N-Confused Porphyrins on Solid Supports: Synthesis, Characterization, and Cation Sensing
Indium-Catalyzed Annulation of o-Acylanilines with Alkoxyheteroarenes: Synthesis of Heteroaryl[b]quinolines and Subsequent Transformation to Cryptolepine Derivatives

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Abstract: We disclose herein the first synthetic method that is capable of offering heteroaryl[b]quinolines (HA[b]Qs) with structural diversity, which include tricyclic and tetracyclic structures with (benzo)thienyl, (benzo)furanyl, and indolyl rings. The target HA[b]Q is addressed by the annulation of o-acylanilines and MeO–heteroarenes with the aid of an indium Lewis acid that effectively works to make two different types of the N–C and C–C bonds in one batch. A series of indolo[3,2-b]quinolines prepared here can be subsequently transformed to structurally unprecedented cryptolepine derivatives. Mechanistic studies showed that the N–C bond formation is followed by the C–C bond formation. The indium-catalyzed annulation reaction thus starts with the nucleophilic attack of the NH$_2$ group of o-acylanilines to the MeO-connected carbon atom of the heteroaryl ring in an S$_\text{N}$Ar fashion, and thereby the N–C bond is formed. The resulting intermediate then cyclizes to make the C–C bond through the nucleophilic attack of the heteroaryl-ring-based carbon atom to the carbonyl carbon atom, providing the HA[b]Q after aromatizing dehydration.

Keywords: anti-cancer activity; anti-malarial activity; heteroarenes; indium; Lewis acids; pyridine; one-pot; quindolines; tandem reaction

1. Introduction

Heteroaryl[b]quinolines (HA[b]Qs), wherein electron-rich heteroaryl rings are fused to the [b] site of quinoline, are important frameworks found in natural products [1–3] and biologically active molecules [1,4–6] as well as functional organic materials [7–9]. Due to their significance, numerous synthetic approaches have been developed for the construction of such structural motifs. These approaches could be categorized simply into three strategies on the basis of the ring-constructing method (Figure 1), which are the heteroaryl ring formation (strategy a) [10–22], the central pyridyl ring formation (strategy b) [23–39], and the formation of both rings (strategy c) [4,40–53]. Although there are advantages and disadvantages to each strategy from various aspects, the strategy b seems to be the most user-friendly in terms of the accessibility of the starting substrates.

On the other hand, we have recently reported a new C(heteroaryl)–N bond-forming reaction by reacting electron-rich methoxyheteroarenes with amines via a nucleophilic aromatic substitution (S$_\text{N}$Ar) reaction [54]. In addition to this, we have also developed several new C(heteroaryl)–C bond-forming reactions by reacting alkynes [55–57] or carbonyl compounds [58–60] with heteroarenes. All of these reactions are effectively catalyzed by a salt of an indium(III) Lewis acid, which has been also employed
for various organic transformations by other research groups [61–71]. We therefore envisaged that conducting the two different types of reactions in a tandem fashion would be a new methodology of the strategy b to offer the HA[b]Q in an easy way, thereby also leading to the further expansion of our indium-based technology. Our working hypothesis is illustrated more intelligibly in Scheme 1. We thus expected that the synthesis of HA[b]Qs 4 could be achieved by mixing o-alkynylanilines 1 or o-acylanilines 2 with methoxyheteroarenes 3 in the presence of a catalytic indium Lewis acid (InX$_3$ = ln). The first stage is the SN$_{Ar}$-based N–C bond-forming reaction through the nucleophilic attack of the amino group of 1 or 2 to electrophilic complex A to afford 5 or 6, respectively. Intermediate 5 or 6 successively cyclizes by forming the C–C bond in an intramolecular fashion, thus giving 7 or 8, respectively, via the activation mode of B or C. The isomerization or dehydration as the final stage results in the formation of desired HA[b]Q 4. We also expected that combining the two indium transformations, both of which are compatible with a broad range of substrates, should lead to the development of the HA[b]Q synthesis with good substrate generality. As stated above, a lot of studies that synthesize the HA[b]Q have appeared so far in literature, but these studies have been limited to preparing HA[b]Qs with one to three types of heteroaryl rings, to the best of our knowledge [72–74]. We report herein that an indium salt effectively catalyzes the N–C and C–C bond-forming sequence to afford a range of HA[b]Qs including tricyclic and tetracyclic [2,3-b] and [3,2-b] structures with sulfur-, oxygen-, and nitrogen-based five-membered heteroaryl rings. Among the products, indolo[3,2-b]quinolines, which can be easily converted to cryptolepine derivatives that have been known to exhibit anti-malarial and anti-cancer activities, are included [75].

