Supporting Information
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# Supporting Information

Electrophilic Activation of Amides for the Preparation of Polysubstituted Pyrimidines.

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1. General Information

All glassware was flame-dried before use and all reactions were performed under an atmosphere of argon. All solvents were distilled from appropriate drying agents prior to use. Triflic anhydride was distilled over P₄O₁₀ prior to use. All other reagents were used as received from commercial suppliers unless otherwise stated. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium plates coated with silica gel F₂₅₄ with 0.2 mm thickness. Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using potassium permanganate. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck and co.). Neat infra-red spectra were recorded using a Perkin-Elmer Spectrum 100 FT-IR spectrometer. Wavenumbers (νₘₐₓ) are reported in cm⁻¹. Mass spectra were obtained using a Finnigan MAT 8200 or (70 eV) or an Agilent 5973 (70 eV) spectrometer, using electrospray ionization (ESI). All ¹H NMR, ¹³C NMR and ¹⁹F NMR spectra were recorded using a Bruker AV-400, AV-600 or AV-700 spectrometer at 300K. Chemical shifts were given in parts per million (ppm, δ), referenced to the solvent peak of CDCl₃, defined at δ = 7.26 ppm (¹H NMR) and δ = 77.16 (¹³C NMR). Coupling constants are quoted in Hz (J). ¹H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), pentet (p). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Selected ¹³C NMR spectra were recorded using the attached proton test (APT) to facilitate the confirmation and assignment of the structure.
2. Optimization

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Amide (equiv)</th>
<th>Alkyne (equiv)</th>
<th>Tf₂O (equiv)</th>
<th>X-pyridine (equiv)</th>
<th>Solvent</th>
<th>Temp / time</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOST-922</td>
<td>2.5</td>
<td>1.0</td>
<td>2.2</td>
<td>2-iodo (2.5)</td>
<td>DCE</td>
<td>90 °C / 20 h</td>
<td>46%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Isolated after 5 days</td>
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<tr>
<td>TOST-928</td>
<td>3.0</td>
<td>1.0</td>
<td>3.0</td>
<td>2-iodo (3.0)</td>
<td>DCE</td>
<td>90 °C / 20 h</td>
<td>60%</td>
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<tr>
<td>TOST-929</td>
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<td>1.0</td>
<td>2.2</td>
<td>2-iodo (2.5)</td>
<td>DCE</td>
<td>90 °C / 20 h</td>
<td>52%</td>
<td>Isolated immediately</td>
</tr>
<tr>
<td>TOST-930</td>
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<td>1.0</td>
<td>2.2</td>
<td>2-iodo (2.5)</td>
<td>DCE</td>
<td>60 °C / 20 h</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>TOST-932</td>
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<td>1.0</td>
<td>1.1</td>
<td>2-iodo (2.5)</td>
<td>DCE</td>
<td>90 °C / 20 h</td>
<td>...&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.2 equiv of amide added with the alkyne</td>
</tr>
<tr>
<td>TOST-937</td>
<td>3.0</td>
<td>1.0</td>
<td>3.0</td>
<td>2-Fluoro (3.0)</td>
<td>DCE</td>
<td>90 °C / 17 h</td>
<td>77%&lt;sup&gt;b&lt;/sup&gt; (72%)</td>
<td></td>
</tr>
<tr>
<td>TOST-938</td>
<td>3.0</td>
<td>1.0</td>
<td>3.0</td>
<td>2-iodo (3.0)</td>
<td>DCE</td>
<td>90 °C / 17 h</td>
<td>42%</td>
<td></td>
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<tr>
<td>TOST-939</td>
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<td>1.0</td>
<td>3.0</td>
<td>2-iodo (3.0)</td>
<td>DCE</td>
<td>90 °C / 17 h</td>
<td>74%</td>
<td>(0.2 M)</td>
</tr>
<tr>
<td>TOST-940</td>
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<td>1.0</td>
<td>3.0</td>
<td>2-Cloro (3.0)</td>
<td>DCE</td>
<td>90 °C / 18 h</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>TOST-941</td>
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<td>1.0</td>
<td>3.0</td>
<td>2-iodo (3.0)</td>
<td>DCE</td>
<td>90 °C / 18 h</td>
<td>88%</td>
<td>sat. NaHCO₃ (1 h)</td>
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<tr>
<td>TOST-942</td>
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<td>1.0</td>
<td>3.0</td>
<td>2-Fluoro (3.0)</td>
<td>DCE</td>
<td>90 °C / 18 h</td>
<td>50%</td>
<td>(0.2 M)</td>
</tr>
<tr>
<td>TOST-944</td>
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<td>1.0</td>
<td>2.5</td>
<td>2-iodo (2.5)</td>
<td>DCE</td>
<td>90 °C / 18 h</td>
<td>69%</td>
<td>sat. NaHCO₃ (1 h)</td>
</tr>
<tr>
<td>TOST-945</td>
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<td>1.0</td>
<td>2.5</td>
<td>2-iodo (2.5)</td>
<td>DCE</td>
<td>90 °C / 18 h</td>
<td>68%</td>
<td>(0.2 M) sat. NaHCO₃ (1 h)</td>
</tr>
<tr>
<td>TOST-946</td>
<td>2.5</td>
<td>1.0</td>
<td>2.5</td>
<td>2-Chloro (2.5)</td>
<td>DCE</td>
<td>90 °C / 18 h</td>
<td>79%</td>
<td>sat. NaHCO₃ (1 h)</td>
</tr>
</tbody>
</table>

