Rapid and Efficient Microwave-Assisted Synthesis of 4-, 5-, 6- and 7-Azaindoles

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Abstract: Under microwave irradiation conditions, the imines/enamines formed between aminopyridines and ketones are converted in moderate to good yields to the corresponding 4-, 5-, 6- or 7-azaindoles via the Hegedus–Mori–Heck reaction (intramolecular Heck reaction). A systematic examination of all isomeric azaindoles synthesis revealed this one-pot procedure to be general in scope.

Key words: microwave, azaindole, pyrrolopyridine, palladium, Heck reaction

The preparation of important heterocycles such as azaindoles is of interest in synthetic organic and medicinal chemistry due to their potential biological properties.1,2 Application of the Hegedus–Mori–Heck reaction (intramolecular Heck reaction) to the synthesis of azaindoles was first explored on enamines with NaHCO3 and Pd(PPh3)4 in HMPA at 140 °C.3,4 Under these conditions, the scope of this palladium-catalyzed cross-coupling was limited to the preparation of 4-azaindoles and N-methyl 7-azaindoles. In a recent paper, Nazaré published the synthesis of substituted 4- and 7-azaindoles involving a palladium coupling reaction with Pd[P(r-Bu)3]2 between chloroaminopyridines and ketones by thermal heating in a sealed tube (4–16 h at 140 °C).5 In contrast to the well documented Fischer indole reaction applied to the azaindoles synthesis,6–8 the Hegedus–Mori–Heck reaction has never been reported for the preparation of 5- and 6-azaindoles.

Since its introduction in 1986,9 microwave irradiation has found increasing application in organic synthesis.10 For the more challenging synthesis of 5- and 6-azaindoles, we envisioned that the use of microwave irradiation would improve the corresponding Hegedus–Mori–Heck reaction, as observed for the intermolecular Heck reaction.11 To the best of our knowledge, a rapid and general synthesis of the four isomeric azaindoles from readily accessible starting materials has not been described. As part of our medicinal chemistry research program, we needed an efficient route to azaindoles compatible with sensitive groups such as bromine, ketones and esters.12 We wish to report herein a rapid, one-pot, two-step procedure employing microwave conditions allowing the synthesis of 4-, 5-, 6- and 7-azaindoles.

The essential aspects of our approach are shown in Scheme 1. Haloaminopyridine A first reacts with ketone B to afford enamine D, which subsequently undergoes an intramolecular palladium-catalyzed Heck reaction to produce azaindole C.

Preliminary studies focused on optimization of the intramolecular Heck reaction (D → C). The enamine 1 was selected as the model substrate to explore the palladium-catalyzed coupling reaction (Scheme 2). Several palladium catalysts {Pd(OAc)2, Pd2Br2[P(r-Bu)3]2, Pd(PPh3)4}, bases (i-Pr2NEt, Cy2NMe), solvents (DMF, DMA, 1,4-dioxane, toluene, pyridine) and temperatures (160–180 °C for 10–20 min) under non-degassed microwave irradiation were examined.13 Under these conditions, yields of the desired 5,6,7,8-tetrahydro-9H-pyrrolo[3,2-b]indol-9-one 2 ranged from 50–95%. Investigation of the palladium source and the solvent effect revealed that Pd(PPh3)4 and pyridine are the most appropriate reagents to perform this intramolecular Heck reaction under microwave irradiation. Also, heating the reaction at a higher temperature than 160 °C led to lower yields of azaindole 2 with increased decomposition.

After the exploration of the reaction conditions, we focused our attention on optimizing the isolation of the reaction product. It was noted that on using an aqueous...
work-up for the isolation of azaindole 2, a lower yield than the conversion determined by HPLC was obtained. Therefore, we sought non-aqueous workup conditions since we suspected 2 to be water-soluble. The optimized purification protocol involves a direct flash chromatography over silica gel (5–15% MeOH in CHCl₃) of the reaction mixture followed by trituration with CH₂Cl₂. By doing so, the desired azaindole 2 was now prepared from enamine 1 in 95% isolated yield. Under thermal heating, a yield of 39% for the synthesis of azaindole 2 from 1 has been reported.³ More recently, the same heterocycle 2 has been prepared in 54% yield under Stille cross-coupling conditions.¹⁴