**Figure 1.** Synthetic strategies for the construction of the heteroaryl[b]quinoline (HA[b]Q) structure.

**Scheme 1.** A working hypothesis for the synthesis of HA[b]Qs 4. In = InX$_3$. 
2. Results and Discussion

In order to verify the working hypothesis, we first investigated the possibility of whether o-ethynylaniline (1a) works as a substrate for the synthesis of the HA[b]Q under indium catalysis, and selected 3-methoxybenzothiophene (3a) as the substrate partner (Table 1). Upon treatment of 1a and 3a with 5 mol % of In(NTf$_2$)$_3$ (Tf = SO$_2$CF$_3$) in PhCl at 110 °C for 24 h, we were pleased to observe that the desired annulation proceeded to give 11-methyl[1]benzothieno[3,2-b]quinoline (4aa), albeit in low yield (entry 1). While the screening of other indium salts provided no significant improvements in the yield of 4aa, a small amount of o-acetylaniline (2a) was formed along with 4aa when using In(ONf)$_3$ (Nf = SO$_2$C$_4$F$_9$) as a catalyst (entries 2–6). In this context, a wide variety of Lewis acids, including indium salts, have been known to act as catalysts for the hydration of a C≡C bond to create a carbonyl functionality [76,77]. A possible explanation for the formation of 2a is thus the indium-catalyzed hydration of 1a with H$_2$O, which could have been present in a small quantity in the reaction mixture. Accordingly, we presumed that, as routes for the formation of 4aa, there would be two possibilities: one is directly from 1a, and the other is indirectly from 2a formed in situ after the hydration of 1a. In order to get an insight into which routes operate here, the following experiments were conducted. Thus, the annulation carried out under the conditions of entry 3, additionally including five molar equivalents of H$_2$O, resulted in higher yields of both 4aa and 2a (entry 7). Moreover, the prolonged reaction time from 24 h to 36 h raised the yield of 4aa to 61% with the complete consumption of 2a (entry 8). These results suggest that 4aa is likely to be formed through the generation of 2a by the hydration of 1a, whereas the contribution of the direct route from 1a cannot be completely excluded.

Table 1. Indium-catalyzed annulation of o-ethynylaniline with 3-methoxybenzothiophene $^a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>InX$_3$</th>
<th>t (h)</th>
<th>Yield of 4aa (%) $^b$</th>
<th>Yield of 2a (%) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In(NTf$_2$)$_3$</td>
<td>24</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>In(OTf)$_3$</td>
<td>24</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>In(ONf)$_3$</td>
<td>24</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>InCl$_3$</td>
<td>24</td>
<td>2</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>InBr$_3$</td>
<td>24</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>InI$_3$</td>
<td>24</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7 $^c$</td>
<td>In(ONf)$_3$</td>
<td>24</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>8 $^c$</td>
<td>In(ONf)$_3$</td>
<td>36</td>
<td>61 (61) $^d$</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

$^a$ Reagents and conditions (unless otherwise specified): 1a (0.250 mmol), 3a (0.300 mmol), InX$_3$ (12.5 µmol, 5 mol %), PhCl (0.20 mL), and performed under argon (1 atm). $^b$ Determined by $^1$H-NMR using MeNO$_2$ as an internal standard. $^c$ Performed in the presence of H$_2$O (1.25 mmol, 5 equiv.). $^d$ The isolated yield of 4aa is shown in parentheses.

