Synthesis of 5,7-Dichloro-6-azaindoles and Functionalization via a Highly Selective Lithium–Chlorine Exchange

Nicolas Lachance,* Louis-Philippe Bonhomme-Beaulieu, Pascal Joly
Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe Claire-Dorval, QC, H9R 4P8, Canada
Fax +1(514)4284900; E-mail: nicolas_lachance@merck.com
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Abstract: The synthesis of a range of novel 5,7-dichloro-6-azaindoles through the use of a Fischer cyclization with pyridine hydrochloride in N-methylpyrrolidin-2-one is described. Dichloro-6-azaindoles are versatile compounds that can be selectively substituted through a palladium-catalyzed cross-coupling reaction or a high-yielding lithium–chlorine exchange.

Key words: azaindole, pyrrolopyridine, Fischer cyclizations, metatations, palladium

The chemistry of indole heterocycles is of great interest to the pharmaceutical industry as a result of the diverse biological properties observed for this core.1–3 More recently, interest has increased around the use of azaindoles as in-doles surrogates, as a consequence of the differential activity and in vivo properties these basic indoles often display.4,5 As part of our research program on azaindoles,6,7 we required an efficient route to access 5,7-disubstituted 6-azaindoles. Although numerous methods are available for the preparation of 6-azaindoles,5a,b,d these methods suffer from lengthy synthesis, low compatibility to labile functional groups, and difficulty in the synthesis of complex starting materials. A better approach for our purposes would be to avoid a de novo synthesis for each substrate and to rather synthesize a common functionalized 5,7-disubstituted 6-azaindole which could readily be diversified to yield different analogues. We envisioned that a common 5,7-dichloro-6-azaindole would allow entry into more functionalized molecules, through halogen substitution or cross-coupling reactions.8,9 Critical to the realization of this approach would be the discovery of conditions that enable the selective functionalization of the 5,7-dichloro-6-azaindole template.

Herein, we report the preparation and further transformation of 5,7-dichloro-6-azaindoles. These compounds can be converted into diverse 6-azaindole derivatives via a highly selective lithium–chlorine exchange that allows for the functionalization of 6-azaindoles in the 7-position. In addition, we have discovered suitable conditions for the selective arylation of 6-azaindoles in the 7-position under Suzuki–Miyaura cross-coupling conditions.

To the best of our knowledge, the synthesis of 5,7-dichloro-6-azaindoles and their synthetic utility appears to be undocumented.4b We elected the Fischer indole reaction as a route of choice for the synthesis of the desired 5,7-dichloro-6-azaindoles 5, since the palladium-catalyzed cross-coupling reaction between ketones and 3-amino-2,4-dichloropyridines is known to lead to 7-chloro-4-azaindoles.10 Our approach relies on access to the corresponding 2,6-dichloro-3-hydrizinopyridine (2) intermediate. Following established literature conditions,1b the requisite hydrazine precursor 2 was synthesized in 80% yield from commercially available 3-amino-2,6-dichloropyridine (1) on a 120 mmol scale (20 g) (Scheme 1).

Having in hand this starting material 2, preliminary studies focused on optimization of the Fischer cyclization.11 We selected the hydrazone 4a, easily prepared from cyclohexanone 3a and hydrazine 2, to screen a variety of acids (Py·HCl, ZnCl₂, NH₄Cl, AcOH) and solvents (neat, Ph₃O, 1,2-dichlorobenzene, NMP, pyridine). By submitting the hydrazone 4a under the combination of pyridine hydrochloride in N-methylpyrrolidin-2-one at 160 °C for 30 minutes, a 57% isolated yield of the azaindole 5a was obtained. The optimal conditions that we found, starting from the hydrazone 2, are as follows: step 1: hydrazine 2 (9.27 mmol), ketone (1.1 equiv), NMP (1.2 M), r.t., 1 h; step 2: Py·HCl (3.0 equiv), 160 °C, 1 h. As we evaluated the effects of solvent, it was noted that the presence of pyridine completely inhibited the reaction. This fact highlights the need to keep the system open to the air, or in a similar way, to allow free pyridine liberated from pyridine hydrochloride to be removed.12 We noted that purification

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of the preformed hydrazone 4a had no impact on the outcome of the reaction.