Having established rapid and high yielding conditions for the palladium cross-coupling of enamine 1 to azaindole 2, we wanted to examine the scope of this method. Table 1 summarizes the results of azaindole syntheses starting from imines/enamines. Most of these condensed starting materials required for our studies were prepared following literature procedures.³,⁴,¹⁵,¹⁶ Surprisingly under these conditions and with higher temperatures or longer reaction time, 4-amino-3-bromopyridine remains unreacted in the presence of 1,3-cyclohexanedione. As highlighted in Table 1, the use of microwave irradiation allows for easy access to various isomeric azaindoles. The syntheses of 7-azaindole 9 and 6-azaindole 11 were accomplished in excellent yields (Table 1, entries 2 and 4). For comparison, 9 and 11 have been previously prepared in 10% and 22% yields, respectively, under photocyclization conditions.³,⁴ Also, this method gives access to substituted heterocycles such as the bromoaazaindole 10 in good yields (Table 1, entry 3, condition B).

We next investigated the reaction of cyclic imines under the above reaction conditions (Table 1, entries 5–7, conditions A and B). After submitting compounds 6–8 to the microwave-assisted Hegedus–Mori–Heck reaction, azaindoles 12–14 were isolated in high yields (Table 1, entries 5–7). Exploration of time and temperature effects (Table 1, entries 5–7, conditions A–C) on the formation of cycloalkanoazaindoles 12–14 established the reactivity of ring size: the 5-membered ring compound 12 was the easiest to form and the 6-membered ring compound 13 was the most difficult. Finally to accomplish the purification of these non-polar azaindoles 12–14, a better eluent (10–50% EtOAc in hexane containing 10% Et₃N) and solvent (CICH₂CH₂Cl or heptane) were required than in the previously described protocol.

During the course of this study, we discovered that the presence of a strong base such as Cy₂NMe was not always necessary for the palladium cross-coupling reaction to occur. As an example, the Hegedus–Mori–Heck reaction of enamine 1 (2.25 mmol) with 5 mol% of Pd(PPh₃)₄ and pyridine (1.5 mL) under microwave irradiation at 160 °C for 20 minutes delivered azaindole 2 in 97% isolated yield.¹⁷ However, exposure of the enamine 4 under the same reaction conditions only led to recovery of starting material after 40 minutes at 160 °C.

Since azaindole 2 could be prepared under mild basic conditions favorable for the condensation step, we were interested in determining if we could develop a one-step procedure to prepare these azaindoles (Table 2).⁵,¹⁸ Under microwave irradiation, the synthesis of 4-azaindole 13 and 14 (Table 2, entries 1–3) was achieved in good yields in 20–40 minutes by direct reaction of 3-amino-2-chloropyridine (15) with cyclic ketals 17 and 18 or ketone 19. When the reaction was performed with a ketone (Table 2, entry 3), PPTS and a dehydrating agent such as Si(OEt)₄ were required.²⁰ However, the reaction with ketals did not need the dehydrating agent. Using these conditions adapted for ketals and monitoring the consumption of 4-amino-3-bromopyridine (16), the synthesis of 5-azaindole 20

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction conditions¹</th>
<th>Yield (%)²</th>
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<td>1</td>
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<td>2</td>
<td>A 95</td>
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<tr>
<td>2</td>
<td>3</td>
<td>9</td>
<td>A 89</td>
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<td>4</td>
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<tr>
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<td>6</td>
<td>7</td>
<td>13</td>
<td>A 47 B 83</td>
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<td>7</td>
<td>8</td>
<td>14</td>
<td>A 85 C 12</td>
<td></td>
</tr>
</tbody>
</table>

¹ Reaction conditions: Substrate (2.25 mmol) was allowed to react with Pd(PPh₃)₄ (5 mol%) and Cy₂NMe (1.2 equiv) in pyridine (1.5 mL). A: Heated under microwave irradiation for 20 min at 160 °C; B: 40 min at 160 °C; C: 20 min at 140 °C.
² Isolated yield.
(Table 2, entry 4) was realized in only 27% yield after 35 hours under microwave irradiation at 160 °C. The major side product was the reduction of 4-amino-3-bromopyridine (16) into 4-aminopyridine in a 47% isolated yield. Based on the large amount of this side product recovered and the unsuccessful reaction of 16 with 1,3-cyclohexanedione, we concluded that the condensation with a 4-aminopyridine was a more difficult step compared with a 2- or 3-aminopyridine (Scheme 1).

