmol of methyl 2-(4-trifluoromethylphenyl)oxazole-4-carboxylate (1f) and 1.2 mmol of n-butylboronic acid (2a) afforded 60% of 3f after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1, v/v) as the effluent. Offwhite solid, m.p. 57-59 °C. 1H NMR (CDCl3, 400 MHz): δ = 8.19 (d, 2H, J = 8.0 Hz), 7.72 (d, 2H, J = 8.0 Hz), 3.96 (s, 3H), 3.14 (t, 2H, J = 7.6 Hz), 1.76 (p, 2H, J = 7.6 Hz), 1.44 (h, 2H, J = 7.6 Hz), 0.98 (t, 3H, J = 7.6 Hz) ppm; 13C NMR (CDCl3, 100 MHz): δ = 162.5, 161.1, 158.2, 132.3 (q, J = 32.6 Hz), 129.7, 128.5, 126.8, 125.8 (d, J = 11.1 Hz), 125.7 (d, J = 3.7 Hz), 52.1, 29.8, 25.8, 22.2, 13.6 ppm; HRMS m/z (ESI) calcd for [C16H16F3NO3]+ 328.1161, found 328.1155.

Methyl 5-n-Butyl-2-(4-fluorophenyl)oxazole-4-carboxylate (3g):

The reaction of 0.3 mmol of methyl 2-(4-fluorophenyl)oxazole-4-carboxylate (1g) and 1.2 mmol of n-butylboronic acid (2a) afforded 75% of 3f after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Offwhite solid, m.p. 41-42 °C. 1H NMR (CDCl3, 400 MHz): δ = 8.08-8.05 (m, 2H), 7.17-7.12 (m, 2H), 3.95 (s, 3H), 3.11 (t, 2H, J = 7.6 Hz), 1.74 (p, 2H, J = 7.6 Hz), 1.43 (h, 2H, J = 7.6 Hz), 0.97 (t, 3H, J = 7.6 Hz) ppm; 13C NMR (CDCl3, 100 MHz): δ = 164.2 (d, J = 250.3 Hz), 162.7, 160.4, 158.8, 128.7 (d, J = 8.6 Hz), 128.1, 122.9 (d, J = 3.1 Hz), 115.9 (d, J = 22.2 Hz), 115.8, 51.9, 29.8, 25.7, 22.2, 13.6 ppm; HRMS m/z (ESI) calcd for [C15H15FNO3]+ 278.1193, found 278.1189.

Methyl 5-n-Butyl-2-(3-fluorophenyl)oxazole-4-carboxylate (3h):

The reaction of 0.3 mmol of methyl 2-(3-fluorophenyl)oxazole-4-carboxylate (1h) and 1.2 mmol of n-butylboronic acid (2a) afforded 68% of 3g after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Offwhite solid, m.p. 54-56 °C. 1H NMR (CDCl3, 400 MHz): δ = 7.87 (t, 1H, J = 8.0 Hz), 7.79-7.75 (m, 1H), 7.46-7.40 (m, 1H), 7.19-7.14 (m, 1H), 3.95 (s, 3H), 3.12 (t, 2H, J = 7.6 Hz), 1.75 (p,
Methyl 5-n-Butyl-2-(2-fluorophenyl)oxazole-4-carboxylate (3i):

The reaction of 0.3 mmol of methyl 2-(2-fluorophenyl)oxazole-4-carboxylate (1i) and 1.2 mmol of n-butylboronic acid (2a) afforded 72% of 3h after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Offwhite solid, m.p. 36-37 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.08\) (t, 1H, \(J = 7.6\) Hz), 7.48-7.42 (m, 1H), 7.26-7.17 (m, 2H), 3.95 (s, 3H), 3.14 (t, 2H, \(J = 7.6\) Hz), 1.75 (p, 2H, \(J = 7.6\) Hz), 1.43 (h, 2H, \(J = 7.6\) Hz), 0.97 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 162.7, 160.7\) (d, \(J = 1.3\) Hz), 160.0 (d, \(J = 255.8\) Hz), 156.2 (d, \(J = 4.3\) Hz), 132.4 (d, \(J = 8.5\) Hz), 129.8 (d, \(J = 1.3\) Hz), 128.0, 124.2 (d, \(J = 3.7\) Hz), 116.7 (d, \(J = 21.1\) Hz), 114.9 (d, \(J = 11.0\) Hz), 51.9, 29.7, 25.7, 22.2, 13.6 ppm; HRMS m/z (ESI) calcd for [C\(_{15}\)H\(_{16}\)FNO\(_3\)+H]\(^+\) 278.1193, found 278.1188.