Using the Fischer cyclizations conditions developed with pyridine hydrochloride at 160 °C, a range of 5,7-dichloro-6-azaindoles 5a–e were prepared in good to moderate yields (Table 1). Regiochemistry of 6-azaindoles 5a–e has been confirmed with NOE experiments (Figure 1). Better yields were obtained with the larger ring cyclohexanone (3a) and cycloheptanone (3b) than with the smaller ring cyclopentanone (3c) (Table 1, entries 1–3). For the latter, the low yield may be ascribed to the Fischer cyclization step where extensive decomposition occurred and the starting aminopyridine 1 was isolated in 28% yield.13 Considering the Fischer indolization, the 29–63% yields obtained for the 6-azaindoles 5a–e still compares favorably with formation of the corresponding dehalogenated 6-azaindoles for which the yields vary between 3–10%.11 Also, for comparison, a 7-chloro-6-azaindole has been previously prepared by Tacconi with zinc chloride/sodium chloride at 165–170 °C in 27% isolated yield.14

Having established conditions suitable for the synthesis of the 5,7-dichloro-6-azaindole templates 5a–e, our efforts turned to finding methods that would allow selective functionalization of the chlorine atoms, in order to gain access to substituted 6-azaindoles. We initially investigated the reduction of the chlorine atoms present on 5,7-dichloro-6-azaindoles 5a–e (Scheme 2). After methylation of the indole nitrogen, both chlorine atoms on the azaindole 6 could be removed by catalytic hydrogenation with Pearlman’s catalyst to give a 92% isolated yield of 6-azaindole 7.

We next explored a lithium–chlorine exchange on azaindole 6 as a means to selectively functionalize one of the chlorinated positions of the 5,7-dichloro-6-azaindole (Scheme 2).15,16 Treatment of azaindole 6 with tert-butyl lithium and quenching the resultant anion with water afforded 5-chloro-6-azaindole 8 in 95% yield. Surprisingly, this compound 8 remains unreacted after being submitted again to the lithium–chlorine exchange conditions. Moreover, when the medium was quenched with deuterium oxide in the metalation experiments with azaindoles 6 and 8, it produced, counterintuitively, the same deuterated azaindole 9. Indeed, the lithiation occurs favorably at the 7-position and 1H NMR of the unpurified reaction mixture did not show any incorporation of deuterium on the 2-alkyl substituent, or at the 4-position, as expected.17 These results are in contrast to literature ortho-lithiations directed by the chlorine atom on 4-chloro-7-azaindoles or with halogenated pyridines.18,19

![Scheme 2](image)

**Scheme 2** Reactivity of chlorine atoms on azaindole 6

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**Table 1** Synthesis of 5,7-Dichloro-6-azaindoles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Product</th>
<th>Time</th>
<th>Yieldb (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>5a</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>5b</td>
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<td>55</td>
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<td>39</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>5e</td>
<td>6</td>
<td>29c</td>
</tr>
</tbody>
</table>

a Reaction conditions: step 1: hydrazine 2 (9.27 mmol), ketones 3a–e (1.1 equiv), NMP (1.2 M), r.t., 30–60 min; step 2: Py·HCl (3.0 equiv), 160 °C, 1–6 h.

b Isolated yield.

c Step 1: 15 min at 160 °C.
We sought to take advantage of this remarkably selective lithium–chlorine exchange at the 7-position of 5,7-dichloro-6-azaindole as a means to prepare a series of 5,7-disubstituted 6-azaindoles. We further explored the metalation with tert-butyllithium using a series of 6-azaindoles and selected electrophiles. Table 2 presents our results in introducing several functional groups to the azaindole core via a metalation strategy. For example, the 7-chlorine atom can be replaced by the more reactive bromine in 95% yield by using 1,2-dibromo-1,1,2,2-tetrafluoroethane as the bromine source (Table 2, entry 1). Employing N,N-dimethylformamide as the electrophile, the 7-formyl derivative 11 was isolated in 96% yield (Table 2, entry 2). In addition, an acrylic ethyl ester group could be introduced in 83–84% yield after in situ Wadsworth–Horner–Emmons reaction by the sequential addition of N,N-dimethylformamide and triethyl phosphonoacetate (Table 2, entries 3 and 7). The tert-butyl ester group can be introduced directly at the 7-position in 61% yield by using di-tert-butyl dicarbonate as the electrophile (Table 2, entry 4), and tertiary alcohols 14 and 16 were synthesized from 6-azaindoles 6 and 15 using acetone as

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>6</td>
<td>Br·CF2·CF·Br</td>
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<td>95</td>
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<tr>
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</tr>
<tr>
<td>3</td>
<td>6</td>
<td>1. DMF 2. (EtO)2P(O)CH2CO2Et</td>
<td>12</td>
<td>84</td>
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<tr>
<td>8</td>
<td>8</td>
<td>CCl3CCl3</td>
<td>6</td>
<td>94</td>
</tr>
</tbody>
</table>