<sup>a</sup> NMR yield using 1,3,5-trimethoxybenzene as IS. <sup>b</sup> Isolated yield. <sup>c</sup> No conversion.
3. Amides

3.1. Synthesis of Amides

**General Procedure A:**
To a solution of the amine (1.00 equiv.) and triethylamine (2.00 equiv.) in DCM (0.1 M) at 0°C, the corresponding acyl chloride (1.20 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring overnight (14 h). After this time, a saturated aqueous solution of sodium bicarbonate was added and the biphasic system was separated. The aqueous phase was extracted with DCM (1 ×) and the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

**Procedure B:**
To a solution of the amine (1.00 equiv.), triethylamine (1.00 equiv.), hydroxybenzotriazole (HOBt, 1.00 equiv.) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI*HCl, 1.00 equiv.) in DCM (0.1 M), the corresponding carboxylic acid was added and the resulting solution was stirred at room temperature overnight (14 h). After this time, the organic solution was extracted sequentially with 1 M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The washed solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

**Procedure C:**
To a solution of the carboxylic acid (1.00 equiv.) and 1 drop of DMF in DCM (0.1 M) was added dropwise thionyl chloride (2.00 equiv.) at room temperature. The resulting solution was stirred at room temperature overnight (14 h). After this time, the thionyl chloride and solvent were removed under reduced pressure to afford the acyl chloride.
To a solution of the amine (1.00 equiv.) and triethylamine (1.50 equiv.) in DCM (0.1 M) at 0°C, the corresponding acyl chloride (1.00 equiv.) was added dropwise and the resulting reaction mixture was allowed to warm to room temperature while stirring overnight (14 h). After this time, a saturated
aqueous solution of sodium bicarbonate was added and the biphasic system was separated. The aqueous phase was extracted with DCM (1 ×) and the organic phases were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The resulting crude material was purified by flash column chromatography on silica gel (heptane/ethyl acetate) to afford the desired compound.

3.2. Characterization

N-Cyclopentylbenzamide (1a)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\text{Cyclopentyl} & \quad \text{NH}
\end{align*}
\]

General Procedure A; (97%). All analytical data were in good accordance with data reported in the literature.¹

N-Isopropylbenzamide (S1)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\text{Isopropyl} & \quad \text{Me}
\end{align*}
\]

General Procedure A; (quant.). All analytical data were in good accordance with data reported in the literature.²

N-Propylbenzamide (S2)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\text{Propyl} & \quad \text{Me}
\end{align*}
\]

General Procedure A; (quant.). All analytical data were in good accordance with data reported in the literature.³

N-Cyclopentyl-2-methylbenzamide (1h)

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{N} & \quad \text{H} \\
\text{Cyclopentyl} & \quad \text{NH}
\end{align*}
\]

General Procedure A; (quant.). All analytical data were in good accordance with data reported in the literature.⁴
**N-Cyclopentyl-3-methylbenzamide (1i)**

General Procedure A; (95%). All analytical data were in good accordance with data reported in the literature.\(^5\)

\[
\text{Me} \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \\
\text{C} \quad \text{Cyclopentyl}
\]

