Supporting Information

An efficient D-glucosamine-based copper catalyst for C-X couplings and its application in the synthesis of Nilotinib intermediate

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1. General
The starting materials were commercially available and were used without further purification except solvents. The products were isolated by column chromatography on silica gel (200-300 mesh) using petroleum ether (60-90 °C) and ethyl acetate. Melting points were determined on an X-5 Data microscopic melting point apparatus. $^1$H NMR spectra were recorded on a Bruker Advance 400 spectrometer at ambient temperature with CDCl$_3$ or DMSO-$d_6$ as solvent unless otherwise noted and tetramethylsilane (TMS) as the internal standard. $^1$H NMR data were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet and br = broad), coupling constant (J values, Hz). Mass spectra (EI-MS) were acquired on an Agilent 5975 spectrometer. Analytical thin layer chromatography (TLC) was performed on Merk precoated TLC (silica gel 60 F254) plates.

2. Experimental Section

2.1 General Procedure for C-N Cross-Coupling Reactions
A mixture of aryl halides (1 mmol), nitrogen nucleophile (1.2 mmol), CuI (0.1 mmol), D-glucosamine (0.1 mmol), and 2 mL of DMSO-H$_2$O (1:1) in a tube was heated to 100 °C under air. The progress of the reaction was monitored by TLC using EtOAc and hexane as eluent. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. After drying with anhydrous MgSO$_4$ overnight, the liquid was analyzed by GC-MS and then the residue was purified on short pad of silica gel using EtOAc and hexane as eluent. All compounds were characterized by $^1$H NMR and mass spectroscopy, which were consistent with those reported in the literature.$^{1-5}$ The 3-bromo-5-(trifluoro methyl) aniline $^6$ was prepared to corresponding reference.$^6$

2.2 General Procedure for C-S Cross-Coupling Reactions
A mixture of aryl halides (1 mmol), phenyl disulfide (0.6 mmol), CuI (0.1 mmol), D-glucosamine (0.1 mmol), and 3 mL of DMSO-H$_2$O (1:1) in a tube was heated to at 80-110 °C under air. Monitoring of the reaction, workup procedure, and purification of the C-S cross-coupled products were performed as described for the C-N cross-coupling reactions. All compounds were characterized by $^1$H NMR and GC-MS spectroscopy, which were consistent with those reported in the literature.$^7$-$^9$

3. Characterization of the Products

1-(4-methoxy-phenyl)-1H-imidazole 3a$^1$:  

\[
\begin{align*}
\text{Rufous solid; m.p.: } & 60–62 °C. \\
^1\text{H NMR (400 MHz, DMSO-d6): } & \delta 8.13 (s, 1H), 7.63 (s, 1H), 7.55 (d, J = 7.2 Hz, 2H), 7.09 (t, J = 9.6 Hz, 3H), 3.80 (s, 3H); \\
\text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_{10}\text{H}_{10}\text{N}_2\text{O}: 174.1, \text{ found: 174.}
\end{align*}
\]

1-(p-tolyl)-1H-imidazole 3b$^{1,2}$:

\[
\begin{align*}
\text{White solid; m.p.: } & 45–47 °C. \\
^1\text{H NMR (400 MHz, DMSO-d6): } & \delta 8.21 (s, 1H), 7.69 (s, 1H), 7.53 (d, J = 6.8 Hz, 2H), 7.31 (d, J = 6.4 Hz, 2H), 7.11 (s, 1H), 2.34 (s, 3H); \\
\text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_{10}\text{H}_{10}\text{N}_2: 158.1, \text{ found: 158.}
\end{align*}
\]

4-(1H-imidazol-1-yl)aniline 3c$^{1,2}$:

\[
\begin{align*}
\text{White needles; m.p.: } & 141–143 °C. \\
^1\text{H NMR (400 MHz, DMSO-d6): } & \delta 8.60 (s, 1H), 8.38 (d, J = 7.2 Hz, 2H), 8.01 (t, J = 7.2 Hz, 3H), 7.24 (s, 1H); \\
\text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_9\text{H}_9\text{N}_3: 159.1, \text{ found: 159.}
\end{align*}
\]

1-biphenyl-4-yl-1H-imidazole 3d$^1$:

\[
\begin{align*}
\text{Yellow solid; m.p.: } & 150–152 °C. \\
^1\text{H NMR (400 MHz, DMSO-d6): } & \delta 8.34 (s, 1H), 7.81 (t, J = 4.4 Hz, 3H), 7.75 (d, J = 6.8 Hz, 2H), 7.72 (d, J = 5.6 Hz, 2H), 7.50 (t, J = 6 Hz, 2H), 7.40 (t, J = 5.6 Hz, 1H), 7.16 (s, 1H); \\
\text{GC-MS (EI) }
\end{align*}
\]
[M]+: m/z calcd. for C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}: 220.1, found: 220.