*a Reaction conditions: step 1: substrate (0.5 mmol), t-BuLi (1.7 equiv), −78 °C, 2 h; step 2: electrophile (2.0 equiv), −78 °C, 1 h.
*b Isolated yield.
an electrophile (Table 2, entries 5 and 6). Moreover, groups easier to remove than the methyl on the indole nitrogen could be used, such as 2-(trimethylsilyl)ethoxy)methyl (SEM), to perform the highly selective lithium–chlorine exchange (Table 2, entry 7). Finally, a complementary method to the Fischer cyclization for the preparation of a 5,7-dichloro-6-azaindole could start from the corresponding 5-chloro-6-azaindole (Table 2, entry 8).4c

While chlorine at the 5-position of the azaindole is unreactive under lithium–chlorine exchange conditions, it can be converted into new functional groups using Suzuki–Miyaura cross-coupling chemistry (Scheme 3). Under Guram’s conditions,21 the coupling of azaindole 8 (0.5 mmol scale) with boronic acid 19 could be realized by employing only 3 mol% of the highly active palladium catalyst 20. After purification, the 5-aryl-6-azaindole 21 was obtained in 91% yield.

As a further demonstration of the differential reactivity of the chlorine atoms in the 5,7-dichloro-6-azaindole 6, we performed a palladium-catalyzed cross-coupling reaction with 5,7-dichloro-6-azaindole 6 and 1.1 equivalent of the boronic acid 19 (Equation 1). Here, the 7-aryl-6-azaindole 22 and the 5,7-diaryl-6-azaindoles 23 were isolated in 82% and 12% respectively; regiochemistry of 22 has been confirmed with NOE experiments (Figure 1).22 This result demonstrates once again the greater reactivity of the chlorine at the 7-position of azaindole 6.

Interestingly, as documented for pyridines,23 the basic nitrogen in the 6-azaindole core directs an ortho-lithiation onto an aromatic ring resulting in further elaboration of 21 and 22 into 24 and 25 (Equations 2 and 3). Regiochemistry of 6-azaindoles 24 and 25 has been confirmed with NOESY and gHSQCAD experiments (Figure 2).

**Scheme 3** Suzuki–Miyaura coupling of 5-chloro-6-azaindole 8

**Equation 1** Selective Suzuki–Miyaura coupling of 5-chloro-6-azaindole 6

**Figure 1** NOE experiments
Equation 2

\[
\begin{align*}
\text{ortho-Lithiation of 5-aryl-6-azaindole 21} \\
1. \text{t-BuLi} \\
2. \text{CCl}_2\text{CO}_3 \\
\end{align*}
\]

Equation 3

\[
\begin{align*}
\text{ortho-Lithiation of 7-aryl-6-azaindole 22} \\
1. \text{t-BuLi} \\
2. \text{DMF} \\
3. (\text{EtO})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{Et} \\
\end{align*}
\]

Figure 2 NOESY experiments

In summary, we have described the first synthesis of 5,7-dichloro-6-azaindoles by use of a Fischer indole reaction with pyridine hydrochloride in N-methylpyrrolidin-2-one at 160 °C. These 5,7-dichloro-6-azaindoles are versatile templates that can be selectively functionalized via a lithium–chlorine exchange or Suzuki–Miyaura cross-coupling reaction. The efficiency of this method, which relies on an unprecedented lithium–chlorine exchange on azaindoles (instead of an expected ortho-lithiation), makes this an important addition to the synthetic methodology for 5,7-disubstituted 6-azaindole analogues. Further efforts to improve the synthesis and selective functionalization of 5,7-dichloro-6-azaindoles are currently being investigated within our laboratory.

Melting points were determined on a Mettler FP61 apparatus and are uncorrected. \(^1\)H and \(^13\)C NMR spectra were recorded in acetone-d\(_6\) or DMSO-d\(_6\) at room temperature on a Bruker Avance II 400 MHz spectrometer. Additional 2D experiments were conducted on Varian Inova 600 MHz spectrometer equipped with a cryogenic probe. The spectra were referenced to residual protons in the NMR solvent (acetone-d\(_6\)). \(^1\)H NMR δ = 2.04 (quintet), \(^13\)C NMR δ = 29.8 (heptet), 206.0 (singlet); DMTO-d\(_6\): \(^1\)H NMR δ = 2.49 (quintet); \(^13\)C NMR δ = 39.5 (heptet). HRMS (ESI) data were acquired on an Agilent LC/MSD TOF high-resolution mass spectrometer. TLC analyses were performed on Merck Kieselgel 60 F\(_{254}\) plates. 3-Amino-2,6-dichloropyridine (I) was obtained from Acros. 1.7 M t-BuLi in pentane and Pd catalyst 20 were purchased from Aldrich. Hygroscopic electrophiles (Table 2) were placed under high vacuum for drying, prior to use. Column chromatography was conducted with silica gel 230–400 mesh. Elemental analyses were determined by Prevalere Life Science, Inc., Whitesboro, NY.