**2-Bromo-N-cyclopentylbenzamide (1j)**

General Procedure A; (quant.); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.56 (dd, \(J = 8.0, 1.0\) Hz, 1H), 7.52 (dd, \(J = 7.6, 1.7\) Hz, 1H), 7.34 (td, \(J = 7.5, 1.1\) Hz, 1H), 7.26 – 7.22 (m, 1H), 5.93 (br. s, 1H), 4.46 – 4.37 (m, 1H), 2.10 – 2.03 (m, 2H), 1.75 – 1.63 (m, 4H), 1.58 – 1.52 (m, 2H); \(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 167.2, 138.2, 133.4, 131.2, 129.8, 127.7, 119.4, 52.0, 33.1, 23.9; IR (neat) \(\nu_{\text{max}}\): 3244, 3066, 2952, 2866, 1628, 1593, 1541, 1468, 1430, 1360, 1320, 1277, 1259, 1187, 1044, 1027, 754, 729, 694; HRMS (ESI+): exact mass calculated for [M+H]\(^+\) (C\(_{12}\)H\(_{15}\)BrNO) requires \(m/z\) 268.0332, found \(m/z\) 268.0336.

**N-Cyclopentyl-4-fluorobenzamide (1k)**

General Procedure A; (96%); \(^1\)H NMR (700 MHz, CDCl\(_3\)): \(\delta\) 7.78 – 7.71 (m, 2H), 7.12 – 7.04 (m, 2H), 6.02 (s, 1H), 4.42 – 4.33 (m, 1H), 2.13 – 2.05 (m, 2H), 1.75 – 1.62 (m, 4H), 1.53 – 1.44 (m, 2H); \(^13\)C NMR (176 MHz, CDCl\(_3\)): \(\delta\) 165.8 (d, \(J = 140.4\) Hz), 164.0, 131.2 (d, \(J = 2.6\) Hz), 129.3 (d, \(J = 8.9\) Hz), 115.6 (d, \(J = 21.9\) Hz), 51.9, 33.4, 23.9; \(^19\)F NMR (659 MHz, CDCl\(_3\)): \(\delta\) -108.7; IR (neat) \(\nu_{\text{max}}\): 3277, 3077, 2957, 2870, 1628, 1602, 1543, 1501, 1364, 1324, 1289, 1160, 1099, 1015, 850, 768; HRMS (ESI+): exact mass calculated for [M+Na]\(^+\) (C\(_{12}\)H\(_{14}\)FNaO) requires \(m/z\) 230.0952, found \(m/z\) 230.0956.

**N-cyclopentyl-4-methoxybenzamide (1l)**

General Procedure A; (90%). All analytical data were in good accordance with data reported in the literature.\(^6\)
**N-Cyclopentyl pivalamide (1m)**

![Chemical Structure: N-Cyclopentyl pivalamide](image1)

General Procedure A; (92%). All analytical data were in good accordance with data reported in the literature.\(^7\)

**N-Cyclopentylcinnamamide (1n)**

![Chemical Structure: N-Cyclopentylcinnamamide](image2)

Procedure B; (84%). All analytical data were in good accordance with data reported in the literature.\(^8\)

**Methyl 4-(cyclopentyl carbamoyl)benzoate (1o)**

![Chemical Structure: Methyl 4-(cyclopentyl carbamoyl)benzoate](image3)

Procedure C; (85%); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta \) 8.09 – 8.06 (m, 2H), 7.82 – 7.77 (m, 2H), 6.09 (d, \(J = 5.9\) Hz, 1H), 4.44 – 4.38 (m, 1H), 3.94 (s, 3H), 2.15 – 2.07 (m, 2H), 1.78 – 1.63 (m, 4H), 1.54 – 1.46 (m, 2H); \(^13\)C NMR (151 MHz, CDCl\(_3\)): \(\delta \) 166.5, 166.4, 139.0, 132.7, 130.0, 127.1, 52.5, 52.0, 33.4, 24.0; IR (neat) \(\nu_{\text{max}}\): 3297, 2957, 2870, 1719, 1632, 1541, 1435, 1280, 1108, 869, 749; HRMS (ESI\(^+\)): exact mass calculated for [M+Na]\(^+\)(C\(_{14}\)H\(_{17}\)NNaO\(_3\)) requires \(m/z\) 270.1101, found \(m/z\) 270.1104.
4. Formation of pyrimidines

4.1. General Procedure D

All reactions were run on a 0.2 mmol scale.

