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 $NaHCO_3$ and $Pd(PPh_3)_4$ 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 $Pd[P(t\text{-}Bu)_3]_2$ 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.

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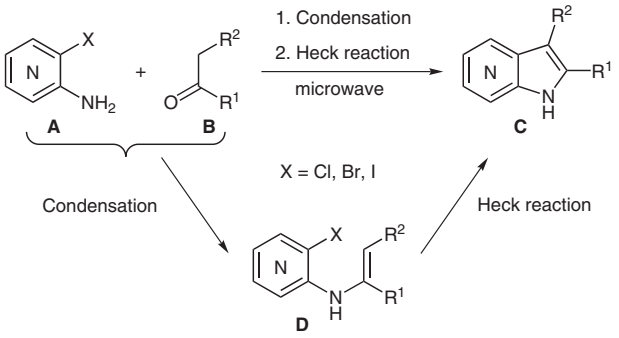
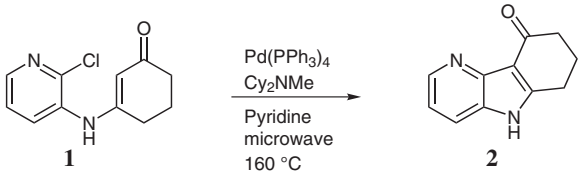
The essential aspects of our approach are shown in Scheme 1. Haloaminopyridine **A** first reacts with ketone **B** to afford enamine **D**, which subsequently undergoes an intramolecular palladium-catalyzed Heck reaction to produce azaindole **C**.



Scheme 1 One-pot, two-step synthesis of azaindoles

Preliminary studies focused on optimization of the intramolecular Heck reaction (**D** → **C**). The enamine **1**[3] was selected as the model substrate to explore the palladium-catalyzed coupling reaction (Scheme 2). Several palladium catalysts {$Pd(OAc)_2$, $Pd_2Br_2[P(t\text{-}Bu)_3]_2$, $Pd(PPh_3)_4$}, bases ($i\text{-}Pr_2NEt$, Cy_2NMe), 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-9*H*-pyrido[3,2-*b*]indol-9-one (**2**) ranged from 50–95%. Investigation of the palladium source and the solvent effect revealed that $Pd(PPh_3)_4$ 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.

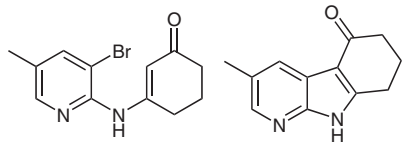
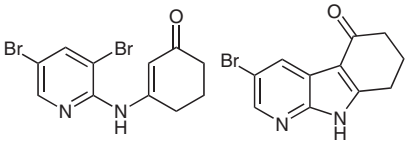
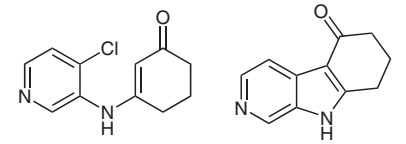
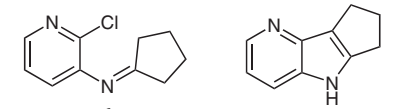
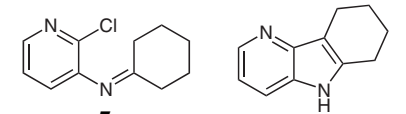
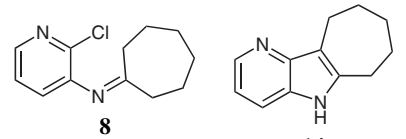
After the exploration of the reaction conditions, we focused our attention on optimizing the isolation of the reaction product. It was noted that on using an aqueous



Scheme 2 Hegedus–Mori–Heck reaction

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 $CHCl_3$) of the reaction mixture followed by trituration with CH_2Cl_2. 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]

Table 1 Synthesis of Azaindoles from Imines/Enamines

Entry	Substrate	Product	Reaction conditions[a]	Yield (%)[b]
1	**1**	**2**	A	95
2	 **3**	**9**	A	89
3	 **4**	**10**	A B	43 57
4	 **5**	**11**	A	95
5	 **6**	**12**	A C	87 89
6	 **7**	**13**	A B	47 83
7	 **8**	**14**	A C	85 12

[a] Reaction conditions: Substrate (2.25 mmol) was allowed to react with $Pd(PPh_3)_4$ (5 mol%) and Cy_2NMe (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.
[b] Isolated yield.