On the basis of the above results, we turned our attention to the annulation with 2a instead of 1a (Table 2). As expected, under the same reaction conditions as those for entry 3 of Table 1, 4aa was produced in significantly higher yield of 62% (entry 1). Inspired by this result, we continuously examined the effect of various indium salts other than In(ONf)$_3$ for the same annulation reaction of 2a with 3a. Thus, In(OTf)$_3$ and In(NTf$_2$)$_3$ with the strong electron-withdrawing ligands as In(ONf)$_3$ also catalyzed the annulation, and the yield of 4aa increased to 74% in the use of In(NTf$_2$)$_3$ (entries 2 and 3). Among the indium halides examined, InBr$_3$ and InI$_3$ were found to be highly effective, giving 4aa in 92% yield in both the cases, in sharp contrast to the inactivity of the fluoride salt (entries 4–7). However, the corresponding hydroxide and acetate salts were totally inactive (entries 8 and 9). Due to the remarkable catalytic activity of InBr$_3$, metal bromides of, for instance, Sc, Fe, Co, Pd, Cu, Ag, Zn, Pb, and Bi were tested, but proved to be less effective (entries 10–18). No 4aa was formed in the absence
of a catalyst, which is thus indispensable for the progress of the annulation (entry 19). With InBr$_3$ as the promising catalyst, a continuous survey of the solvent effect indicated that PhCl would be the most suitable solvent of choice for the annulation, and that the reaction rate greatly decreases in H$_2$O (entries 20–27). While the lowering of the catalyst loading to 1 mol % accompanies the decrease of the reaction rate, the good yield of 4aa can be secured by extending the reaction time to 96 h (entry 28). Favorably, the annulation can also be carried out under an atmosphere of air instead of argon to afford 4aa in 88% yield (entry 29).

**Table 2.** Lewis acid-catalyzed annulation of o-acetylaniline with 3-methoxybenzothiophene $^a$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Conversion of 2a (%) $^b$</th>
<th>Yield of 4aa (%) $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>In(ONf)$_3$</td>
<td>PhCl</td>
<td>86</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>In(OTf)$_3$</td>
<td>PhCl</td>
<td>73</td>
<td>55</td>
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<tr>
<td>3</td>
<td>In(NTf$_2$)$_3$</td>
<td>PhCl</td>
<td>79</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>InF$_3$</td>
<td>PhCl</td>
<td>4</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>InCl$_3$</td>
<td>PhCl</td>
<td>95</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>InBr$_3$</td>
<td>PhCl</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>InI$_3$</td>
<td>PhCl</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>In(OH)$_3$</td>
<td>PhCl</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>9</td>
<td>In(OAc)$_3$</td>
<td>PhCl</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>10</td>
<td>ScBr$_3$</td>
<td>PhCl</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>FeBr$_3$</td>
<td>PhCl</td>
<td>86</td>
<td>62</td>
</tr>
<tr>
<td>12</td>
<td>CoBr$_2$</td>
<td>PhCl</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>13</td>
<td>PdBr$_2$</td>
<td>PhCl</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>14</td>
<td>CuBr$_2$</td>
<td>PhCl</td>
<td>28</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>AgBr</td>
<td>PhCl</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>16</td>
<td>ZnBr$_2$</td>
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<tr>
<td>17</td>
<td>PbBr$_2$</td>
<td>PhCl</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>18</td>
<td>BiBr$_3$</td>
<td>PhCl</td>
<td>45</td>
<td>33</td>
</tr>
<tr>
<td>19</td>
<td>None</td>
<td>PhCl</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>20</td>
<td>InBr$_3$</td>
<td>PhMe</td>
<td>91</td>
<td>82</td>
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<tr>
<td>21</td>
<td>InBr$_3$</td>
<td>Bu$_3$O</td>
<td>85</td>
<td>74</td>
</tr>
<tr>
<td>22</td>
<td>InBr$_3$</td>
<td>1,2-Diethoxyethane</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>23</td>
<td>InBr$_3$</td>
<td>1,4-Dioxane</td>
<td>87</td>
<td>66</td>
</tr>
<tr>
<td>24</td>
<td>InBr$_3$</td>
<td>MeNO$_2$</td>
<td>86</td>
<td>76 $^d$</td>
</tr>
<tr>
<td>25</td>
<td>InBr$_3$</td>
<td>PrCN</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>26</td>
<td>InBr$_3$</td>
<td>BuOH</td>
<td>92</td>
<td>73</td>
</tr>
<tr>
<td>27</td>
<td>InBr$_3$</td>
<td>H$_2$O</td>
<td>48</td>
<td>37</td>
</tr>
<tr>
<td>28 $^e$</td>
<td>InBr$_3$</td>
<td>PhCl</td>
<td>89</td>
<td>70</td>
</tr>
<tr>
<td>29 $^f$</td>
<td>InBr$_3$</td>
<td>PhCl</td>
<td>97</td>
<td>88</td>
</tr>
</tbody>
</table>

$^a$ Reagents and conditions (unless otherwise specified): 2a (0.250 mmol), 3a (0.300 mmol), Lewis acid (12.5 µmol, 5 mol %), solvent (0.20 mL), and performed under argon (1 atm). $^b$ Determined by GC using n-dodecane as an internal standard. $^c$ Determined by $^1$H-NMR using MeNO$_2$ as an internal standard. $^d$ Determined by $^1$H-NMR using CH$_2$Br$_2$ instead of MeNO$_2$ as an internal standard. $^e$Performed with InBr$_3$ (2.50 µmol, 1 mol %) for 96 h. $^f$Performed under air (1 atm).