To a solution of amide (0.6 mmol, 3 equiv.) and 2-iodopyridine (3 equiv.) in 1,2-dichloroethane (3 mL), triflic anhydride (3 equiv.) was added at 0 °C. The reaction mixture was stirred for 15 minutes at 0 °C. The alkyne (1 equiv.) was then added and the reaction was stirred at 90 °C during 18 hours. After cooling to room temperature, the reaction was quenched with a saturated solution of NaHCO₃ (3 mL) and stirred during 1 hour. Then the aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography on Silica gel.
4.2. Characterization

All the following compounds were prepared according to general procedure D.

5-Methyl-2,4,6-triphenylpyrimidine (2a)

83% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.62 – 8.57\) (m, 2H), \(7.79 – 7.73\) (m, 4H), \(7.58 – 7.45\) (m, 9H), \(2.40\) (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 167.1, 161.6, 139.4, 138.1, 130.4, 129.5, 129.2, 128.5, 128.42, 128.35, 123.3, 17.9\); HRMS (ESI\(^{+}\)): exact mass calculated for \([M+H]^+\) (C\(_{23}\)H\(_{19}\)N\(_2\)) requires \(m/z\) 323.1543, found \(m/z\) 323.1539.

All analytical data were in good accordance with data reported in the literature.\(^9\)

5-Ethyl-2,4,6-triphenylpyrimidine (2b)

72% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.59 – 8.40\) (m, 2H), \(7.67 – 7.62\) (m, 4H), \(7.55 – 7.48\) (m, 6H), \(7.48 – 7.41\) (m, 3H), \(2.84\) (q, \(J = 7.5\) Hz, 2H), \(0.80\) (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 167.3, 161.4, 139.8, 138.0, 130.4, 129.9, 128.90, 128.88, 128.5, 128.4, 21.8, 14.6\); HRMS (ESI\(^{+}\)): exact mass calculated for \([M+H]^+\) (C\(_{24}\)H\(_{21}\)N\(_2\)) requires \(m/z\) 337.1699, found \(m/z\) 337.1694.

All analytical data were in good accordance with data reported in the literature.\(^10\)

2,4,5,6-Tetraphenylpyrimidine (2c)

71% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.68 – 8.62\) (m, 2H), \(7.54 – 7.47\) (m, 3H), \(7.45 – 7.38\) (m, 4H), \(7.32 – 7.27\) (m, 3H), \(7.26 – 7.21\) (m, 3H), \(7.20 – 7.13\) (m, 3H), \(7.03 – 6.97\) (m, 2H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 165.5, 163.0, 139.0, 137.9, 136.8, 131.3, 130.7, 130.1, 129.2, 128.8, 128.6, 128.6, 128.4, 127.9, 127.4\); HRMS (ESI\(^{+}\)): exact mass calculated for \([M+Na]^+\) (C\(_{28}\)H\(_{20}\)NaN\(_2\)) requires \(m/z\) 407.1519, found \(m/z\) 407.1509.

All analytical data were in good accordance with data reported in the literature.\(^11\)
2,4,6-Triphenylpyrimidine (2d)

46% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.79 – 8.68 (m, 2H), 8.38 – 8.24 (m, 4H), 8.03 (s, 1H), 7.64 – 7.47 (m, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 165.0, 164.7, 138.3, 137.8, 130.9, 130.8, 129.1, 128.64, 128.60, 127.5, 110.5; HRMS (ESI+): exact mass calculated for [M+H]$^+$ (C$_{22}$H$_{17}$N$_2$) requires m/z 309.1386, found m/z 309.1386.

All analytical data were in good accordance with data reported in the literature.$^9$

4-(2-Chlorophenyl)-5-methyl-2,6-diphenylpyrimidine (2e)

58% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.54 (dd, J = 6.7, 2.9 Hz, 2H), 7.81 – 7.74 (m, 2H), 7.57 – 7.38 (m, 10H), 2.22 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 166.4, 166.0, 161.8, 139.1, 138.6, 137.9, 132.6, 130.4, 130.1, 129.9, 129.5, 129.3, 128.5, 128.4, 127.2, 124.8, 16.3; IR (neat) $\nu_{\text{max}}$: 3059, 2959, 2926, 2862, 1596, 1534, 1393, 1194, 1095, 1069, 1040, 1028, 984; HRMS (ESI+): exact mass calculated for [M+Na]$^+$ (C$_{23}$H$_{17}$ClNaN$_2$) requires m/z 379.0972, found m/z 379.0970.