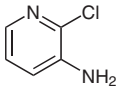
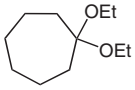
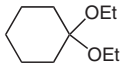
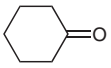
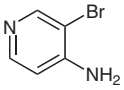
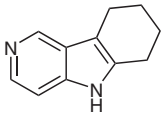
Having established rapid and high yielding conditions for the palladium cross-coupling of enamine **1** to azaindole **2**, we wanted to examine the scope of this method. Table 1 summarizes the results of azaindole syntheses starting from imines/enamines. Most of these condensed starting materials required 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 bromoazaindole **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**[16] 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% Et_3N) and solvent ($ClCH_2CH_2Cl$ 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 Cy_2NMe 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 $Pd(PPh_3)_4$ 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-azaindoles **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**[19] 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 2 One-Step Synthesis of Azaindoles

Entry	Substrate	Ketal/ketone	Product	Reaction conditions[a]	Yield (%)[b]
1	 **15**	 **17**	**14**	A	81
2	**15**	 **18**	**13**	A[c]	83
3	**15**	 **19**	**13**	B	87
4	 **16**	**18**	 **20**	A[d]	27

[a] 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.
[b] Isolated yield.
[c] 40 min.
[d] PPTS (0.1 equiv) and 35 h.

(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).

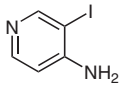
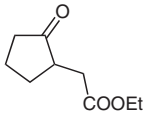
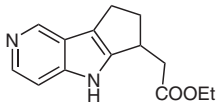
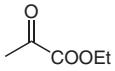
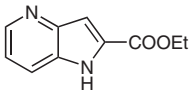
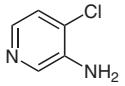
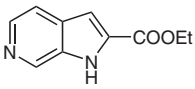
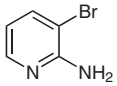
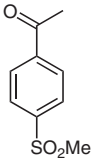
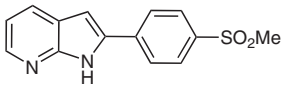
To circumvent the reduction of the halogen bond observed during slow reaction (Table 2, entry 4), we evaluated a two-step synthesis as a solution to prepare rapidly all the isomeric azaindoles.[21] A range of temperatures and times for the condensation step between ketals or ketones with haloaminopyridines were examined (Table 3). As an example, 3-halo-4-aminopyridines **16** and **21**[22] 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 Cy_2NMe (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, entry 1). This compares favourably to the 27% yield obtained under the one-step synthesis (Table 2, entry 4). However, it is worth noting that the yield went up from 48% to 66% on changing from the bromopyridine **16** to the iodopyridine **21** (Table 3, entries 1 and 2). In addition, the presence of ester groups is well tolerated in this reaction (Table 3, entries 3–5). This method gives access to 2-ethyl carboxylate azaindoles **28** and **29** (Table 3, entries 4 and 5), which are not always accessible by the Hemetsberger synthesis.[24] Finally, performing the reaction with aromatic ketone **26** (Table 3, entry 6) has led to a 2-phenylazaindole **30**, which constitutes an alternative procedure to the Larock indole synthesis.[25]

In summary, the intramolecular Heck reaction of imines/enamines under microwave conditions provides good yields of azaindoles. Under our optimized conditions, we have demonstrated that this reaction can be performed with chloro-, bromo- and iodoaminopyridines and tolerates sensitive groups such as bromine, ketones and esters to deliver functionalized azaindoles. In addition, our method is general and uses microwave irradiation to reduce the reaction time and promote the palladium coupling with more traditional palladium catalyst. Finally, this paper is the first to describe the synthesis of 5- and 6-azaindoles via an intramolecular Heck reaction.