1-(4-chlorophenyl)-1\textsubscript{H}-imidazole 3e:\n
\[
\text{Cl} - \text{C} \equiv \text{C} \equiv \text{N} - \text{N} \equiv \text{N}
\]

brown oil; \(\text{^1H NMR (400 MHz, DMSO-}\text{d}_6): \delta \text{ 8.28 (s, 1H), 7.76 (s, 1H), 7.71 (d, } J = 7.2 \text{ Hz, 2H), 7.58 (d, } J = 6.8 \text{ Hz, 2H), 7.13 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for C}_9\text{H}_7\text{ClN}_2: 178.0, \text{ found: 178.}\)

1-(4-(trifluoromethyl)phenyl)-1\textsubscript{H}-imidazole 3f:\n
\[
\text{F}_3\text{C} - \text{C} \equiv \text{C} \equiv \text{N} - \text{N} \equiv \text{N}
\]

brown solid; m.p.: 69–71 °C. \(\text{^1H NMR (400MHz, DMSO): } \delta \text{ 7.93 (s, 1H), 7.76 (d, } J = 8.0 \text{ Hz, 2H), 7.53 (d, } J = 8.0 \text{ Hz, 2H), 7.34 (s, 1H), 7.27 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for C}_{10}\text{H}_{3}\text{F}_3\text{N}_2: 212.1, \text{ found: 212.}\)

1-phenyl-1\textsubscript{H}-imidazole 3g:\n
\[
\text{N} \equiv \text{C} \equiv \text{N} - \text{N} \equiv \text{N}
\]

slightly yellow oil; \(\text{^1H NMR (400 MHz, DMSO-}\text{d}_6): \delta \text{ 8.27 (s, 1H), 7.75 (s, 1H), 7.66 (d, } J = 6 \text{ Hz, 2H), 7.53 (t, } J = 6 \text{ Hz, 2H), 7.38 (t, } J = 5.6 \text{ Hz, 1H), 7.13 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for C}_9\text{H}_8\text{N}_2: 144.1, \text{ found: 144.}\)

1-(1H-pyrazol-4-yl)-1\textsubscript{H}-imidazole 3h:\n
\[
\text{HN} - \text{C} \equiv \text{C} \equiv \text{N} - \text{N} \equiv \text{N}
\]

brown oil; \(\text{^1H NMR (400 MHz, DMSO-}\text{d}_6): \delta \text{ 8.42 (s, 1H), 7.93 (t, } J = 7.2 \text{ Hz, 4H), 7.17 (s, 1H); GC-MS (EI) [M]+: m/z calcd. for C}_9\text{H}_8\text{N}_4: 134.1, \text{ found: 134.}\)

1-(4-methoxyphenyl)-4-methyl-1\textsubscript{H}-imidazole 3i:\n
\[
\text{O} - \text{C} \equiv \text{C} \equiv \text{N} - \text{N} \equiv \text{N}
\]

white needles; m.p.: 78–80 °C. \(\text{^1H NMR (400 MHz, DMSO-}\text{d}_6): \delta \text{ 7.64 (s, 1H), 7.27 (d, } J = 9.5 \text{, 2H), 6.97 (d, } J = 9.2 \text{ H), 6.82 (s, 1H) 3.84 (s, 3H) 2.29 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for C}_{11}\text{H}_{12}\text{O}: 188.1, \text{ found: 188.}\)
1-(4-methoxyphenyl)-1H-indole 3j:

\[
\begin{align*}
\text{white crystalline solid; mp } & 59-61 \, ^\circ\text{C}. \quad ^1\text{H NMR (400 MHz, DMSO-}\text{d}_6): \delta 7.61 (d, J = 7.32 \, Hz, 1 \, H), 7.39-7.36 (m, 3 \, H), 7.23-7.20 (m, 1 \, H), 7.15-7.06 (m, 2 \, H), 6.99-6.96 (m, 2 \, H), 6.58-6.57 (d, J = 2.93 \, Hz, 1 \, H), 3.85 (s, 3 \, H); \text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_{15}\text{H}_{13}\text{NO: 223.1, found: 223.}
\end{align*}
\]

1-(4-methoxyphenyl)pyrrolidine 3k:

\[
\begin{align*}
\text{yellow solid; m.p.: } & 46-48 \, ^\circ\text{C. } \quad ^1\text{H NMR (400 MHz, DMSO-}\text{d}_6): \delta 1.97-2.01 (m, 4 \, H), 2.22-3.26 (m, 4 \, H), 3.74 (s, 3 \, H), 6.58-6.61 (d, 2 \, H), 6.81-6.85 (m, 2 \, H); \text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_{11}\text{H}_{15}\text{NO: 177.1, found: 177.}
\end{align*}
\]