To circumvent the reduction of the halogen bond observed during slow reaction (Table 2, entry 4), we evaluated a two-step synthesis as a solution to prepare rapidly all the isomeric azaindoles.21 A range of temperatures and times for the condensation step between ketals or ketones with haloaminopyridines were examined (Table 3). As an example, 3-halo-4-aminopyridines 16 and 2122 were condensed with ketal 18 or ketone 24 under microwave irradiation at 220 °C (Table 3, entries 1–3), whereas this step was performed at room temperature with ethyl pyruvate 25 (Table 3, entries 4 and 5).23 Following the condensation step, the intramolecular Heck reaction was realized in the same flask with Pd(PPh 3)4 (5 mol%) and Cy2NMe (1.3 equiv) under microwave conditions. Using this one-pot, two-step procedure, 5-azaindole 20 could now be obtained in 48% yield in less than three hours (Table 3, entries 1–3), whereas this step was performed at room temperature with ethyl pyruvate 25 (Table 3, entries 4 and 5).23

Melting points were determined on a Mettler apparatus and are uncorrected. 1H and 13C NMR spectra were recorded in DMSO-d6 solution at room temperature on a Bruker Avance 500 MHz or AMX 500 MHz spectrometer. ESI mass spectra were obtained on a PE SCIEX/API 2000 instrument. TLC analyses were performed on Merck Kieselgel 60 F 254 plates. Neutralization of TLC plates was performed by first eluting with 10–50% EtOAc in hexane containing 10% Et3N. Haloaminopyridines and compounds 18 and 25 were obtained from Lancaster. Compounds 19 and 26 were purchased from Aldrich and compound 24 from Acros. Pd(PPh 3)4 was acquired from Strem. HCl salts of haloaminopyridines were neutralized by using aq NaHCO3. Column chromatography was conducted with silica gel 230–400 mesh. Elemental analyses were determined

### Table 2 One-Step Synthesis of Azaindoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ketal/ketone</th>
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<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>13</td>
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<td>13</td>
<td>B</td>
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<tr>
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<td>16</td>
<td>18</td>
<td>20</td>
<td>A&lt;sup&gt;d&lt;/sup&gt;</td>
<td>27</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions under microwave irradiation at 160 °C: Substrate (2.25 mmol) was allowed to react with ketal/ketone (2.0 equiv), Pd(PPh 3)4 (5 mol%); A: In pyridine (1.5 mL) for 20 min; B: PPTS (0.25 equiv), Si(OEt) 4 (1.0 equiv) in pyridine (0.75 mL) for 40 min.  
<sup>b</sup> Isolated yield.  
<sup>c</sup> 40 min.  
<sup>d</sup> PPTS (0.1 equiv) and 35 h.
Synthesis of Azaindoles from Imines/Enamines (Table 1); General Procedure I

A pyrex cylindrical reaction tube adapted to the Smith Creator™ was charged with the imine/enamine (2.25 mmol), Pd(PPh₃)₄ (5 mol%), Cy₂NMe (1.2 equiv), pyridine (0.75–1.5 mL), and a magnetic stirrer bar. The tube was septum-sealed and irradiated with microwaves at the set temperature and reaction time given in Table 1. The reaction mixture was cooled to r.t., treated with Cy₂NMe (1.3 equiv), and purified by column chromatography on silica gel with the suitable CHCl₃–MeOH mixture (or hexane–EtOAc–Et₃N mixture) followed by trituration with CH₂Cl₂ (or ClCH₂CH₂Cl) to give the corresponding azaindole.

One-Step Synthesis of Azaindoles (Table 2); General Procedure II

A pyrex cylindrical reaction tube adapted to the Smith Creator™ was charged with haloaminopyridine (2.25 mmol), ketone (2.0 equiv), Si(OEt)₄ (1.0 equiv), PPTS (10–25 mol%), Pd(PPh₃)₄ (5 mol%), pyridine (0.75–1.5 mL), and a magnetic stirrer bar. The tube was septum-sealed and irradiated with microwaves at the set temperature and reaction time given in Table 2. The reaction mixture was cooled to r.t., treated with Cy₂NMe (1.2 equiv), and puri-

by Prevalere Life Science, Inc., Whitesboro, NY. Reactions under microwave conditions were performed on a Smith Creator™ micro-wave reactor purchased from Biotage/Personal Chemistry.