Melting points were determined on a Mettler apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 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% Et_3N. 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 $NaHCO_3$. Column chromatography was conducted with silica gel 230–400 mesh. Elemental analyses were determined

Table 3 One-Pot, Two-Step Synthesis of Azaindoles

Entry	Substrate	Ketal/ketone	Product	Reaction conditions[a]	Yield (%)[b]
1	**16**	**18**	**20**	A	48
2	 **21**	**18**	**20**	A[c]	66
3	**21**	 **24**	 **27**	A[d]	46
4	**15**	 **25**	 **28**	B	80
5	 **22**	**25**	 **29**	B[d]	63
6	 **23**	 **26**	 **30**	C	41

[a] Reaction conditions under microwave irradiation. A: [Condensation (Step 1): Substrate (2.25 mmol) was allowed to react with ketal/ketone (2.0 equiv), $Si(OEt)_4$ (1.0 equiv) if required and PPTS (0.10–0.25 equiv) in pyridine (0.75–1.5 mL), heated successively for 20 min at 160 °C, 180 °C, 200 °C and 220 °C; Heck reaction (Step 2): $Pd(PPh_3)_4$ (5 mol%) and Cy_2NMe (1.3 equiv) were added and reaction was heated for 80 min at 160 °C]; B: [Step 1: 48 h at r.t.; Step 2: 20 min]; C: [Step 1: 160 °C, 180 °C, 200 °C; Step 2: 2 h].
[b] Isolated yield.
[c] Step 2: 20 min.
[d] Step 2: 40 min.

by Prevalere Life Science, Inc., Whitesboro, NY. Reactions under microwave conditions were performed on a Smith Creator™ microwave 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·H_2O (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 CH_2Cl_2, basified with aq $NaHCO_3$ and extracted with CH_2Cl_2 (2 ×). The organic layers were combined, dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc–MeOH–Et_3N, 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).

^{1}H 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).

^{13}C 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].

Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.28; H, 4.84; N, 12.61.

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), $Pd(PPh_3)_4$ (5 mol%), Cy_2NMe (1.2 equiv), pyridine (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., and purified by column chromatography on silica gel with the suitable $CHCl_3$–MeOH mixture (or hexane–EtOAc–Et_3N mixture) followed by trituration with CH_2Cl_2 (or $ClCH_2CH_2Cl$ or heptane) 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), ketal or ketone (2.0 equiv), $Si(OEt)_4$ (0–1.0 equiv), PPTS (10–25 mol%), $Pd(PPh_3)_4$ (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 Cy_2NMe (1.2 equiv), and puri-

fied by column chromatography on silica gel with the suitable $CHCl_3$–MeOH mixture (or CH_2Cl_2–MeOH–NH_4OH mixture or hexane–EtOAc–Et_3N mixture) followed by trituration with CH_2Cl_2 (or 50% CH_2Cl_2 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 haloaminopyridine (2.25 mmol), ketal 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, $Pd(PPh_3)_4$ (5 mol%) and Cy_2NMe (1.3 equiv) were added before the tube was septum-sealed and irradiated again with microwaves at the set temperature and reaction time given in Table 3 for the palladium cross-coupling. The reaction mixture was cooled to r.t. and purified by column chromatography on silica gel with the suitable $CHCl_3$–MeOH mixture (or CH_2Cl_2–MeOH–NH_4OH mixture or hexane–EtOAc–Et_3N mixture) followed by trituration with 1–50% CH_2Cl_2 in heptane (or 60% $ClCH_2CH_2Cl$ in heptane) to give the corresponding azaindole.

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

Method 1: Following the General Procedure I, the reaction of **1**[3] (502 mg, 2.25 mmol), $Pd(PPh_3)_4$ (133 mg, 0.12 mmol), Cy_2NMe (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification [column chromatography: 0–15% MeOH in $CHCl_3$; trituration: CH_2Cl_2], afforded **2** as a white solid (398 mg, 95%).