2,6-Dichloro-3-hydrizinopyridinidine (2)

Into a 2-L Erlenmeyer flask equipped with a large magnetic stirrer bar, 3-amino-2,6-dichloropyridine (I, 20.00 g, 123 mmol) was mixed with concd HCl (37%, 180 mL) and stirred at r.t. for 30 min and then it was cooled to ~20 °C. Then, a soln of NaNO\(_2\) (10.58 g, 153 mmol) dissolved in H\(_2\)O (50 mL) was added to the suspension over 15 min, keeping the internal temperature between ~20 to ~10 °C. After completion of the addition, the mixture was slowly warmed to 0 °C over 20 min and maintained at this temperature for an additional 1.5 h with continuous stirring. Finally, the suspension was cooled again to ~10 °C before a soln of SnCl\(_2\) (70.05 g, 369 mmol) in concd HCl (37%, 180 mL) was added over 40 min, keeping the internal temperature below 0 °C. The final mixture was slowly warmed to r.t. over 1 h and kept at this temperature for 2 h with continuous stirring. The acidic soln was basified with 10 M NaOH (700 mL), without exceeding an internal temperature of 20 °C. The suspension was extracted with CHCl\(_3\) (2 × 500 mL). All the organic phases were combined, dried (MgSO\(_4\)), and filtered and the filtrate was concentrated in vacuo.

\(^1\)H NMR (DMSO-d\(_6\)): \(\delta = 7.56\) (d, \(J = 8.5\) Hz, 1 H), 7.34 (d, \(J = 8.5\) Hz, 1 H), 7.08 (br s, 1 H), 4.32 (br s, 2 H).

\(^13\)C NMR (DMSO-d\(_6\)): \(\delta = 143.9, 133.3, 131.1, 123.7, 122.6\). HRMS (ESI): \(m/z\) [M + H\(^+\)] calcd for C\(_{13}\)H\(_{12}\)Cl\(_2\)N\(_2\): 177.9933; found: 177.9933.

Anal. Calcd for C\(_{13}\)H\(_{12}\)Cl\(_2\)N\(_2\): C, 33.73; H, 2.83; N, 24.02. Found: C, 33.97; H, 2.72; N, 24.02.

Cyclohexanone (2,6-Dichloropyridin-3-yl)hydrazone (4a)

A neat mixture of cyclohexanone (3a, 6.00 mL, 57.9 mmol) and 2 (4.55 g, 25.6 mmol) was stirred at r.t. for 30 min. Then, excess of 3a was distilled off by gentle heating under high vacuum. The residue was purified by column chromatography (silica gel, 0–30% EtOAc–hexanes) followed by trituration (heptane, –78 °C) to give 4a (86%) as a yellow solid; mp 50–52 °C.

\(^1\)H NMR (DMSO-d\(_6\)): \(\delta = 8.35\) (s, 1 H), 7.74 (d, \(J = 8.5\) Hz, 1 H), 7.37 (d, \(J = 8.5\) Hz, 1 H), 2.44–2.38 (m, 2 H), 2.32–2.26 (m, 2 H), 1.74–1.50 (m, 6 H).

\(^13\)C NMR (DMSO-d\(_6\)): \(\delta = 158.1, 139.4, 136.0, 132.5, 124.5, 124.0, 34.9, 26.71, 26.66, 25.3, 25.1\). HRMS (ESI): \(m/z\) [M + H\(^+\)] calcd for C\(_{14}\)H\(_{14}\)Cl\(_2\)N\(_2\): 258.0559; found: 258.0559.

5,7-Dichloro-6-azaindoles 5a–e; General Procedure for Fischer Cyclizations

The reactions were performed under the ambient atmosphere: i.e. no septum, no cap, no reflux condenser, and no N\(_2\) flow were used (except 5e: a flow of N\(_2\) was placed for the last 5 h of heating). All Fischer cyclizations (Table 1) were typically performed on an 8.43 mmol scale. Into a 25-mL round bottom flask, ketone 3 (1.1 equiv) was added to a soln of 2 (1.50 g, 8.43 mmol) in NMP (7.50 mL) and the mixture was stirred at r.t. for 30–60 min (except 5e: additional 15 min at 160 °C). Anhyd Py·HCl (2.92 g, 25.3 mmol) was added to the mixture at r.t., then immersed into a preheated oil bath at 160 °C. After heating for 1–6 h (see Table 1; the reaction progresses by removal of free pyridine), the reaction was cooled to r.t., neutralized with aq NaHCO\(_3\) and extracted with EtOAc. When necessary, the phases were filtered through a Celite pad before their separation.