With the proper reaction conditions in hand, we next examined the scope of the o-acetylaniline substrate to 3a (Table 3). Similar to o-acetylaniline (2a), its derivatives with the OH, OMe, or methylenedioxy group successfully participated in the annulation (4aa–4da). The formation of 4ba in such high yield shows that the OH group does not interfere with the progress of the desired annulation by acting as the nucleophilic site, as the NH$_2$ group does. No undesired ring fragmentation of the acetal moiety in 4da was observed, even under the Lewis acidic conditions [78]. The bulkier
isopropyl group on the carbonyl carbon atom does not affect the efficiency of the annulation, giving 4ea in 97% yield. A CF₃ group, the C–F bond of which is known to increase metabolic stability and membrane permeability, thus leading to improvement in bioavailability [79], can be also installed onto the C11-position of the benzothieno[3,2-b]quinoline structure (4fa and 4ga). A commercially available hydrochloride–hydrate adduct of o-acylaniline 2g can be used as a substrate without neutralizing and drying. Our protocol is applicable as well to o-acylanilines with a series of aryl groups with different electronic and steric natures, in which the simple phenyl group for 4ha and 4ia, p-MeOC₆H₄ for 4ja, p-FC₆H₄ for 4ka, o-MeC₆H₄ for 4la, and o-fused-arylC₆H₄ for 4ma are included. The atmosphere of air was again confirmed to be available on the synthesis of 4ha. In the reaction of aminoanthraquinone 2m with two carbonyl moieties, only the one adjacent to the NH₂ group worked as a reaction site to provide hexacyclic-fused ring system 4ma in one shot. Of importance to note is that the MeO, Cl, and F groups on the aryl ring are known to behave as leaving groups in the general SₙAr reaction, but were found to be compatible with the reaction conditions, thus contributing to the high-yield formation of the target molecules (4ca, 4ga, 4ia, 4ja, and 4ka) [80].

Besides the benzothieno[3,2-b]quinoline, our method is applicable to preparing a range of HA[b]Qs by using other sulfur- and oxygen-based methoxyheteroarenes (Table 4). The replacement of 3a with 2-methoxybenzothiophene (3b) enables the switch of the fused-ring orientation from the [3,2-b] to the [2,3-b], and products 4ab and 4bb were obtained in high yields. However, in contrast to the successful construction of thieno[2,3-b]quinoline 4ac, 4hc, and 4ad, changing the fused-ring orientation to the [3,2-b] in this case resulted in low yield of 4he. In the reaction of 3-methoxythiophene (3e), a self-condensation reaction, in which two molecules of 2h react with each other to form cyclic diimine 9, occurred as a major side reaction (Figure 2). This result is likely to be related, at least in part, to the relatively low reaction rate of the desired SₙAr process between 2h and 3e, and, in fact, 70% of 3e loaded for the reaction remained unconsumed. In this context, we have previously confirmed that the SₙAr amination reaction of 3-methoxythiophene (3e) requires a higher loading of an indium catalyst as well as higher temperature compared to those for the reaction of 2-methoxythiophene (3c) [54]. In addition to the sulfur-containing HA[b]Qs, the tetracyclic and tricyclic oxygen-containing analogues can be addressed by our method in moderate to good yields (4af, 4hf, and 4ag). When preparing 4ag, InI₃ worked as a catalyst more efficiently than InBr₃. Unfortunately, no annulation reaction of 2a with 2-methoxy-1-phenylpyrrole (3h) for the synthesis of pyrrolo[2,3-b]quinoline 4ah proceeded, due to some undesired side reactions, including N-methylation of 2a by the MeO group of 3h acting as a source of a methyl group.