Methyl 5-n-Butyl-2-(4-chlorophenyl)oxazole-4-carboxylate (3j):

The reaction of 0.3 mmol of methyl 2-(4-chlorophenyl)oxazole-4-carboxylate (1j) and 1.2 mmol of n-butylboronic acid (2a) afforded 69% of 3i after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Light yellow solid, m.p. 71-73 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.01\) (d, 2H, \(J = 8.8\) Hz), 7.43 (d, 2H, \(J = 8.8\) Hz), 3.95 (s, 3H), 3.11 (t, 2H, \(J = 7.6\) Hz), 1.74 (p, 2H, \(J = 7.6\) Hz), 1.43 (h, 2H, \(J = 7.6\) Hz), 0.97 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 162.6, 160.5, 158.7, 136.9, 129.0, 128.2, 127.8, 125.1, 52.0, 29.8, 25.7, 22.2, 13.6\) ppm; HRMS m/z (ESI) calcd for [C\(_{15}\)H\(_{16}\)ClNO\(_3\)+H]\(^+\) 294.0891, found 294.0887.

Methyl 5-n-Butyl-2-(4-bromophenyl)oxazole-4-carboxylate (3k):

The reaction of 0.3 mmol of methyl 2-(4-bromophenyl)oxazole-4-carboxylate (1k) and 1.2 mmol of n-butylboronic acid (2a) afforded 72% of 3h after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Offwhite solid, m.p. 36-37 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.01\) (d, 2H, \(J = 8.8\) Hz), 7.43 (d, 2H, \(J = 8.8\) Hz), 3.95 (s, 3H), 3.11 (t, 2H, \(J = 7.6\) Hz), 1.74 (p, 2H, \(J = 7.6\) Hz), 1.43 (h, 2H, \(J = 7.6\) Hz), 0.97 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 162.6, 160.5, 158.7, 136.9, 129.0, 128.2, 127.8, 125.1, 52.0, 29.8, 25.7, 22.2, 13.6\) ppm; HRMS m/z (ESI) calcd for [C\(_{15}\)H\(_{16}\)BrNO\(_3\)+H]\(^+\) 294.0891, found 294.0887.
carboxylate (1k) and 1.2 mmol of \(n\)-butylboronic acid (2a) afforded 62% of 3j after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, \(v/v\)) as the effluent. Light yellow solid, m.p. 62-63 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 7.94\) (d, 2H, \(J = 8.4\) Hz), 7.59 (d, 2H, \(J = 8.4\) Hz), 3.95 (s, 3H), 3.11 (t, 2H, \(J = 7.6\) Hz), 1.74 (p, 2H, \(J = 7.6\) Hz), 1.43 (h, 2H, \(J = 7.6\) Hz), 0.97 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 162.6, 160.6, 158.7, 132.0, 128.2, 127.9 125.5, 125.3, 52.0, 29.8, 25.7, 22.2, 13.6\) ppm; HRMS m/z (ESI) calcd for \([C_{15}H_{16}BrNO_3+H]^+\) 338.0392, found 338.0385.