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The aqueous phase was further extracted with EtOAc. The organic layers were combined, washed with water and brine, dried (Na₂SO₄), and filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–50% EtOAc–hexanes) to give the corresponding azaindoles 5a–e.

1,3-Dichloro-6,7,8,9-tetrahydro-5H-β-carboline (5a)

Method 1: Into a 25-mL round-bottom flask open to the air, a mixture of 4a (2.5 g, 9.68 mmol) and Py-HCl (3.36 g, 29.1 mmol) in NMP (8.00 mL) was immersed into a preheated oil bath at 160 °C. After 30 min, the reaction was cooled to r.t., neutralized with aq NaHCO₃ and extracted with EtOAc (2 ×), the organic layers were combined, washed with H₂O and brine, dried (Na₂SO₄), and filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–50% EtOAc–hexanes) to afford 5a (57%) as a white solid.

Method 2: Following the general procedure (Fischer cyclizations) using 2 and 3a (960 µL, 9.27 mmol) gave 5a (63%) as a white solid; mp 192–193 °C.

1H NMR (DMSO-d₆): δ = 11.75 (br s, 1 H), 7.44 (s, 1 H), 2.74 (t, J = 6.0 Hz, 2 H), 2.58 (t, J = 5.9 Hz, 2 H), 1.85–1.73 (m, 4 H).

13C NMR (DMSO-d₆): δ = 147.4, 137.4, 136.0, 130.3, 128.3, 111.4, 110.0, 22.9, 22.3, 22.2, 20.3.


1,3-Dichloro-6,7,8,9,10-hexahydrocycloheptatetra-4,5,10pyrrolo[2,3-c]pyridine (5b)

Following the general procedure (Fischer cyclizations) using 2 and 3b (1.09 mL, 9.27 mmol) gave 5b (55%) as a beige solid; mp 161–163 °C.

1H NMR (DMSO-d₆): δ = 11.78 (br s, 1 H), 7.51 (s, 1 H), 2.92–2.86 (m, 2 H), 2.73–2.67 (m, 2 H), 1.86–1.78 (m, 2 H), 1.72–1.57 (m, 4 H).

13C NMR (DMSO-d₆): δ = 144.3, 136.3, 135.9, 130.3, 128.3, 111.4, 110.0, 22.9, 22.3, 22.2, 20.3.


1,3-Dichloro-6,7,8,9-tetrahydrocyclopenta[4,5]pyrrolo[2,3-c]pyridine (5c)

Following the general procedure (Fischer cyclizations) using 2 and 3c (820 µL, 9.27 mmol) and after a second purification by column chromatography (silica gel, 0–100% CH₂Cl₂–hexane), gave 5c (37%) as a white solid; mp 177–179 °C (toluene).

1H NMR (DMSO-d₆): δ = 11.96 (br s, 1 H), 7.43 (s, 1 H), 2.87 (t, J = 7.3 Hz, 2 H), 2.72 (t, J = 7.0 Hz, 2 H), 2.51–2.43 (m, 2 H).

13C NMR (DMSO-d₆): δ = 153.4, 136.4, 133.1, 132.6, 110.0, 9.5.


Anal. Calcd for C₁₀H₉Cl₂N₂: C, 52.89; H, 3.55; N, 12.34. Found: C, 52.92; H, 3.41; N, 12.44.

5,7-Dichloro-3-methyl-2-phenyl-1H-pyrrolo[2,3-c]pyridine (5e)

Following the general procedure (Fischer cyclizations) using 2 and 3e (1.23 mL, 9.27 mmol) (step 1: 160 °C for an additional 15 min) gave 5e (29%) as a beige solid; mp 129–131 °C.

1H NMR (DMSO-d₆): δ = 12.12 (br s, 1 H), 7.73–7.68 (m, 3 H), 7.55 (t, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.3 Hz, 1 H), 2.34 (s, 3 H).

13C NMR (DMSO-d₆): δ = 141.9, 138.3, 136.3, 131.2, 130.8, 129.0 (2 C), 128.8, 128.7, 128.6 (2 C), 112.5, 108.4, 9.5.


Anal. Calcd for C₁₄H₁₁Cl₂N₂: C, 60.67; H, 3.64; N, 10.11. Found: C, 60.76; H, 3.48; N, 10.07.