As collected separately in Table 5, we successively present the result of constructing the framework of the indololo[3,2-b]quinoline, which is alternatively named quindoline, having been known to show cytotoxic activity against human cancer cell lines [81]. As in our preceding SₙAr amination [54], commercially unavailable 3-methoxyindole was not required, but rather commercially available 3-acetyl氧indole (3i) can be used here again as a substrate. Thus, mixing 2a, 3i, and InBr₃ (5 mol %) in PhCl, and then heating the mixture at 110 °C for 24 h gave 4ai in 55% yield. Other quindoline derivatives 4di, 4fi, and 4gi could also be synthesized by our method. Unlike the annulation of 2g–HCl–H₂O with 3-methoxybenzothiophene (3a) (see 4ga in Table 3), the pre-removal of HCl and H₂O from 2g–HCl–H₂O as a commercial source is required here to obtain 4gi in reasonable yield. With 2g–HCl–H₂O instead, the formation of 4gi resulted in only 1% NMR yield. These results inspired us to address cryptolepine derivatives, due to their potentialities as anti-malarial and/or anti-cancer drugs.
Table 3. Indium-catalyzed annulation of o-acylanilines with 3-methoxybenzothiophene \(^a\).

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>R(^4)</th>
<th>R(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

\[ \text{IndiumBr}_3 (5 \text{ mol }\%) + \text{PhCl, 110 }^\circ\text{C, 24 h} \]

<table>
<thead>
<tr>
<th>4aa</th>
<th>90% yield</th>
<th>87% yield (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4ba</td>
<td>94% yield</td>
<td></td>
</tr>
<tr>
<td>4ca</td>
<td>74% yield</td>
<td></td>
</tr>
<tr>
<td>4da</td>
<td>67% yield (^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reagents and conditions (unless otherwise specified): 2 (0.250 mmol), 3a (0.300 mmol), \text{InBr}_3 (12.5 \mu\text{mol, 5 mol }\%), \text{PhCl} (0.20 \text{ mL}), and performed under argon (1 atm). Yields of isolated 4 based on 2 are shown here. \(^b\) Yields when performed under air (1 atm). \(^c\) Performed in \text{PhCl} (0.40 \text{ mL}) for 36 h. \(^d\) Performed with a HCl–H\(_2\)O adduct of 2g. \(^e\) Performed in PhCl (0.50 mL) at 130 \(^\circ\)C.
Table 4. Indium-catalyzed annulation of o-acylanilines with methoxyheteroarenes.\(^a\)

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>1:1.2</th>
<th>MeO(^+)</th>
<th>PhCl, T (^{\circ}\text{C}), 24 h</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
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<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
</tr>
</tbody>
</table>

\(^a\) Reagents and conditions (unless otherwise specified): 2 (0.250 mmol), 3 (0.300 mmol), InBr\(_3\) (12.5 \(\mu\)mol, 5 mol %), PhCl (0.20 mL), and performed under argon (1 atm). Yields of isolated 4 based on 2 are shown here. \(^b\) Performed with a 1.2:1 mixture of 2b (0.300 mmol) and 3b (0.250 mmol). \(^c\) Performed with 3 (0.500 mmol, 2 equiv.). \(^d\) Performed with InBr\(_3\) (37.5 \(\mu\)mol, 15 mol %). \(^e\) Performed for 3 h. \(^f\) Performed with InI\(_3\) instead of InBr\(_3\).

Figure 2. A major byproduct formed in the reaction of 2h with 3e.
As previously demonstrated, the HOTf adduct of the 11-methylated cryptolepine (11-Me-10) shows higher anti-malarial and antityrpanosomal activities than that of the original cryptolepine (10) (Figure 3). Since the N-methylation of the pyridine ring of 4ai with methyl triflate (MeOTf) has been already reported [82], we targeted the synthesis of analogues thereof from other quindoline derivatives 4di, 4fi, and 4gi (Table 6). The N-methylation in accordance with the modified literature procedure successfully delivered 10di, 10fi, and 10gi, which are new compounds unreported in the literature [82]. Especially, 10fi, which has the 11-CF$_3$ group instead of the 11-CH$_3$ group in 11-Me-10, might be expected to be promising in view of anti-malarial and antityrpanosomal activities, due to the possible higher bioavailability. Moreover, since the acid-free cryptolepine derivatives have been the focus of examining anti-cancer activity (11 and 11-Me-11 in Figure 3), there should be a demand for the acid-free form. Accordingly, we confirmed that the neutralization of, for instance, 10fi with a Na$_2$CO$_3$ aqueous solution provides 11fi with no TfOH in quantitative yield (Scheme 2).