Methyl 5-\(n\)-Butyl-2-\(n\)-propyloxazole-4-carboxylate (3l):

The reaction of 0.3 mmol of methyl 2-\(n\)-propyloxazole-4-carboxylate (1l) and 1.2 mmol of \(n\)-butylboronic acid (2a) afforded 65% of 3l after flash chromatography on silica gel using petroleum ether and ethyl acetate (50:1, \(v/v\)) as the effluent. Colorless oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 3.89\) (s, 3H), 3.01 (t, 2H, \(J = 7.6\) Hz), 2.72 (t, 2H, \(J = 7.6\) Hz), 1.79 (q, 2H, \(J = 7.6\) Hz), 1.66 (p, 2H, \(J = 7.6\) Hz), 1.37 (h, 2H, \(J = 7.6\) Hz), 0.98 (t, 3H, \(J = 7.6\) Hz), 0.94 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 162.9, 160.0, 143.6, 126.6, 31.7, 29.8, 29.7, 25.5, 22.1, 20.4, 13.6, 13.6\) ppm; HRMS m/z (ESI) calcd for \([C_{12}H_{19}NO_3+Na]^+\) 248.1263, found 248.1263.

\(N\)-Ethyl 5-\(n\)-Butyl-2-phenyloxazole-4-formamide (3m):

The reaction of 0.3 mmol of \(N\)-ethyl 2-phenyloxazole-4-formamide (1m) and 1.2 mmol of \(n\)-butylboronic acid (2a) afforded 70% of 3m after flash chromatography on silica gel using petroleum ether and ethyl acetate (12:1, \(v/v\)) as the effluent. Yellow solid, m.p. 55-57 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.02-7.99\) (m, 2H), 7.47-7.44 (m, 3H), 7.09 (s, 1H), 3.50-3.44 (m, 2H), 3.16 (t, 2H, \(J = 7.6\) Hz), 1.74 (p, 2H, \(J = 7.6\) Hz), 1.44 (h, 2H, \(J = 7.6\) Hz), 1.26 (t, 3H, \(J = 7.2\) Hz), 0.96 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 161.8, 158.4, 156.7, 130.4, 129.9, 128.7, 126.9, 126.2, 33.7, 30.0, 25.5, 22.3, 14.9, 13.7\) ppm; HRMS m/z (ESI) calcd for \([C_{16}H_{20}N_2O_2+H]^+\) 273.1603, found 273.1598.

\(N\)-\(n\)-Butyl 5-\(n\)-Butyl-2-phenyloxazole-4-formamide (3n):

The reaction of 0.3 mmol of \(N\)-\(n\)-butyl 2-phenyloxazole-4-formamide (1n) and 1.2 mmol of \(n\)-butylboronic acid (2a) afforded 68% of 3n after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, \(v/v\)) as the effluent. Yellow solid, m.p. 61-63 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 8.03-7.99\) (m, 2H), 7.49-7.45 (m, 3H), 7.06 (s, 1H), 3.50-3.44 (m, 2H), 3.16 (t, 2H, \(J = 7.6\) Hz), 1.74 (p, 2H, \(J = 7.6\) Hz), 1.44 (h, 2H, \(J = 7.6\) Hz), 1.26 (t, 3H, \(J = 7.2\) Hz), 0.96 (t, 3H, \(J = 7.6\) Hz) ppm; \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 159.8, 158.4, 156.7, 130.4, 129.9, 128.7, 126.9, 126.2, 33.7, 30.0, 25.5, 22.3, 14.9, 13.7\) ppm; HRMS m/z (ESI) calcd for \([C_{16}H_{22}N_2O_2+H]^+\) 275.1603, found 275.1598.
and 1.2 mmol of $n$-butylboronic acid (2a) afforded 69% of 3n after flash chromatography on silica gel using petroleum ether and ethyl acetate (10:1, v/v) as the effluent. Light yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.02-7.99 (m, 2H), 7.46-7.44 (m, 3H), 7.13-7.11 (m, 1H), 3.42 (q, 2H, $J$ = 7.2 Hz), 3.16 (t, 2H, $J$ = 7.6 Hz), 1.74 (p, 2H, $J$ = 7.6 Hz), 1.61 (p, 2H, $J$ = 7.2 Hz), 1.46-1.40 (m, 4H), 0.98-0.94 (m, 6H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 161.9, 158.4, 156.7, 130.4, 130.0, 128.7, 126.9, 126.2, 38.6, 31.8, 30.0, 25.5, 22.3, 20.1, 13.7, 13.7 ppm; HRMS m/z (ESI) calcd for [C$_{18}$H$_{24}$N$_2$O$_2$+H]$^+$ 301.1916, found 301.1909.