N-Alkyl-5,7-dichloro-6-azaindoles 6, 15, and 17; General Procedure for N-Alkylation

To a stirred suspension (or soln) of dichloro-6-azaindole (1.0 equiv) in DMSO (0.4 M) at 0 °C, was added carefully NaH (60% w/w) (1.25 equiv). The mixture was stirred at 0 °C for 10 min, then, alkyl halide (1.25 equiv) was added and the final suspension was warmed to r.t. After 30 min, the suspension was poured into aq NaHCO₃ and extracted with EtOAc (2 ×). The organic layers were combined, washed with H₂O (2 ×) and brine, dried (Na₂SO₄), and filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0–30% EtOAc–hexanes), or by trituration with heptane, to give the corresponding N-alkylated azaindoles 6, 15, and 17.

5-Chloro-6-azaindoles 6, 8–14, 16, 18, 24, and 25; General Procedure for Lithium–Chlorine Exchange

Crystalline 6-azaindole reagents were milled with a mortar and pestle to a fine powder before use. All lithium–chlorine exchanges (Table 2, Scheme 2, and Equations 2 and 3) were typically performed on a 0.5 mmol scale based on the 6-azaindole. To a suspension (or soln) of 6-azaindole (0.5 mmol) in anhyd Et₂O (7 mL) under N₂ at −78 °C, t-BuLi (500 µL, 0.85 mmol) was slowly added dropwise over 5 min and the resulting mixture was stirred at −78 °C for 2 h after the addition. Electrophile (3.0 equiv) was then added rapidly, and the resulting mixture was stirred at −78 °C for 1 h. [Only for in situ Wadsworth–Horner–Emmons reactions of the synthesis of 12, 18, and 25: Prior to the quench, the mixture was treated with triethyl phosphonoacetate (300 µL, 1.51 mmol) and was allowed to warm to r.t. for 1 h.] The cold reaction mixture was then quenched by the addition of aq NaHCO₃ (3 mL). The suspension was poured into aq NaHCO₃ and extracted with EtOAc (2 ×). The organic layers were combined, washed with brine, dried (Na₂SO₄), and filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, suitable EtOAc–hexanes mixtures and/or CH₂Cl₂–hexanes mixture), or by trituration (heptane), to give the corresponding azaindoles 6, 8–14, 16, 18, 24, and 25.

1,3-Dichloro-9-methyl-6,7,8,9-tetrahydro-5H-β-carboline (6)

Method 1: Following the general procedure (N-alkylations) using 5a (1.40 g, 5.81 mmol), DMF (14 mL), NaH (60% w/w) (290 mg, 7.25 mmol), and MeI (450 µL, 7.26 mmol) and after purification by trituration (heptane) gave 6 (97%) as a white solid.
Method 2: Following the general procedure (lithium–chlorine exchange) using 8 (110 mg, 0.50 mmol) and hexachloroethane (354 mg, 1.50 mmol) and after purification by column chromatography (silica gel, 0–20% EtOAc–hexanes) gave 6 (94%) as a white solid; mp 145–146 °C.

1H NMR (acetone-d6): δ = 7.38 (s, 1 H), 3.67 (s, 3 H), 2.72 (t, J = 6.1 Hz, 2 H), 2.58 (t, J = 6.0 Hz, 2 H), 1.89–1.80 (m, 2 H), 1.78–1.70 (m, 2 H).

13C NMR (DMSO-d6): δ = 143.0, 138.6, 133.8, 132.8, 130.7 (t, JCD = 27.4 Hz, 111.0, 108.1, 29.3, 22.3, 22.2, 21.4, 20.3).


1-Bromo-3-chloro-9-methyl-6,7,8,9-tetrahydro-5H-β-carboline (10)
Following the general procedure (lithium–chlorine exchange) using 6 (128 mg, 0.50 mmol) and 1,2-dibromo-1,1,2,2-tetrafluoroethane (180 µL, 1.50 mmol) and purification by trituration (heptane, 2–3 mL) gave 10 (95%) as a beige solid; mp 152–153 °C.

1H NMR (acetone-d6): δ = 7.36 (s, 1 H), 3.99 (s, 3 H), 2.80–2.74 (m, 2 H), 2.63 (t, J = 6.1 Hz, 2 H), 1.98–1.87 (m, 2 H), 1.86–1.78 (m, 2 H).

13C NMR (acetone-d6): δ = 145.8, 138.0, 137.5, 131.1, 120.5, 112.2, 110.5, 32.1, 23.4, 23.3, 23.0, 21.1.