In order to get insight into the reaction pathway of the present annulation reaction, some experiments were performed (Scheme 3). At first, upon treating 2e with 3a at room temperature rather than the standard heating temperature, only the S$_N$Ar-based intermolecular N–C bond-forming reaction proceeded to furnish 6ea in 53% yield with 60% conversion of 2e, thus being not contaminated by 12ea derived from the C–C bond formation as a possible alternative first stage, and by final annulation product 4ea [Equation (1) in Scheme 3]. Subsequently, 6ea isolated from the reaction of Equation (1) was heated under the standard reaction conditions, and thereby 4ea was obtained highly efficiently via the intramolecular C–C bond-forming annulation [Equation (2) in Scheme 3]. On the other hand, Me$_2$2e, wherein the nitrogen atom is dimethylated and would thus no longer act as a nucleophilic site, did not participate in making a C–C bond with 3a, leading possibly to Me$_2$12ea. As a result, Me$_2$2e was recovered quantitatively, even under the standard heating reaction conditions [Equation (3) in Scheme 3]. Accordingly, these results strongly suggest that the annulation reaction proceeds in the order of the S$_N$Ar-based intermolecular N–C bond formation, followed by the S$_E$Ar-based intramolecular C–C bond formation. Experimental procedures for Equations (1) and (2) as well as spectral and analytical data (melting point, NMR, and HRMS), and NMR charts for products 6ea and 4ea are provided in Supplementary Materials.
Figure 3. Anti-malarial, antitrypanosomal and anti-cancer activities of cryptolepine, 11-methylcryptolepine, and their HOTf adducts [82].


<table>
<thead>
<tr>
<th>Compound</th>
<th>anti-malarial activity</th>
<th>antitrypanosomal activity</th>
<th>activity against malaria parasites (P. falciparum K1 strain) [IC₅₀ (μM)]</th>
<th>activity against trypanosoma parasites (T. cruzi epimastigotes) [IC₅₀ (μM)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>&lt;</td>
<td>&lt;</td>
<td>0.33 ± 0.05</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>11-Me-10</td>
<td></td>
<td>&lt;</td>
<td>0.062 ± 0.023</td>
<td>0.30 ± 0.05</td>
</tr>
</tbody>
</table>

a Reagents: 4 (0.100 mmol), MeOTF (0.190 mmol), solvent [CH₂Cl₂ (1.2 mL) or toluene (0.60 mL)]. Yields of isolated 10 based on 4 are shown here.

Scheme 2. Neutralization of 10fi.
On the basis of the above experimental results as well as the previous ones, a proposed reaction mechanism is illustrated in Scheme 4 that exemplifies the reaction of 2e with 3a. First up is the $S_N$Ar-based intermolecular amination of 3a by the nucleophilic attack of the nitrogen atom of 2e via previously proposed transition state A [54], followed by the release of the indium catalyst (In) and MeOH to give intermediate 6ea. Next is the nucleophilic attack of the thienyl ring to the carbonyl moiety activated by In as shown in transition state B, hereby providing 8ea, and then desired structure 4ea after aromatizing dehydration. The ring-closing C–C bond-forming process might be accelerated by the electron flow from the lone pair on the nitrogen atom. However, due to the fact that 6ea is the only intermediate confirmed during the annulation process [Equation (1) in Scheme 3], the rate-determining step is likely to be present at the intramolecular C–C bond-forming stage.
3. Materials and Methods