4-(4-Chlorophenyl)-5-methyl-2,6-diphenylpyrimidine (2f)

59% yield; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.64 – 8.51 (m, 2H), 7.81 – 7.67 (m, 4H), 7.58 – 7.42 (m, 8H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): δ 167.3, 165.8, 161.7, 139.2, 137.9, 137.8, 135.5, 131.0, 130.5, 129.5, 129.3, 128.7, 128.5, 128.4, 128.3, 123.2, 17.8; IR (neat) $\nu_{\text{max}}$: 3061, 2962, 2926, 1597, 1572, 1533, 1489, 1445, 1391, 1090, 1005; HRMS (ESI+): exact mass calculated for [M+Na]$^+$ (C$_{23}$H$_{17}$ClNaN$_2$) requires m/z 379.0972, found m/z 379.0964.
4-(4-Fluoro-2-methylphenyl)-2,6-diphenylpyrimidine (2g)

\[
\text{Ph} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{F} \\
\text{Ph} \\
\]

57% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.74 – 8.67 (m, 2H), 8.31 – 8.26 (m, 2H), 8.14 (dd, \(J = 7.3, 1.5\) Hz, 1H), 8.11 – 8.07 (m, 1H), 7.94 (s, 1H), 7.61 – 7.49 (m, 6H), 7.18 (t, \(J = 8.8\) Hz, 1H), 2.43 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 164.6, 164.4 (d, \(J = 127.2\) Hz), 164.2, 162.5, 138.2, 137.6, 133.4 (d, \(J = 3.4\) Hz), 130.9, 130.8, 130.7 (d, \(J = 5.8\) Hz), 129.0, 128.6, 127.4, 126.7 (d, \(J = 8.7\) Hz), 125.6 (d, \(J = 17.7\) Hz), 115.7 (d, \(J = 22.8\) Hz), 110.0, 14.9 (d, \(J = 3.4\) Hz); \(^{19}\)F NMR (659 MHz, CDCl\(_3\)): \(\delta\) -114.0; IR (neat) \(\nu_{\text{max}}\): 3063, 3038, 2930, 1590, 1569, 1529, 1497, 1361, 1248, 1179, 1117, 1027; HRMS (ESI\(^+\)): exact mass calculated for [M+H\(^+\)] (C\(_{23}\)H\(_{18}\)F\(_2\)N\(_2\)) requires \(m/z\) 341.1449, found \(m/z\) 341.1446.

5-Methyl-4-phenyl-2,6-di-o-tolylpyrimidine (2h)

\[
\text{Me} \quad \text{Me} \\
\text{Me} \quad \text{N} \quad \text{N} \quad \text{Ph} \\
\text{Ph} \\
\]

64% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.30 (dd, \(J = 4.5, 1.7\) Hz, 1H), 7.81 (dd, \(J = 7.6, 2.0\) Hz, 1H), 7.67 – 7.60 (m, 3H), 7.46 – 7.37 (m, 3H), 7.28 – 7.15 (m, 5H), 2.53 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 168.5, 166.1, 164.6, 150.9, 139.1, 139.0, 138.6, 137.7, 137.3, 135.3, 135.2, 131.2, 130.7, 130.6, 129.4, 129.2, 129.1, 128.7, 128.4, 126.0, 125.9, 123.6, 123.1, 21.5, 19.8, 16.4; IR (neat) \(\nu_{\text{max}}\): 3059, 3022, 2956, 2921, 2855, 1602, 1529, 1487, 1391, 1379, 1002, 875, 772, 762, 732, 704; HRMS (ESI\(^+\)): exact mass calculated for [M+Na\(^+\)] (C\(_{25}\)H\(_{22}\)NaN\(_2\)) requires \(m/z\) 373.1675, found \(m/z\) 373.1673.
5-Methyl-4-phenyl-2,6-di-m-tolylpyrimidine (2i)

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{N} & \quad \text{Ph} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