3-[(4-Chloropyridin-3-yl)amino]cyclohex-2-en-1-one (5)

A solution of 22 (1.00 g, 7.78 mmol), 1,3-cyclohexanedione (2.28 g, 20.3 mmol) and p-TsOH·H₂O (76 mg, 0.40 mmol) in benzene (100 mL) was refluxed in a Dean–Stark apparatus for 2.5 h. After cooling, the reaction mixture was concentrated in vacuo. The residue was diluted with CH₂Cl₂, basified with aq NaHCO₃ and extracted with CH₂Cl₂ (2×). The organic layers were combined, dried (Na₂SO₄), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–MeOH–Et₃N, 9:0:1 → 8:1:1) followed by trituration with toluene to afford 5 as a white solid (950 mg, 55%); mp 137–138 °C (toluene).

1H NMR: δ = 8.84 (s, 1 H), 8.51 (s, 1 H), 8.43 (d, J = 5.3 Hz, 1 H), 7.67 (d, J = 5.3 Hz, 1 H), 4.63 (s, 1 H), 2.52 (t, J = 6.1 Hz, 2 H), 2.14 (t, J = 6.4 Hz, 2 H), 1.92–1.86 (m, 2 H).

13C NMR: δ = 195.6, 163.2, 149.6, 148.4, 139.7, 132.9, 125.1, 99.0, 36.3, 27.8, 21.5

MS (ESI): m/z = 225, 223 [M + 1].


3-[(4-Chloropyridin-3-yl)amino]cyclohex-2-en-1-one (5)

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1H NMR: δ = 8.84 (s, 1 H), 8.51 (s, 1 H), 8.43 (d, J = 5.3 Hz, 1 H), 7.67 (d, J = 5.3 Hz, 1 H), 4.63 (s, 1 H), 2.52 (t, J = 6.1 Hz, 2 H), 2.14 (t, J = 6.4 Hz, 2 H), 1.92–1.86 (m, 2 H).

13C NMR: δ = 195.6, 163.2, 149.6, 148.4, 139.7, 132.9, 125.1, 99.0, 36.3, 27.8, 21.5

MS (ESI): m/z = 225, 223 [M + 1].

fied by column chromatography on silica gel with the suitable CHCl3–MeOH mixture (or CH2Cl2–MeOH–NH4OH mixture or hexane–EtOAc–Et3N mixture) followed by trituration with CHCl3 (or 50% CH2Cl2 in heptane, or heptane) to give the corresponding azaindole.

**One-Pot, Two-Step Synthesis of Azaindoles (Table 3); General Procedure III**

A pyrex cylindrical reaction tube adapted to the Smith Creator™ was charged with haloanilinopyridine (2.25 mmol), ketol or ketone (1.5–2.0 equiv), Si(OEt)4 (0–1.0 equiv), PPTS (10–25 mol%), pyridine (0.75–1.5 mL), and a magnetic stirrer bar. The tube was septum-sealed and irradiated with microwaves (or not) at the set temperature and reaction time given in Table 3 for the condensation step. Then Pd(PPh3)4 (5 mol%) and Cy2NMe (1.5 mL), heated for 20 min at 160 °C and after purification (column chromatography: 0–5% MeOH in CHCl3; trituration: CH2Cl2), afforded 11 as a white solid (396 mg, 95%); mp > 260 °C (EtOAc–heptane).

**6,7,8-Tetrahydro-9H-pyrido[3,2-b]indole-9-one (2)**

***Method 1; Following the General Procedure I, the reaction of***

<table>
<thead>
<tr>
<th>Compound</th>
<th>조건</th>
<th>_yield</th>
<th>_mp/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(0.58 mL, 2.73 mmol) pyridine (1.5 mL), heated for 20 min at 160 °C and after purification (column chromatography: 0–5% MeOH in CHCl3; trituration: CH2Cl2), afforded 2 as a white solid (398 mg, 95%).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 2 | (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification (column chromatography: 0–5% MeOH in CHCl3; trituration: CH2Cl2), afforded 2 as a white solid (404 mg, 89%); mp 275–277 °C (EtOAc–heptane) (Lit.3 mp > 260 °C).