*N*-Cyclohexyl 5-$n$-Butyl-2-phenyloxazole-4-formamide (3o):

The reaction of 0.3 mmol of *N*-cyclohexyl 2-phenyloxazole-4-formamide (1o) and 1.2 mmol of $n$-butylboronic acid (2a) afforded 63% of 3o after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Light yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.02-8.00 (m, 2H), 7.47-7.45 (m, 3H), 7.00-6.98 (m, 1H), 3.97-3.90 (m, 1H), 3.16 (t, 2H, $J$ = 7.6 Hz), 2.04-2.00 (m, 2H), 1.79-1.64 (m, 4H), 1.46-1.20 (m, 8H), 0.96 (t, 3H, $J$ = 7.6 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 161.0, 158.3, 156.7, 130.4, 130.0, 128.7, 126.9, 126.2, 47.7, 33.2, 30.0, 25.5, 25.5, 24.9, 22.3, 13.7 ppm; HRMS m/z (ESI) calcd for [C$_{20}$H$_{26}$N$_2$O$_2$+H]$^+$ 327.2073, found 327.2066.

*N,N*-Diethyl 5-$n$-Butyl-2-phenyloxazole-4-formamide (3p):

The reaction of 0.3 mmol of *N,N*-diethyl 2-phenyloxazole-4-formamide (1p) and 1.2 mmol of $n$-butylboronic acid (2a) afforded 45% of 3p after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Light yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ = 8.01-7.99 (m, 2H), 7.47-7.45 (m, 3H), 7.00-6.98 (m, 1H), 3.97-3.90 (m, 1H), 3.16 (t, 2H, $J$ = 7.6 Hz), 2.04-2.00 (m, 2H), 1.79-1.64 (m, 4H), 1.46-1.20 (m, 8H), 0.96 (t, 3H, $J$ = 7.6 Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ = 163.0, 157.8, 157.1, 131.7, 130.1, 128.7, 127.4, 126.1, 43.1, 40.6, 30.1, 25.7, 22.3, 14.6, 13.7, 12.9 ppm; HRMS m/z (ESI) calcd for [C$_{18}$H$_{24}$N$_2$O$_2$+H]$^+$ 301.1916, found 301.1910.

*N,N*-Diethyl 5-$n$-Butyl-2,4-diphenyloxazole (3q):

The reaction of 0.3 mmol of *N,N*-diethyl 2,4-diphenyloxazole (1q) and 1.2
mmol of \( n \)-butylboronic acid (2a) afforded 78% of 3q after flash chromatography on silica gel using petroleum ether and ethyl acetate (50:1, v/v) as the effluent. Light yellow oil. \( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta = 8.10-8.07 \) (m, 2H), 7.73-7.71 (m, 2H) 7.47-7.40 (m, 6H), 2.94 (t, 2H, \( J = 7.6 \) Hz), 1.78 (p, 2H, \( J = 7.6 \) Hz), 1.46 (h, 2H, \( J = 7.6 \) Hz), 0.96 (t, 3H, \( J = 7.6 \) Hz) ppm; \(^{13}C \) NMR (CDCl\(_3\), 100 MHz): \( \delta = 159.4, 148.2, 135.8, 132.5, 129.9, 128.6, 128.6, 127.7, 127.3, 127.0, 126.1, 30.4, 25.7, 22.4, 13.8 \) ppm; HRMS m/z (ESI) calcd for \([C_{19}H_{19}NO+H]^+\) 278.1545, found 278.1543.