3-Chloro-9-methyl-6,7,8,9-tetrahydro-5H-β-carboline-1-carboxylic acid (11)
Following the general procedure (lithium–chlorine exchange) using 6 (128 mg, 0.50 mmol) and DMP (120 µL, 1.51 mmol) and purification by column chromatography (silica gel, 0–70% EtOAc–hexanes) gave 11 (96%) as a yellow solid; mp 196–198 °C.

1H NMR (DMSO-d6): δ = 10.00 (s, 1 H), 7.76 (s, 1 H), 3.86 (s, 3 H), 2.76 (t, J = 6.2 Hz, 2 H), 2.62 (t, J = 6.0 Hz, 2 H), 1.92–1.83 (m, 2 H), 1.79–1.71 (m, 2 H).


Ethyl (2E)-3-(3-Chloro-9-methyl-6,7,8,9-tetrahydro-5H-β-carboline-1-yl)acrylate (12)
Following the general procedure (lithium–chlorine exchange) using 6 (128 mg, 0.50 mmol), DMP (120 µL, 1.51 mmol), and triethyl phosphonoacetate (300 µL, 1.51 mmol) and purification by column chromatography (silica gel, 0–40% EtOAc–hexanes) gave 12 (84%) as a yellow solid; mp 163–165 °C.

1H NMR (acetone-d6): δ = 8.34 (d, J = 14.9 Hz, 1 H), 7.36 (s, 1 H), 6.99 (d, J = 14.9 Hz, 1 H), 4.25 (q, J = 7.1 Hz, 2 H), 3.93 (s, 3 H), 2.83–2.76 (m, 2 H), 2.63 (t, J = 6.1 Hz, 2 H), 1.99–1.90 (m, 2 H), 1.86–1.78 (m, 2 H), 1.31 (t, J = 7.1 Hz, 3 H).

13C NMR (acetone-d6): δ = 166.9, 145.3, 139.9, 139.2, 138.6, 136.0, 132.7, 132.6, 113.4, 109.9, 61.0, 33.3, 23.5, 23.3, 23.0, 21.1, 14.6.


2-(3-Chloro-9-methyl-6,7,8,9-tetrahydro-5H-β-carbolin-1-yl)prop-2-en-1 (14)
Following the general procedure (lithium–chlorine exchange) using 6 (128 mg, 0.50 mmol) and acetonitrile (110.1 µL, 1.50 mmol) and purifcation by column chromatography (silica gel, 0–40% EtOAc–hexanes) gave 14 (75%) as an off-white solid; mp 126–127 °C.

1H NMR (acetone-d6): δ = 7.33 (s, 1 H), 6.86–6.79 (m, 2 H), 1.98–1.84 (m, 2 H), 1.80–1.77 (m, 2 H), 1.75 (s, 6 H).

13C NMR (acetone-d6): δ = 144.2, 127.8, 123.4, 118.2, 115.3, 112.5, 110.3, 33.0, 29.0, 22.9, 22.6, 11.5.


Ethyl (2E)-3-[5-(Chloro-2,3-dimethyl-1H-pyrazol-3-yl)ethoxy]-1H-pyrole-2,3-dicarboxylic acid methyl ester (18)
Following the general procedure (lithium–chlorine exchange) using 17 (173 mg, 0.50 mmol), DMF (120 µL, 1.51 mmol) and triethyl phosphonoacetate (300 µL, 1.51 mmol) and purifcation by column chromatography (silica gel, 0–50% EtOAc–hexanes) gave 18 (83%) as a yellow solid; mp 85–87 °C.

1H NMR (acetone-d6): δ = 7.99 (d, J = 15.0 Hz, 1 H), 7.43 (s, 1 H), 7.09 (d, J = 15.0 Hz, 1 H), 5.57 (s, 2 H), 4.25 (q, J = 7.1 Hz, 2 H), 3.74 (t, J = 8.0 Hz, 2 H), 2.48 (s, 3 H), 2.20 (s, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.00 (t, J = 8.0 Hz, 2 H), –0.01 (s, 9 H).

13C NMR (acetone-d6): δ = 168.6, 141.9, 120.6, 140.5, 10.0, 136.4, 132.2, 124.3, 113.7, 108.4, 74.2, 65.8, 60.9, 18.4, 14.6, 10.6, 8.4, –1.3 (3 C).