**5,6,7,8-Tetrahydro-9H-pyrido[3,2-b]indolo-9-one (2)**

**Method 2; Following the General Procedure II, the reaction of***

<table>
<thead>
<tr>
<th>Compound</th>
<th>조건</th>
<th>_yield</th>
<th>_mp/°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(291 mg, 2.26 mmol), Pd(PPh3)4 (130 mg, 0.11 mmol), Cy2NMe (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification (column chromatography: 0–5% MeOH in CHCl3; trituration: CH2Cl2), afforded 11 as a white solid (396 mg, 95%); mp &gt; 260 °C (EtOAc–heptane).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(0.54 mL, 4.50 mmol), Pd(PPh3)4 (136 mg, 0.12 mmol) and pyridine (1.5 mL), heated for 40 min at 160 °C and after purification (column chromatography: hexane–EtOAc–Et3N, 9:1:1; trituration: CH2Cl2), afforded 12 as a white solid (323 mg, 83%).</td>
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</tr>
</tbody>
</table>

**6,7,8-Tetrahydro-5H-b-carbolin-5-one (11)**

Following the General Procedure I, the reaction of 5 (496 mg, 2.22 mmol), Pd(PPh3)4 (133 mg, 0.12 mmol), Cy2NMe (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification (column chromatography: 0–5% MeOH in CHCl3; trituration: CH2Cl2), afforded 11 as a white solid (396 mg, 95%); mp > 260 °C (EtOAc–heptane).
Method 1: Following the General Procedure II, the reaction of 15 (295 mg, 2.29 mmol), 19 (0.47 mL, 4.53 mmol), PPTS (140 mg, 0.56 mmol), Si(OEt)4 (0.51 mL, 2.28 mmol), Pd(PPh3)4 (139 mg, 0.12 mmol) and pyridine (0.75 mL), heated for 40 min at 160 °C and after purification [Cy2NMe (0.58 mL); column chromatography: hexane–EtOAc–Et3N, 9:1:1 → 5:4:1; trituration: heptane], afforded 13 as a white solid (344 mg, 87%); mp 206–208 °C (EtOAc–heptane) (Lit.2 mp 202–203 °C).

1H NMR: δ = 10.87 (s, 1 H), 8.17 (dd, J = 1.4, 4.6 Hz, 1 H), 7.55 (dd, J = 1.4, 8.0 Hz, 1 H), 6.95 (dd, J = 4.6, 8.0 Hz, 1 H), 2.72 (t, J = 6.1 Hz, 2 H), 2.67 (t, J = 6.0 Hz, 2 H), 1.86–1.76 (m, 4 H).

1C NMR: δ = 145.2, 140.9, 138.8, 113.6, 111.5, 110.5, 108.7, 23.0, 22.7, 22.0.

MS (ESI): m/z = 173 [M + 1].


5.6.7,8,9-Hexadecyloctahydropyrrolo[4,5,6]pyridine (14)

Method 1: Following the General Procedure I, the reaction of 18 (509 mg, 2.29 mmol), Pd(PPh3)4 (134 mg, 0.12 mmol), Cy2NMe (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification [column chromatography: hexane–EtOAc–Et3N, 9:1:1 → 5:4:1; trituration: heptane], afforded 14 as a white solid (363 mg, 85%).

1H NMR: δ = 10.88 (s, 1 H), 8.18 (d, J = 4.6 Hz, 1 H), 7.54 (d, J = 8.1 Hz, 1 H), 6.93 (dd, J = 4.6, 8.1 Hz, 1 H), 2.85–2.82 (m, 4 H), 1.87–1.83 (m, 2 H), 1.72–1.62 (m, 4 H).

1C NMR: δ = 146.1, 142.4, 141.2, 127.0, 117.0, 115.1, 112.9, 31.8, 29.2, 28.6, 27.2, 23.2.

MS (ESI): m/z = 245 [M + 1].

Anal. Calcd for C21H16N2O: C, 76.83; H, 6.60; N, 11.47. Found: C, 76.56; H, 6.32; N, 11.29.