70% yield; \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.30 – 8.25 (m, 2H), 7.68 – 7.61 (m, 2H), 7.47 – 7.34 (m, 5H), 7.33 – 7.12 (m, 4H), 2.37 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)): \( \delta \) 167.3, 166.9, 161.8, 139.5, 139.4, 138.1, 138.0, 131.1, 130.0, 129.9, 129.5, 129.2, 128.8, 128.4, 128.3, 126.5, 125.6, 123.2, 21.6, 17.8, 17.8; IR (neat) \( \nu_{\text{max}} \): 3062, 3029, 2957, 2924, 2857, 2734, 1529, 1389, 1376, 1010, 787, 765, 695; HRMS (ESI\(^+\)): exact mass calculated for [M+Na]\(^+\) (C\(_{25}\)H\(_{22}\)NaN\(_2\)) requires \( m/z \) 373.1675, found \( m/z \) 373.1671.

2,4-Bis(2-bromophenyl)-5-methyl-6-phenylpyrimidine (2j)

\[
\begin{align*}
\text{Br} & \quad \text{N} \\
\text{N} & \quad \text{Ph} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

59% yield; \( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.22 – 7.78 (m, 13H), 2.23 (s, 3H); \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)): \( \delta \) 167.1, 166.3, 163.3, 139.9, 139.8, 138.3, 133.6, 132.9, 131.7, 130.2, 130.2, 130.0, 129.4, 129.3, 128.4, 127.8, 127.4, 124.9, 122.0, 121.9, 16.3; IR (neat) \( \nu_{\text{max}} \): 3055, 2926, 2857, 2226, 1557, 1534, 1391, 906, 755, 726, 699; HRMS (ESI\(^+\)): exact mass calculated for [M+H]\(^+\) (C\(_{23}\)H\(_{17}\)Br\(_2\)N\(_2\)) requires \( m/z \) 478.9753, found \( m/z \) 478.9752.

2,4-Bis(4-fluorophenyl)-5-methyl-6-phenylpyrimidine (2k)

\[
\begin{align*}
\text{F} & \quad \text{N} \\
\text{N} & \quad \text{Ph} \\
\text{F} & \quad \text{F}
\end{align*}
\]

90% yield; \( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta \) 8.59 – 8.54 (m, 2H), 7.78 – 7.71 (m, 4H), 7.56 – 7.49 (m, 3H), 7.22 (t, \( J = 8.7 \) Hz, 2H), 7.14 (t, \( J = 8.7 \) Hz, 2H), 2.39 (s, 3H); \( ^{13}C \) NMR (151 MHz, CDCl\(_3\)): \( \delta \) 167.8, 166.9, 161.8, 139.5, 139.4, 138.1, 138.0, 131.1, 130.0, 129.9, 129.5, 129.2, 128.8, 128.4, 128.3, 126.5, 125.6, 123.2, 21.6, 17.8, 17.8; IR (neat) \( \nu_{\text{max}} \): 3062, 3029, 2957, 2924, 2857, 2734, 1529, 1389, 1376, 1010, 787, 765, 695; HRMS (ESI\(^+\)): exact mass calculated for [M+Na]\(^+\) (C\(_{25}\)H\(_{22}\)NaN\(_2\)) requires \( m/z \) 373.1675, found \( m/z \) 373.1671.
**CDCl₃:** δ 167.3, 166.0, 164.9 (d, J = 176.7 Hz), 163.2 (d, J = 176.4 Hz), 160.7, 139.1, 135.3 (d, J = 3.3 Hz), 134.1 (d, J = 2.8 Hz), 131.5 (d, J = 8.4 Hz), 130.4 (d, J = 8.5 Hz), 129.4, 129.4, 128.5, 123.1, 115.5 (d, J = 11.1 Hz), 115.4 (d, J = 11.0 Hz), 17.9; **¹⁹F NMR (565 MHz, CDCl₃):** δ -111.1 (tt, J = 8.4, 5.6 Hz), -111.8 (tt, J = 8.6, 5.5 Hz); **IR (neat) ν max:** 3057, 3025, 2928, 2861, 1713, 1601, 1532, 1507, 1392, 1379, 1222, 1149, 1006, 842, 808, 772, 734, 697; **HRMS (ESI+):** exact mass calculated for [M+Na]^+ (C₂₃H₁₆F₂NaN₂) requires m/z 381.1174, found m/z 381.1168.