1-(4-methoxyphenyl)-1H-benzo[d]imidazol-2-amine 3l:

\[
\begin{align*}
\text{yellow solid; m.p.: } & 195-197 \, ^\circ\text{C. } \quad ^1\text{H NMR (400 MHz, DMSO-}\text{d}_6): \delta 7.40 (d, J = 6.8 \, Hz, 2 \, H), 7.23 (d, J = 6 \, Hz, 1 \, H), 7.16 (d, J = 4 \, Hz, 2 \, H), 7.02 (t, J = 6.8 \, Hz, 1 \, H), 6.88 (t, J = 8 \, Hz, 1 \, H), 6.80 (d, J = 6.4 \, Hz, 1 \, H), 6.21 (s, 2 \, H); \text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_{14}\text{H}_{13}\text{N}_3\text{O: 239.1, found: 239.}
\end{align*}
\]

4-methoxyphenyl phenyl sulfide 5a:

\[
\begin{align*}
\text{colorless oil; } ^1\text{H NMR (400 MHz, CDCl}_3): \delta 7.41 (d, J = 8.8 \, Hz, 2 \, H), 7.27-7.08 (m, 5 \, H), 6.88 ( J = 8.8 \, Hz, 2 \, H), 3.80 (s, 3 \, H); \text{GC-MS (EI) } [M]^+: m/z \text{ calcd. for C}_{13}\text{H}_{12}\text{OS: 216.1, found: 216.}
\end{align*}
\]

(4-nitrophenyl)(phenyl)sulfane 5b:

\[
\begin{align*}
\text{colorless oil; } ^1\text{H NMR (400 MHz, CDCl}_3): \delta 8.07 (dd, J = 8.8, 2.4 \, Hz, 2 \, H), 7.55-7.53 (m, 2 \, H), 7.47-7.45 (m, 3 \, H), 7.16 (dd, J = 8.8, 2.8 \, Hz, 2 \, H);
\end{align*}
\]
GC-MS (EI) [M]+: m/z calcd. for C_{12}H_{9}NO_{2}S: 231.0, found: 231.

4-chlorophenyl phenyl sulfide 5c:
\[
\begin{array}{c}
\text{Cl} \quad \text{S} \\
\end{array}
\]
colorless oil; \(^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.35-7.23 (m, 9H). GC-MS (EI) [M]+: m/z calcd. for C_{12}H_{9}ClS: 220.0, found: 220.

(Naphthalen-2-yl)(phenyl)sulfane 5d:
\[
\begin{array}{c}
\text{S} \\
\end{array}
\]
colorless oil; \(^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.83-7.76 (m, 2H), 7.74-7.70 (m, 2H), 7.48-7.44 (m, 2H), 7.41-7.36 (m, 2H), 7.32-7.23 (m, 4H); GC-MS (EI) [M]+: m/z calcd. for C_{18}H_{14}S: 262.1, found: 262.

phenyl(o-tolyl)sulfane 5e:
\[
\begin{array}{c}
\text{S} \\
\end{array}
\]
colorless oil; \(^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 2.42 (s, 3H), 7.16-7.37 (m, 9H). GC-MS (EI) [M]+: m/z calcd. for C_{13}H_{12}S: 200.1, found: 200.

4-(phenylthio)-1\textit{H}-pyrazole 5f:
\[
\begin{array}{c}
\text{HN} \quad \text{N} \\
\text{S} \\
\end{array}
\]
colorless oil; \(^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 6.95-7.07 (m, 3H), 7.09-7.19 (m, 2H), 7.68 (s, 2H); GC-MS (EI) [M]+: m/z calcd. for C_{9}H_{8}N_{2}S: 176.0, found: 176.

diphenyl sulfide 5g:
\[
\begin{array}{c}
\text{S} \\
\end{array}
\]
colorless oil; \(^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.37-7.16 (m, 10H). GC-MS (EI) [M]+: m/z calcd. for C_{12}H_{10}S: 186.1, found: 186.