Method 2: Following the General Procedure II, the reaction of **1**[3] (498 mg, 2.24 mmol), $Pd(PPh_3)_4$ (131 mg, 0.11 mmol), and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification [Cy_2NMe (0.58 mL); column chromatography: 0–15% MeOH in $CHCl_3$; trituration: CH_2Cl_2], afforded **2** as a white solid (404 mg, 97%); mp 268–270 °C (H_2O) (Lit.[3] mp 272–274 °C).

^{1}H NMR: δ = 12.06 (s, 1 H), 8.38 (dd, *J* = 1.4, 4.7 Hz, 1 H), 7.76 (dd, *J* = 1.4, 8.1 Hz, 1 H), 7.15 (dd, *J* = 4.7, 8.1 Hz, 1 H), 3.00 (t, *J* = 6.2 Hz, 2 H), 2.43 (t, *J* = 6.4 Hz, 2 H), 2.14–2.08 (m, 2 H).

^{13}C NMR: δ = 191.4, 154.8, 144.0, 143.0, 128.7, 118.5, 117.3, 111.3, 38.5, 23.2, 23.0.

MS (ESI): *m*/*z* = 187 [M + 1].

Anal. Calcd for $C_{11}H_{10}N_2O \cdot {}^1/_2H_2O$: C, 67.68; H, 5.68; N, 14.35. Found: C, 67.67; H, 5.60; N, 14.38.

3-Methyl-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-5-one (9)

Following the General Procedure I, the reaction of **3**[4] (638 mg, 2.27 mmol), $Pd(PPh_3)_4$ (138 mg, 0.12 mmol), Cy_2NMe (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 $CHCl_3$; trituration: CH_2Cl_2], afforded **9** as a white solid (404 mg, 89%); mp > 280 °C ($ClCH_2CH_2Cl$).

^{1}H NMR: δ = 12.22 (s, 1 H), 8.06 (s, 1 H), 8.04 (s, 1 H), 2.94 (t, *J* = 6.1 Hz, 2 H), 2.42 (t, *J* = 6.3 Hz, 2 H), 2.36 (s, 3 H), 2.14–2.08 (m, 2 H).

^{13}C NMR: δ = 192.8, 153.2, 147.3, 143.9, 128.0, 126.6, 116.6, 109.9, 37.6, 23.2, 22.6, 18.0.

MS (ESI): *m*/*z* = 201 [M + 1].

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.01; H, 6.03; N, 13.94.

3-Bromo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]indol-5-one (10)

Following the General Procedure I, the reaction of **4**[4] (781 mg, 2.26 mmol), $Pd(PPh_3)_4$ (132 mg, 0.12 mmol), Cy_2NMe (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 40 min at 160 °C and after purification (column chromatography: 0–5% MeOH in $CHCl_3$; trituration: CH_2Cl_2), afforded **10** as an off-white solid (341 mg, 57%); mp > 280 °C (acetone).

^{1}H NMR: δ = 12.60 (s, 1 H), 8.31 (d, *J* = 2.1 Hz, 1 H), 8.29 (d, *J* = 2.1 Hz, 1 H), 2.98 (t, *J* = 6.1 Hz, 2 H), 2.45 (t, *J* = 6.3 Hz, 2 H), 2.16–2.10 (m, 2 H).

^{13}C NMR: δ = 193.1, 155.0, 147.4, 143.6, 129.8, 118.6, 113.4, 110.0, 37.6, 23.1, 22.7.

MS (ESI): *m*/*z* = 267, 265 [M + 1].

Anal. Calcd for $C_{11}H_9BrN_2O$: C, 49.84; H, 3.42; N, 10.57. Found: C, 49.84; H, 3.21; N, 10.59.

6,7,8,9-Tetrahydro-5*H*-β-carbolin-5-one (11)

Following the General Procedure I, the reaction of **5** (496 mg, 2.23 mmol), $Pd(PPh_3)_4$ (133 mg, 0.12 mmol), Cy_2NMe (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 $CHCl_3$; trituration: CH_2Cl_2], afforded **11** as a white solid (396 mg, 95%); mp 275–277 °C (EtOAc–heptane) (Lit.[3] mp > 260 °C).