**2,4-Bis(4-methoxyphenyl)-5-methyl-6-phenylpyrimidine (2I)**

![Chemical structure](image)

70% yield; **¹H NMR (600 MHz, CDCl₃):** δ 8.56 (d, J = 8.9 Hz, 2H), 7.78 – 7.73 (m, 4H), 7.55 – 7.51 (m, 2H), 7.50 – 7.47 (m, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 2.40 (s, 3H); **¹³C NMR (151 MHz, CDCl₃):** δ 166.9, 166.3, 161.5, 161.2, 160.5, 139.6, 131.8, 131.1, 130.9, 129.8, 129.5, 129.1, 128.3, 122.1, 113.7, 55.5, 55.4, 18.0; **IR (neat) ν max:** 3068, 3054, 3004, 2993, 2959, 2834, 1607, 1583, 1529, 1507, 1392, 1377, 1246, 1163, 1030, 834, 806, 776, 712; **HRMS (ESI+):** exact mass calculated for [M+Na]^+ (C₂₅H₂₂NaN₂O₂) requires m/z 405.1570, found m/z 405.1573.

**2,4-Di-tert-butyl-5-methyl-6-phenylpyrimidine (2m)**

![Chemical structure](image)

78% yield; **¹H NMR (400 MHz, CDCl₃):** δ 7.57 – 7.50 (m, 2H), 7.49 – 7.38 (m, 3H), 2.39 (s, 3H), 1.50 (s, 9H), 1.43 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 173.6, 172.3, 166.6, 140.6, 129.5, 128.4, 128.2, 121.7, 40.0, 39.3, 29.9, 29.8, 17.8; **IR (neat) ν max:** 2956, 2925, 2868, 1535, 1495, 1479, 1458, 1400, 1376, 1276, 1261, 1243, 1004, 915, 765, 750, 700; **HRMS (ESI+):** exact mass calculated for [M+H]^+ (C₁₉H₂₇N₂) requires m/z 283.2169, found m/z 283.2172.
5-Methyl-4-phenyl-2,6-di((E)-styrlyl)pyrimidine (2n)

![Chemical structure](image)

27% yield; $^1$H NMR (700 MHz, CDCl$_3$): $\delta$ 8.21 (d, $J = 15.5$ Hz, 1H), 8.10 (d, $J = 16.0$ Hz, 1H), 7.71 (d, $J = 7.4$ Hz, 2H), 7.68 (d, $J = 7.4$ Hz, 2H), 7.63 – 7.61 (m, 2H), 7.54 – 7.51 (m, 2H), 7.50 – 7.47 (m, 1H), 7.46 – 7.32 (m, 8H), 2.42 (s, 3H); $^{13}$C NMR (176 MHz, CDCl$_3$): $\delta$ 166.8, 161.5, 161.1, 139.2, 137.9, 136.9, 136.6, 136.5, 129.3, 129.2, 129.0, 128.9, 128.8, 128.5, 128.3, 127.9, 127.7, 122.9, 122.3, 15.2; IR (neat) $\nu_{\text{max}}$: 3081, 3059, 3024, 2923, 1629, 1575, 1521, 1494, 1447, 1394, 1375, 1296, 1191, 1174, 1114, 1041, 1025, 966, 764, 742; HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ (C$_{27}$H$_{22}$NaN$_2$) requires m/z 397.1675, found m/z 397.1679.

Dimethyl 4,4'-{(5-methyl-6-phenylpyrimidine-2,4-diyl)dibenzoate (2o)

![Chemical structure](image)

21% yield; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.65 – 8.59 (m, 2H), 8.24 – 8.19 (m, 2H), 8.16 – 8.11 (m, 2H), 7.84 – 7.79 (m, 2H), 7.77 – 7.71 (m, 2H), 7.57 – 7.50 (m, 3H), 3.98 (s, 3H), 3.95 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 167.6, 167.1, 166.8, 166.3, 160.8, 143.4, 141.9, 138.9, 131.7, 130.9, 129.8, 129.5, 129.4, 128.6, 128.3, 124.2, 52.5, 52.3, 17.8; IR (neat) $\nu_{\text{max}}$: 3084, 3059, 3027, 2949, 2843, 1719, 1527, 1434, 1388, 1274, 1191, 1112, 1098, 1004, 859, 761; HRMS (ESI$^+$): exact mass calculated for [M+Na]$^+$ (C$_{27}$H$_{22}$NaN$_2$O$_4$) requires m/z 461.1472, found m/z 461.1466.
5. Formation of pyridines

5.1. General Procedure E

All reactions were run on a 0.2 mmol scale.