3.1. General Remarks

All manipulations were conducted with a standard Schlenk technique under an argon atmosphere. Nuclear magnetic resonance (NMR) spectra were taken on a JEOL JMN-ECA 400 (1H, 400 MHz; 13C, 100 MHz; 19F, 376 MHz) or JEOL JMN-ECA 500 (1H, 500 MHz; 13C, 125 MHz; 19F, 471 MHz) spectrometer (JEOL, Tokyo, Japan) using tetramethylsilane (1H and 13C) or trichlorofluoromethane (19F) as an internal standard. Analytical gas chromatography (GC) was performed on a Shimadzu model GC-2014 instrument with a flame ionization detector (Shimadzu, Kyoto, Japan), equipped with a capillary column of InertCap 5 (5% diphenyl- and 95% dimethylpolysiloxane, 30 m × 0.25 mm × 0.25 µm) (GL Sciences, Tokyo, Japan), using nitrogen as carrier gas. Gas chromatography-mass spectrometry (GC-MS) analyses were performed with a Shimadzu model GCMS-QP2010 instrument (Shimadzu, Kyoto, Japan) equipped with a capillary column of InertCap 5 by electron ionization at 70 eV using helium as the carrier gas. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-T100GCV spectrometer (JEOL, Tokyo, Japan). All of the melting points were measured with a Yanaco Micro Melting Point MP-500P apparatus (Yanaco, Kyoto, Japan), and are uncorrected. Kugelrohr bulb-to-bulb distillation was carried out with a Sibata glass tube oven GTO-250RS apparatus (Sibata Scientific Technology, Soka, Japan). Chlorobenzene (PhCl), toluene (PhMe), and dichloromethane (CH2Cl2) were distilled under argon from CaCl2 just prior to use. Dibutyl ether (Bu2O) and 1,4-dioxane were distilled under argon from sodium just prior to use. 1,2-Diethoxymethane, nitromethane (MeNO2), butanol (BuOH) and o-dichlorobenzene (o-C6H4Cl2) were stored over molecular sieves 4Å (MS 4Å) under argon. Butyronitrile (PrCN) was distilled under argon from P2O5 just prior to use. MeOH was stored over molecular sieves 3Å (MS 3Å) under argon. The following indium salts and substrates were synthesized according to the respective literature methods: In(NTf2)3 [83,84], In(ONf)3 [56,85], 1-(2-aminophenyl)-2-methyl-1-propanone (2e) [86], 1-(2-aminophenyl)-2,2,2-trifluoroethanolone (2f) [87], 1-(2-aminophenyl)-(4-methoxyphenyl)methanone (2g) [88], 2-(aminophenyl)-(2-methylphenyl)methanone (2h) [88], 3-methoxybenzo[b]thiophene (3a) [89], 2-methoxybenzo[b]thiophene (3b) [54], 2-methoxy-5-methylthiophene (3d) [54],...
2-methoxybenzo[b]furan (3f) [54], 2-methoxy-5-phenylfuran (3g) [54], 2-methoxy-1-phenyl-1H-pyrrole (3h) [54]. Unless otherwise noted, other substrates and reagents were commercially available, and used as received without further purification.

3.2. Synthesis of Substrates

3.2.1. Synthesis of 1-(2-Amino-5-chlorophenyl)-2,2,2-trifluoroethanone (2g): Removal of HCl and H2O from 2g–HCl–H2O

A hydrochloride–hydrate adduct of 2g (407 mg, 1.46 mmol) was placed in a 15-mL screw-cap vial. To this, a saturated NaHCO3 aqueous solution (2.0 mL) was added, and the resulting mixture was stirred at room temperature for 3 min. The aqueous phase was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine (2 mL) and then dried over anhydrous sodium sulfate (Na2SO4). Filtration and evaporation of the solvent left a residue, which was successively passed through a pad of silica gel using EtOAc to give analytically pure 2g in 99% yield (324 mg) as a yellow solid (m.p. 92–94 °C). Compound 2g has already appeared in the literature [87], and its spectral and analytical data are in good agreement with those reported. Accordingly, only the 1H-NMR data are provided here.

1H-NMR (400 MHz, CDCl3) δ 6.47 (bs, 2H), 6.70 (d, J = 8.9 Hz, 1H), 7.33 (dd, J = 9.0, 2.4 Hz, 1H), 7.66–7.75 (m, 1H).

3.2.2. Synthesis of 1-[2-(Dimethylamino)phenyl]-2-methyl-1-propanone (Me2-2e)

On the basis of the literature procedure that has been used when dimethylating closely related 1-(2-aminophenyl)ethanone derivatives [90], Me2-2e was prepared using the following reagents and conditions: 2e (163 mg, 1.00 mmol), MeI (426 mg, 3.00 mmol), K2CO3 (346 mg, 2.50 mmol), N,N-dimethylformamide (0.60 mL), 80 °C, 8 h, and was isolated by column chromatography on silica gel (n-hexane/EtOAc = 30/1) in 71% yield (136 mg) as a pale yellow oil. Compound Me2-2e has already appeared in the literature [91], and its spectral and analytical data are in good agreement with those reported. Accordingly, only the 1H-NMR data are provided here.

1H-NMR (500 MHz, CDCl3) δ 1.12 (d, J = 6.9 Hz, 6H), 2.76 (s, 6H), 3.66 (sept, J = 6.9 Hz, 1H), 6.95 (td, J = 7.4, 0.9 Hz, 1H), 7.00 (dd, J = 8.3, 0.6 Hz, 1H), 7.28 (dd, J = 7.7, 1.7 Hz, 1H), 7.34 (ddd, J = 8.6, 7.3, 1.7 Hz, 1H).