^{1}H NMR: δ = 12.29 (s, 1 H), 8.73 (s, 1 H), 8.24 (d, *J* = 5.2 Hz, 1 H), 7.82 (d, *J* = 5.2 Hz, 1 H), 3.00 (t, *J* = 6.2 Hz, 2 H), 2.45 (t, *J* = 6.4 Hz, 2 H), 2.16–2.10 (m, 2 H).

^{13}C NMR: δ = 193.1, 155.2, 140.9, 134.1, 133.0, 129.2, 114.6, 111.2, 37.7, 23.1, 22.8.

MS (ESI): *m*/*z* = 187 [M + 1].

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.71; H, 5.37; N, 14.85.

5,6,7,8-Tetrahydrocyclopenta[4,5]pyrrolo[3,2-*b*]pyridine (12)

Following the General Procedure I, the reaction of **6**[16] (440 mg, 2.26 mmol), $Pd(PPh_3)_4$ (137 mg, 0.12 mmol), Cy_2NMe (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–Et_3N, 9:1:1 → 5:4:1; trituration: $ClCH_2CH_2Cl$], afforded **12** as a white solid (312 mg, 87%); mp 258–260 °C (acetone) (Lit.[7] mp 258–260 °C).

^{1}H NMR: δ = 11.03 (s, 1 H), 8.16 (d, *J* = 4.6 Hz, 1 H), 7.59 (d, *J* = 8.1 Hz, 1 H), 6.94 (dd, *J* = 4.6, 8.1 Hz, 1 H), 2.85 (t, *J* = 7.2 Hz, 2 H), 2.77 (t, *J* = 6.9 Hz, 2 H), 2.47–2.43 (m, 2 H).

^{13}C NMR: δ = 148.9, 142.2, 141.2, 133.6, 118.0, 117.4, 114.7, 28.1, 25.6, 23.7.

MS (ESI): *m*/*z* = 159 [M + 1].

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.88; H, 6.50; N, 17.75.

6,7,8,9-Tetrahydro-5*H*-pyrido[3,2-*b*]indole (13)

Method 1: Following the General Procedure I, the reaction of **7**[16] (480 mg, 2.30 mmol), $Pd(PPh_3)_4$ (130 mg, 0.11 mmol), Cy_2NMe (0.58 mL, 2.73 mmol) and pyridine (1.5 mL), heated for 40 min at 160 °C and after purification [column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 5:4:1; trituration: heptane], afforded **13** as a white solid (327 mg, 83%).

Method 2: Following the General Procedure II, the reaction of **15** (291 mg, 2.26 mmol), **18** (0.54 mL, 4.50 mmol), $Pd(PPh_3)_4$ (136 mg, 0.12 mmol) and pyridine (1.5 mL), heated for 40 min at 160 °C and after purification [Cy_2NMe (0.58 mL); column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 5:4:1; trituration: heptane], afforded **13** as a white solid (323 mg, 83%).

Method 3: 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), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol) and pyridine (0.75 mL), heated for 40 min at 160 °C and after purification [Cy_2NMe (0.58 mL); column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 5:4:1; trituration: heptane], afforded **13** as a white solid (344 mg, 87%); mp 206–208 °C (EtOAc–heptane) (Lit.[7] mp 202–203 °C).

^{1}H 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).

^{13}C NMR: δ = 145.2, 140.9, 138.8, 128.3, 116.8, 115.1, 108.7, 23.0, 22.8, 22.7, 20.0.

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

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.95; H, 6.76; N, 16.21.

5,6,7,8,9,10-Hexahydrocyclohepta[4,5]pyrrolo[3,2-*b*]pyridine (14)

Method 1: Following the General Procedure I, the reaction of **8**[16] (509 mg, 2.29 mmol), $Pd(PPh_3)_4$ (134 mg, 0.12 mmol), Cy_2NMe (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–Et_3N, 9:1:1 → 5:4:1; trituration: heptane], afforded **14** as a white solid (363 mg, 85%).