Substituted 6-Azaindoles 21–23; General Procedure for Suzuki–Miyaura Coupling Reactions
The Suzuki–Miyaura coupling reactions (Scheme 3 and Equation 1) were typically performed on a 0.5 mmol scale of the azaindoles 6 and 8 following the procedure of Gourm.23 A mixture of 6-azaindole (1.0 equiv), boronic acid 19 (1.1–1.2 equiv), K2CO3 (139 mg, 1.00 mmol), and Pd catalyst 20 (11 mg, 0.015 mmol) in H2O–toluene (1:9, 2 mL) was stirred at 100 °C in screw-capped glass vial for 1 h. The mixture was cooled to rt and extracted with MTBE (3 x). The organic layers were combined, washed with brine, dried (Na2SO4), and filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel) to give the corresponding azaindoles 21–23.

3-(4-Fluorophenyl)-9-methyl-6,7,8,9-tetrahydro-5H-β-carboline (21)
Following the general procedure (Suzuki–Miyaura coupling) using 8 (110 mg, 0.50 mmol) and 19 (84 mg, 0.60 mmol) and purification by column chromatography (silica gel, 0–70% EtOAc–hexanes) gave 21 (91%) as an off-white solid; mp 145–146 °C.

1H NMR (acetone-d6): δ = 7.51 (s, 1 H), 6.83 (d, J = 8.5, 5.6 Hz, 2 H), 7.87 (s, 1 H), 7.17 (t, J = 8.7 Hz, 2 H), 3.75 (s, 3 H), 2.79–2.72 (m, 2 H), 2.75–2.68 (m, 2 H), 1.97–1.88 (m, 2 H), 1.88–1.80 (m, 2 H).

13C NMR (acetone-d6): δ = 163.2 (d, JCF = 244 Hz), 145.6, 141.6, 138.7 (d, JCF = 294 Hz), 134.9, 131.5, 132.0, 129.9 (d, JCF = 8.0 Hz, 2 C), 115.8 (d, JCF = 21.3 Hz, 2 C), 110.0, 108.9, 29.5, 23.64, 23.62, 22.5, 21.5.


3-Chloro-1-(4-fluorophenyl)-9-methyl-6,7,8,9-tetrahydro-5H-β-carboline (22)
Following the general procedure (Suzuki–Miyaura coupling) using 6 (128 mg, 0.50 mmol) and 19 (77 mg, 0.55 mmol) and purification by column chromatography (silica gel, 0–20% EtOAc–hexanes) gave 22 (82%) as a white solid; mp 161–163 °C.

1H NMR (acetone-d6): δ = 7.59 (dd, J = 8.4, 5.5 Hz, 2 H), 7.36 (s, 1 H), 7.27 (t, J = 8.7 Hz, 2 H), 3.26 (s, 3 H), 2.77–2.65 (m, 4 H), 1.97–1.88 (m, 2 H), 1.87–1.79 (m, 2 H).

13C NMR (acetone-d6): δ = 163.7 (d, JCF = 245 Hz), 144.8, 142.7, 139.2, 137.5, 136.5 (d, JCF = 3.7 Hz), 132.6 (d, JCF = 8.2 Hz, 2 C),
131.8, 115.6 (d, JCF = 21.8 Hz, 2 C), 111.2, 110.0, 32.9, 23.6, 23.4, 23.0, 21.3.


1,3-Bis(4-fluorophenyl)-9-methyl-6,7,8,9-tetrahydro-5H-barboline (23)
This side product was isolated as a white solid (12%) from the preparation of 22; mp 165–166 °C.

1H NMR (acetone-d6): δ = 8.18 (dd, J = 8.5, 5.5 Hz, 2 H), 7.91 (s, 1 H), 7.66 (dd, J = 8.2, 5.5 Hz, 2 H), 7.27 (t, J = 8.6 Hz, 2 H), 7.15 (t, J = 8.7 Hz, 2 H), 3.27 (s, 3 H), 2.76 (t, J = 6.0 Hz, 2 H), 2.70 (t, J = 6.0 Hz, 2 H), 1.99–1.90 (m, 2 H), 1.87–1.82 (m, 2 H).

13C NMR (acetone-d6): δ = 133–135 °C.

Following the general procedure (lithium–chlorine exchange) using 21.51 mmol, and purification by column chromatography (silica gel, 0–100% EtOAc–hexanes) gave 22 (87%) as an off-white solid; mp 165–166 °C.

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References

(2) For review on indole synthesis, see: Gribble, G. W. J. Chem. Soc., Perkin Trans. 1 2000, 1045; and references therein.


(12) The use of a condenser is not recommended.
(13) Typically, aminopyridine 1 was isolated in less than 5%.
(15) For selective lithium–bromine exchange on indoles, see:
   (d) Review: Mongin, F.; Quéguiner, G. Tetrahedron 2001, 57, 4059; and references therein.
(22) Starting material 6 was observed in less than 5% on the 1H NMR of the unpurified reaction mixture.