Method 1: Following the General Procedure II, the reaction of 16 (391 mg, 2.25 mmol), 18 (0.55 mL, 4.58 mmol), PPTS (61 mg, 0.24 mmol), Pd(PPh3)4 (0.136 mg, 0.12 mmol) and pyridine (1.5 mL), heated for 35 h at 160 °C and after purification [Cy2NMe (0.58 mL); column chromatography: CH2Cl2–MeOH–NH4OH, 99:1:0 → 87:10:3; trituration: 50% CH2Cl2 in heptane], afforded 20 as a pale yellow solid (104 mg, 27%) and 4-aminopyridine (99 mg, 47%).

Method 2: Following the General Procedure III, the reaction of 16 (390 mg, 2.25 mmol), 18 (0.55 mL, 4.58 mmol), PPTS (61 mg, 0.24 mmol), and pyridine (1.5 mL) heated successively for 20 min at 160 °C, 180 °C, 200 °C and 220 °C, treated with Pd(PPh3)4 (137 mg, 0.12 mmol) and Cy2NMe (0.62 mL, 2.92 mmol), heated successively for 4 × 20 min (80 min) at 160 °C, and after purification [column chromatography: CH2Cl2–MeOH–NH4OH, 99:1:0 → 87:10:3; trituration: 50% CH2Cl2 in heptane], afforded 20 as a white solid (187 mg, 48%).

Method 3: Following the General Procedure III, the reaction of 16 (495 mg, 2.25 mmol), 18 (0.55 mL, 4.58 mmol), PPTS (61 mg, 0.24 mmol), and pyridine (1.5 mL) heated successively for 20 min at 160 °C, 180 °C, 200 °C and 220 °C, treated with Pd(PPh3)4 (137 mg, 0.12 mmol) and Cy2NMe (0.62 mL, 2.92 mmol), heated for 20 min at 160 °C, and after purification [column chromatography: CH2Cl2–MeOH–NH4OH, 99:1:0 → 87:10:3; trituration: 50% CH2Cl2 in heptane], afforded 20 as a white solid (272 mg, 63%); mp 212–214 °C (toluene) (Lit.2 mp 212–214 °C).
[49x738]2-[4-(Methylsulfonyl)phenyl]-1-pyrrolo[2,3-b]pyridine (30)

Following the General Procedure III, the reaction of 23 (392 mg, 2.27 mmol), 26 (666 mg, 3.36 mmol), PPTS (141 mg, 0.56 mmol), Si(OEt)4 (0.51 mL, 2.28 mmol), and pyridine (0.75 mL) heated successively for 6 × 20 min (2 h) at 160 °C, and after purification [column chromatography: 0–10% MeOH in CHCl3; trituration: 60% CICH2CH2Cl in heptane], afforded 30 as a white solid (251 mg, 41%); mp >280 °C (acetone).

MS (ESI): m/z = 191 [M + 1].
Anal. Calcd for C10H10N2O2: C, 63.15; H, 5.30; N, 14.73. Found: C, 61.63; H, 4.41; N, 10.20.

1H NMR: δ = 12.36 (s, 1 H), 8.27 (dd, J = 1.5, 4.6 Hz, 1 H), 8.19 (d, J = 8.5 Hz, 2 H), 8.01–7.97 (m, 3 H), 7.15 (d, J = 2.0 Hz, 1 H), 7.10 (d, J = 4.6, 7.8 Hz, 1 H), 3.25 (s, 3 H).

13C NMR: δ = 149.9, 144.0, 139.5, 136.4, 136.1, 128.6, 127.6 (2 C), 125.8 (2 C), 120.6, 116.4, 99.8, 43.5.

References

(10) For reviews on microwave irradiation, see: (a) Kappe, C. O. Angew. Chem. Int. Ed. 2004, 43, 6250; and references therein.
(14) Pyrex cylindrical reaction tubes adapted to the Smith Creator™ (Biotage/Personal Chemistry) were used. The temperature was measured by IR detection and maintained constant by modulated irradiation of 8–300 W.
(16) Absence of Pd(PPh3)4 resulted in the recovery of starting enamine 1.
(22) For comparison, we have repeated the condensation step at 160 °C for 20 min with PPTS (0.05 equiv) in refluxing benzene for 2.5 h delivered 5 (55%).
(23) Absence of Pd(PPh3)4 resulted in the recovery of starting enamine 1.