Method 2: Following the General Procedure II, the reaction of **15** (299 mg, 2.33 mmol), **17**[19] (841 mg, 4.51 mmol), $Pd(PPh_3)_4$ (141 mg, 0.12 mmol) and pyridine (1.5 mL), heated for 20 min at 160 °C and after purification [Cy_2NMe (0.58 mL); column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 5:4:1; trituration: heptane], afforded **14** as a white solid (351 mg, 81%); mp 236–238 °C (EtOAc–heptane).

^{1}H 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).

^{13}C 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* = 187 [M + 1].

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.20; H, 7.65; N, 14.95.

6,7,8,9-Tetrahydro-5*H*-pyrido[4,3-*b*]indole (20)

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), $Pd(PPh_3)_4$ (136 mg, 0.12 mmol) and pyridine (1.5 mL), heated for 35 h at 160 °C and after purification [Cy_2NMe (0.58 mL); column chromatography: CH_2Cl_2–MeOH–NH_4OH, 99:1:0 → 87:10:3; trituration: 50% CH_2Cl_2 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 $Pd(PPh_3)_4$ (137 mg, 0.12 mmol) and Cy_2NMe (0.62 mL, 2.92 mmol), heated successively for 4 × 20 min (80 min) at 160 °C, and after purification [column chromatography: CH_2Cl_2–MeOH–NH_4OH, 99:1:0 → 87:10:3; trituration: 50% CH_2Cl_2 in heptane], afforded **20** as a white solid (187 mg, 48%).

Method 3: Following the General Procedure III, the reaction of **21**[26] (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 $Pd(PPh_3)_4$ (137 mg, 0.12 mmol) and Cy_2NMe (0.62 mL, 2.92 mmol), heated for 20 min at 160 °C, and after purification [column chromatography: CH_2Cl_2–MeOH–NH_4OH, 99:1:0 → 87:10:3; trituration: 50% CH_2Cl_2 in heptane], afforded **20** as a white solid (257 mg, 66%); mp 272–274 °C (acetone) (Lit.[8] mp 270–272 °C).

^{1}H NMR: δ = 11.11 (s, 1 H), 8.60 (s, 1 H), 8.06 (d, *J* = 5.5 Hz, 1 H), 7.20 (d, *J* = 5.5 Hz, 1 H), 2.70–2.64 (m, 4 H), 1.83–1.77 (m, 4 H).

^{13}C NMR: δ = 140.0, 139.5, 139.0, 135.6, 124.2, 107.7, 106.0, 22.7, 22.57, 22.55, 20.4.

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

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.26. Found: C, 76.61; H, 6.99; N, 16.30.

Ethyl 5,6,7,8-Tetrahydrocyclopenta[4,5]pyrrolo[3,2-*c*]pyridin-6-ylacetate (27)

Following the General Procedure III, the reaction of **21**[26] (496 mg, 2.25 mmol), **24** (786 mg, 4.62 mmol), PPTS (141 mg, 0.56 mmol), $Si(OEt)_4$ (0.51 mL, 2.28 mmol), and pyridine (0.75 mL) heated successively for 20 min at 160 °C, 180 °C, 200 °C and 220 °C, treated with $Pd(PPh_3)_4$ (136 mg, 0.12 mmol) and Cy_2NMe (0.62 mL, 2.92 mmol), heated successively for 2 × 20 min (40 min) at 160 °C, and after purification [column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 0:9:1; trituration: 1% CH_2Cl_2 in heptane], afforded **27** as a tan solid (252 mg, 46%); mp 123–124 °C (CH_2Cl_2–heptane).

^{1}H NMR: δ = 11.10 (s, 1 H), 8.59 (s, 1 H), 8.06 (d, *J* = 5.6 Hz, 1 H), 7.29 (d, *J* = 5.6 Hz, 1 H), 4.10 (q, *J* = 7.1 Hz, 2 H), 3.56–3.50 (m, 1 H), 2.84–2.68 (m, 4 H), 2.52–2.46 (m, 1 H), 2.16–2.09 (m, 1 H), 1.17 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 171.7, 147.0, 144.1, 140.7, 139.3, 120.9, 116.7, 107.4, 60.0, 38.7, 35.5, 34.9, 22.9, 14.1.