Methyl 5-Ethyl-2-phenyloxazole-4-carboxylate (3r):

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of ethylboronic acid (2b) afforded 70% of 3r after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1, v/v) as the effluent. Offwhite solid, m.p. 72-73 °C. \( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta = 8.09-8.07 \) (m, 2H), 7.47-7.44 (m, 3H), 3.95 (s, 3H), 3.15 (q, 2H, \( J = 7.6 \) Hz), 1.35 (t, 3H, \( J = 7.6 \) Hz) ppm; \(^{13}C \) NMR (CDCl\(_3\), 100 MHz): \( \delta = 162.8, 161.2, 159.6, 130.7, 128.7, 127.6, 126.6, 126.5, 51.9, 19.7, 12.1 \) ppm; HRMS m/z (ESI) calcd for \([C_{13}H_{13}NO_3+H]^+\) 232.0974, found 232.0965.

Methyl 5-n-Propyl-2-phenyloxazole-4-carboxylate (3s):

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of \( n \)-propylboronic acid (2c) afforded 73% of 3s after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Colorless oil. \( ^1H \) NMR (CDCl\(_3\), 400 MHz): \( \delta = 8.09-8.07 \) (m, 2H), 7.46-7.45 (m, 3H), 3.95 (s, 3H), 3.15 (q, 2H, \( J = 7.6 \) Hz), 1.80 (h, 2H, \( J = 7.6 \) Hz), 1.03 (t, 3H, \( J = 7.6 \) Hz) ppm; \(^{13}C \) NMR (CDCl\(_3\), 100 MHz): \( \delta = 162.8, 160.1, 159.6, 130.7, 128.7, 127.6, 126.6, 126.5, 51.9, 27.8, 21.2, 13.6 \) ppm; HRMS m/z (ESI) calcd for \([C_{14}H_{15}NO_3+H]^+\) 246.1130, found 246.1125.

Methyl 5-n-Pentyl-2-phenyloxazole-4-carboxylate (3t):

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of \( n \)-pentylboronic acid (2d) afforded 77% of 3t after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent.
Colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.09$-8.07 (m, 2H), 7.47-7.44 (m, 3H), 3.95 (s, 3H), 3.11 (t, 2H, $J = 7.6$ Hz), 1.76 (p, 2H, $J = 7.6$ Hz), 1.40-1.37 (m, 4H), 0.91 (t, 3H, $J = 7.6$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 162.8$, 160.4, 159.6, 130.7, 128.7, 128.0, 126.6, 126.5, 51.9, 31.2, 27.4, 25.9, 22.2, 13.8 ppm; HRMS $m/z$ (ESI) calcd for [C$_{16}$H$_{19}$NO$_3$+H]$^+$ 274.1443, found 274.1437.

Methyl 5-$n$-Hexyl-2-phenyloxazole-4-carboxylate (3u):

![Chemical Structure](image)

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of $n$-hexylboronic acid (2e) afforded 68% of 3u after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.09$-8.07 (m, 2H), 7.47-7.45 (m, 3H), 3.95 (s, 3H), 3.11 (t, 2H, $J = 7.6$ Hz), 1.76 (p, 2H, $J = 7.6$ Hz), 1.42-1.31 (m, 6H), 0.89 (t, 3H, $J = 7.6$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 162.8$, 160.4, 159.6, 130.7, 128.7, 128.0, 126.6, 126.5, 51.9, 31.3, 28.7, 27.7, 26.0, 22.4, 14.0 ppm; HRMS $m/z$ (ESI) calcd for [C$_{17}$H$_{21}$NO$_3$+H]$^+$ 288.1600, found 288.1593.