Nilotinib intermediate 7:
\[
\begin{array}{c}
\text{HN} \quad \text{N} \\
\text{S} \\
\end{array}
\]
colorless oil ;\(^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 7.79 (s, H), 7.01 (s, H), (m, 2H), 6.94 (s, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 4.18 (b, 2H), 2.30 (s, 3H); GC-MS (EI) [M]+: m/z calcd. for C_{11}H_{8}F_{3}N_{3}O_{2}: 241.0, found: 241.
The selected NMR and GC-MS chromatogram of products:

1-(4-methoxyphenyl)-1H-imidazole 3a:

\[
\text{O} \quad \text{N} \quad \text{N} \quad \text{HNMR:}
\]

1-(p-tolyl)-1H-imidazole 3b:

\[
\text{HNMR:}
\]
4-(1H-imidazol-1-yl)aniline 3c:

\[
\text{H}_2\text{N}\begin{array}{c}
\text{N} \\
\text{N}
\end{array}\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

\[^1\text{HNMR:}\]

1-biphenyl-4-yl-1H-imidazole 3d:

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

\[^1\text{HNMR:}\]
1-(4-chlorophenyl)-1\textit{H}-imidazole 3e:

\[ \text{Cl} \quad \begin{array}{c} \text{N} \\ \text{N} \end{array} \]

\[^1\text{HNMR}:\]

1-(4-(trifluoromethyl)phenyl)-1\textit{H}-imidazole 3f:

\[ \text{F}_3\text{C} \quad \begin{array}{c} \text{N} \\ \text{N} \end{array} \]

\[^1\text{HNMR}:\]
1-phenyl-1\textit{H}-imidazole 3g:

\[
\begin{array}{c}
\text{HN} \\
\text{N} \\
\text{N}
\end{array}
\]

$^1$HNMR:

1-(1\textit{H}-pyrazol-4-yl)-1\textit{H}-imidazole 3h:

\[
\begin{array}{c}
\text{HN} \\
\text{N} \\
\text{N}
\end{array}
\]

$^1$HNMR:
1-(4-methoxyphenyl)-1\textit{H}-benzo[\textit{d}]imidazol-2-amine 3l:

\[ \text{Structure Image} \]

\[^{1}\text{HNMR}:\]

Nilotinib intermediate 7

\[ \text{Structure Image} \]

\[^{1}\text{HNMR}:\]
1-(4-methoxy-phenyl)-1H-imidazole 3a:

\[
\begin{align*}
\text{GC-MS (EI) [M]+: m/z calcd. for C}_{10}\text{H}_{10}\text{N}_{2}\text{O: 174.1, found: 174.}
\end{align*}
\]

1-(p-tolyl)-1H-imidazole 3b:

\[
\begin{align*}
\text{GC-MS (EI) [M]+: m/z calcd. for C}_{10}\text{H}_{10}\text{N}_{2}: 158.1, \text{ found: 158.}
\end{align*}
\]

1-biphenyl-4-yl-1H-imidazole 3d:

\[
\begin{align*}
\text{GC-MS (EI) [M]+: m/z calcd. for C}_{15}\text{H}_{12}\text{N}_{2}: 220.1, \text{ found: 220.}
\end{align*}
\]
1-(4-chlorophenyl)-1H-imidazole 3e:

\[
\begin{aligned}
\text{Cl} & \quad - \quad \text{N} \\
\end{aligned}
\]

GC-MS (EI) [M]+: m/z calcd. for C₉H₇ClN₂: 178.0, found: 178.

1-(4-(trifluoromethyl)phenyl)-1H-imidazole 3f:

\[
\begin{aligned}
\text{F}_₃\text{C} & \quad - \quad \text{N} \\
\end{aligned}
\]

GC-MS (EI) [M]+: m/z calcd. for C₁₀H₇F₃N₂: 212.1, found: 212.
1-phenyl-1\textsubscript{H}-imidazole 3g:

\[
\begin{array}{c}
\text{N} \\
\text{N}
\end{array}
\]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}: 144.1, found: 144.

1-(4-methoxyphenyl)-4-methyl-1\textsubscript{H}-imidazole 3i:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{N}
\end{array}
\]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{11}H\textsubscript{12}N\textsubscript{2}O: 188.1, found: 188.
1-(4-methoxyphenyl)-1H-indole 3j:

\[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{15}H\textsubscript{13}NO: 223.1, found: 223.

4-chlorophenyl phenyl sulfide 5c:

\[
\begin{array}{c}
\text{Cl} \\
\end{array}
\]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{12}H\textsubscript{9}ClS: 220.0, found: 220.
(Naphthalen-2-yl)(phenyl)sulfane 5d:

\[
\begin{array}{c}
\text{Naphthalen-2-yl} \\
\text{Sulfane}
\end{array}
\]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{18}H\textsubscript{14}S: 262.1, found: 262.

phenyl(o-tolyl)sulfane 5e:

\[
\begin{array}{c}
\text{Phenyl-o-tolyl} \\
\text{Sulfane}
\end{array}
\]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{13}H\textsubscript{12}S: 200.1, found: 200.
4-(phenylthio)-1H-pyrazole 5f:

\[
\text{HN} \xrightarrow{\text{S}} \text{N} \xrightarrow{\text{S}} \text{N} \xrightarrow{\text{S}} \text{N} \]

GC-MS (EI) [M]+: m/z calcd. for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}S: 176.0, found: 176.
4. References