To a solution of amide (0.6 mmol, 3 equiv.) and 2-iodopyridine (3 equiv.) in 1,2-dichloroethane (3 mL), triflic anhydride (3 equiv.) was added at 0 °C. The reaction mixture was stirred for 15 minutes at 0 °C. The alkyne (1 equiv.) was then added and the reaction was stirred at 90 °C during 18 hours. After cooling to room temperature, the reaction was quenched with a saturated solution of NaHCO₃ (3 mL) and stirred during 1 hour. Then the aqueous layer was extracted with DCM. The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. The crude residue was purified by flash column chromatography on Silica gel.
5.2. Characterization

All the following compounds were prepared according to general procedure E.

4-(4-Methoxyphenyl)-2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (3a)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{3astructure.png}
\end{center}}
\]

45% yield; \( ^1H \text{NMR (600 MHz, CDCl}_3 \): \( \delta 8.00 - 7.97 \text{ (m, 2H), 7.51 - 7.44 (m, 5H), 7.42 - 7.34 \text{ (m, 1H), 7.04 - 6.99 \text{ (m, 2H), 3.88 \text{ (s, 3H), 3.15 (t, J = 7.6 Hz, 2H), 3.07 (t, J = 7.3 Hz, 2H), 2.16 \text{ (p, J = 7.5 Hz, 2H); ^13C NMR (151 MHz, CDCl}_3 \): \( \delta 166.8, 159.9, 156.6, 145.6, 140.2, 133.0, 131.5, 129.6, 128.5, 127.1, 118.0, 114.2, 55.5, 35.0, 31.0, 23.7; IR (neat) \( \nu_{\text{max}} \): 3060, 3036, 2952, 2836, 1608, 1590, 1556, 1513, 1458, 1440, 1371, 1250, 1177, 1132; HRMS (ESI\(^+\)): exact mass calculated for [M+H\(^+\)]\( (C_{21}H_{20}NO) \) requires \( m/z \) 302.1539, found \( m/z \) 302.1542.}

4-Methyl-2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (3b)

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{3bstructure.png}
\end{center}}
\]

63% yield; \( ^1H \text{NMR (600 MHz, CDCl}_3 \): \( \delta 7.94 - 7.92 \text{ (m, 2H), 7.46 - 7.42 (m, 2H), 7.38 - 7.34 \text{ (m, 1H), 7.29 (s, 1H), 3.09 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.31 (s, 3H), 2.20 - 2.11 (m, 2H); ^13C NMR (151 MHz, CDCl}_3 \): \( \delta 165.4, 156.3 143.4, 140.3, 134.9, 128.7, 128.4, 127.1, 119.6, 34.7, 29.1, 22.7, 19.2; IR (neat) \( \nu_{\text{max}} \): 3057, 2946, 2841, 1595, 1577, 1457, 1437, 1424, 1377, 1228, 1076, 1028, 864; HRMS (ESI\(^+\)): exact mass calculated for [M+H\(^+\)]\( (C_{15}H_{16}N) \) requires \( m/z \) 210.1277, found \( m/z \) 210.1278.}
6. References


(3) Fang, C.; Qian, W.; Bao, W. *Synlett* **2008**, *2008* (16), 2529.


7. Spectra
$1^H$
CDCl$_3$
700MHz

$1^3C$ (APT)
CDCl$_3$
176MHz
$^1H$
CDCl$_3$
400MHz

2a

$^{13}C$
CDCl$_3$
101MHz

2a
$^1$H

CDCl$_3$

400MHz

2b

$^{13}$C

CDCl$_3$

101MHz

2b
$^1$H
CDCl$_3$
400MHz

$^{13}$C (APT)
CDCl$_3$
101MHz
$^{19}\text{F}$

CDCl$_3$

659MHz
$^{19}$F
CDCl$_3$
565MHz
$\text{H}$
CDCl$_3$
700MHz

$\text{C}$
CDCl$_3$
176MHz
$^{1}H$
CDCl$_3$
600MHz

$^{13}C$ (APT)
CDCl$_3$
151MHz