Methyl 5-(2-Phenylethyl)-2-phenyloxazole-4-carboxylate (3v):

![Chemical Structure](image)

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of 2-phenylethylboronic acid (2f) afforded 72% of 3v after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1, v/v) as the effluent. Light yellow solid, m.p. 65-67 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.05$-8.03 (m, 2H), 7.46-7.44 (m, 3H), 7.31-7.21 (m, 5H), 3.92 (s, 3H), 3.43 (t, 2H, $J = 8.0$ Hz), 3.07 (t, 2H, $J = 8.0$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 162.6$, 159.8, 159.0, 140.0, 130.8, 128.7, 128.5, 128.3, 126.6, 126.5, 126.4, 52.0, 34.0, 28.0 ppm; HRMS $m/z$ (ESI) calcd for [C$_{19}$H$_{17}$NO$_3$+H]$^+$ 308.1281, found 308.1278.

Methyl 5-(2-Methylpropyl)-2-phenyloxazole-4-carboxylate (3w):

![Chemical Structure](image)

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1a) and 1.2 mmol of 2-methylpropylboronic acid (2g) afforded 64% of 3w after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1, v/v) as the effluent.
Light yellow solid, m.p. 38-39 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.09-8.07$ (m, 2H), 7.48-7.44 (m, 3H), 3.95 (s, 3H), 3.01 (d, 2H, $J = 6.8$ Hz), 2.21-2.11 (m, 1H), 1.01 (t, 6H, $J = 6.8$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 162.8, 159.7, 159.5, 130.7, 128.8, 128.7, 126.6, 126.5, 51.9, 34.6, 28.1, 22.3$ ppm; HRMS $m/z$ (ESI) calcd for [C$_{15}$H$_{17}$NO$_3$+H]$^+$ 260.1287, found 260.1283.

**Methyl 5-\textit{i}-Propyl-2-phenyloxazole-4-carboxylate (3\textit{x}):**

![Chemical structure](image)

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1\textit{a}) and 1.2 mmol of \textit{i}-propylboronic acid (2\textit{h}) afforded 83% of 3\textit{x} after flash chromatography on silica gel using petroleum ether and ethyl acetate (20:1, v/v) as the effluent. Offwhite solid, m.p. 48-50 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.09-8.07$ (m, 2H), 7.48-7.44 (m, 3H), 3.95 (s, 3H), 3.86 (sept, 1H, $J = 7.2$ Hz), 1.37 (d, 6H, $J = 7.2$ Hz) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 164.3, 162.7, 159.3, 130.6, 128.6, 126.6, 126.5, 51.9, 26.1, 20.6$ ppm; HRMS $m/z$ (ESI) calcd for [C$_{14}$H$_{15}$NO$_3$+H]$^+$ 246.1130, found 246.1125.

**Methyl 5-Cyclohexyl-2-phenyloxazole-4-carboxylate (3\textit{y}):**

![Chemical structure](image)

The reaction of 0.3 mmol of methyl 2-phenyloxazole-4-carboxylate (1\textit{a}) and 1.2 mmol of cyclohexylboronic acid (2\textit{i}) afforded 40% of 3\textit{y} after flash chromatography on silica gel using petroleum ether and ethyl acetate (15:1, v/v) as the effluent. Light yellow solid, m.p. 107-108 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 8.09-8.06$ (m, 2H), 7.46-7.45 (m, 3H), 3.95 (s, 3H), 3.57-3.49 (m, 1H), 1.96-1.61 (m, 6H), 1.50-1.20 (m, 4H) ppm; $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta = 164.0, 162.9, 159.3, 130.7, 128.7, 126.7, 126.7, 126.5, 51.9, 35.6, 30.8, 25.9, 25.7$ ppm; HRMS $m/z$ (ESI) calcd for [C$_{17}$H$_{19}$NO$_3$+H]$^+$ 286.1443, found 286.1438.
Electronic Supplementary Information
Electronic Supplementary Information

![Chemical Structure](image)

**S16**
3p
Electronic Supplementary Information
Electronic Supplementary Information
**Electronic Supplementary Information**

![Chemical Structure](image)

**Bruker**

**S57**
Electronic Supplementary Information

3y

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INSTRNM spect
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LB    0.30 Hz
TB    1.00

S60