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

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.56; H, 6.32; N, 11.29.

Ethyl 1*H*-Pyrrolo[3,2-*b*]pyridine-2-carboxylate (28)

Following the General Procedure III, the reaction of **15** (291 mg, 2.26 mmol), **25** (0.50 mL, 4.52 mmol), PPTS (141 mg, 0.56 mmol), $Si(OEt)_4$ (0.51 mL, 2.28 mmol), and pyridine (0.75 mL) stirred for 48 h at r.t., treated with $Pd(PPh_3)_4$ (136 mg, 0.12 mmol) and Cy_2NMe (0.62 mL, 2.92 mmol), heated for 20 min at 160 °C, and after purification [column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 0:9:1; trituration: 10% CH_2Cl_2 in heptane], afforded **28** as a white solid (343 mg, 80%); mp 179–181 °C (CH_2Cl_2–hexane) (Lit.[27] mp 179 °C).

^{1}H NMR: δ = 12.14 (s, 1 H), 8.45 (dd, *J* = 1.3, 4.4 Hz, 1 H), 7.83 (d, *J* = 8.3 Hz, 1 H), 7.26 (dd, *J* = 4.4, 8.3 Hz, 1 H), 7.20 (d, *J* = 1.3 Hz, 1 H), 4.36 (q, *J* = 7.1 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 161.1, 144.6, 144.3, 130.3, 129.8, 120.1, 119.5, 107.2, 60.8, 14.2.

MS (ESI): *m*/*z* = 191 [M + 1].

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.02; H, 5.33; N, 14.42.

Ethyl 1*H*-Pyrrolo[2,3-*c*]pyridine-2-carboxylate (29)

Following the General Procedure III, the reaction of **22** (291 mg, 2.26 mmol), **25** (0.50 mL, 4.52 mmol), PPTS (140 mg, 0.56 mmol), $Si(OEt)_4$ (0.51 mL, 2.28 mmol), and pyridine (0.75 mL) stirred for 48 h at r.t., treated with $Pd(PPh_3)_4$ (136 mg, 0.12 mmol) and Cy_2NMe (0.62 mL, 2.92 mmol), heated successively for 2 × 20 min (40 min) at 160 °C, and after purification [column chromatography: hexane–EtOAc–Et_3N, 9:1:1 → 0:9:1; trituration: 10% CH_2Cl_2 in heptane], afforded **29** as a white solid (272 mg, 63%); mp 212–214 °C (toluene) (Lit.[28] mp 212–214 °C).

^{1}H NMR: δ = 12.39 (s, 1 H), 8.84 (s, 1 H), 8.16 (d, *J* = 5.5 Hz, 1 H), 7.62 (d, *J* = 5.5 Hz, 1 H), 7.16 (s, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR: δ = 160.9, 138.3, 136.4, 134.0, 130.6, 130.5, 116.0, 106.2, 61.0, 14.2.

MS (ESI): *m*/*z* = 191 [M + 1].

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.09; H, 5.32; N, 14.66.

2-[4-(Methylsulfonyl)phenyl]-1*H*-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 20 min at 160 °C, 180 °C and 200 °C, treated with $Pd(PPh_3)_4$ (136 mg, 0.12 mmol) and Cy_2NMe (0.62 mL, 2.92 mmol), heated successively for 6 × 20 min (2 h) at 160 °C, and after purification [column chromatography: 0–10% MeOH in $CHCl_3$; trituration: 60% $ClCH_2CH_2Cl$ in heptane], afforded **30** as a white solid (251 mg, 41%); mp >280 °C (acetone).

^{1}H 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 (dd, *J* = 4.6, 7.8 Hz, 1 H), 3.25 (s, 3 H).

^{13}C 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.

MS (ESI): *m*/*z* = 273 [M + 1].

Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.63; H, 4.41; N, 10.20.

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(16) Compounds **6**–**8**, see: Couture, A.; Deniau, E.; Grandclaudon, P.; Simion, C. *Synthesis* **1993**, 1227.

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