3.3. Indium-Catalyzed Annulation of o-Acylanilines with Alkoxyheteroarenes: An Experimental Procedure Exemplified by the Synthesis of 4aa

InBr3 (4.43 mg, 12.5 µmol) was placed in a 20-mL Schlenk tube, which was heated at 80 °C in vacuo for 15 min. The tube was cooled down to room temperature, and filled with argon. PhCl (0.20 mL) was added to the tube, and the mixture was then stirred at room temperature for 3 min. To this, 3-methoxybenzothiophene (3a) (49.3 mg, 0.300 mmol) and 1-(2-aminophenyl)ethanone (2a) (33.8 mg, 0.250 mmol) were added in that order, and the mixture was stirred at 110 °C for 24 h, followed by adding a saturated NaHCO3 aqueous solution (0.5 mL). The resulting mixture was stirred for 20 min, and the aqueous phase was then extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine (1 mL), and then dried over anhydrous sodium sulfate (Na2SO4). Filtration and evaporation of the solvent followed by column chromatography on silica gel (n-hexane/EtOAc = 10/1) gave 11-methyl[1]benzothieno[3,2-b]quinoline (4aa) in 90% yield (56.1 mg) as a pale yellow solid (m.p. 145–146 °C). Compound 4aa was characterized by 1H- and 13C-NMR spectroscopy and HRMS, as follows: 1H-NMR (400 MHz, CDCl3) δ 2.94 (s, 3H), 7.53–7.59 (m, 1H), 7.59–7.65 (m, 2H), 7.76 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.87 (dd, J = 7.8, 0.7 Hz, 1H), 8.10–8.16 (m, 1H), 8.27–8.32 (m, 1H), 8.62–8.67 (m, 1H). 13C-NMR (100 MHz, CDCl3) δ 17.4, 122.8, 123.0, 124.0, 125.1, 125.9, 126.1, 128.5, 130.1, 132.0, 135.1, 137.2, 140.7, 146.7, 153.3. HRMS (FD) Calcd for C16H11NS: M, 249.0612. Found: m/z 249.0619.

Besides a general experimental procedure for the synthesis of compounds 4, details of the reaction conditions, purification methods, spectral and analytical data (melting point, NMR, and HRMS), and NMR charts for all products 4 in Tables 3–5 are provided in Supplementary Materials.

Compound 10fi was synthesized based on the modified literature procedure [82], as follows: A flame-dried 20-mL Schlenk tube was charged with 4fi (28.6 mg, 0.100 mol) and toluene (0.60 mL). The resulting solution was degassed by three freeze-pump-thaw cycles, and the tube was then filled with argon. To this solution, MeOTf (31.2 mg, 0.190 mmol) that had been distilled by Kugelrohr at 90 °C/500 Pa prior to use was added, and the mixture was then stirred at 50 °C for 24 h. The resulting mixture, including a solid product, was filtered, and the solid was washed with Et2O (5 mL). The filtrate was concentrated, and the residue was filtered and then washed with Et2O (5 mL). This concentration–filtration–washing sequence was repeated once again, and the combined solid was dried in vacuo to give an analytically pure 5-methyl-11-trifluoromethyl-10H-quindolinium 1,1,1-trifluoromethanesulfonate (10fi) in 94% yield (42.4 mg) as a yellow solid (mp 281–282 °C).

Compound 10fi was characterized by 1H-, 13C- and 19F-NMR spectroscopy and HRMS, as follows:

1H-NMR (500 MHz, dimethyl sulfoxide-d6) δ 5.13 (s, 3H), 7.62 (ddd, J = 8.3, 7.2, 1.1 Hz, 1H), 7.97 (dt, J = 8.3, 0.9 Hz, 1H), 8.06 (ddd, J = 8.3, 7.2, 1.1 Hz, 1H), 8.15 (ddd, J = 8.7, 6.8, 0.9 Hz, 1H), 8.28 (ddd, J = 9.0, 6.9, 1.3 Hz, 1H), 8.51–8.60 (m, 1H), 8.89 (d, J = 8.6 Hz, 1H), 9.87 (d, J = 9.2 Hz, 1H), 12.71 (s, 1H);

13C-NMR (125 MHz, dimethyl sulfoxide-d6) δ 41.7, 113.5, 113.7, 116.8 (q, J = 32.8 Hz), 119.2, 120.6 (q, J = 322.2 Hz), 121.5, 122.5, 123.2 (q, J = 275.9 Hz), 124.2 (q, J = 3.0 Hz), 127.1, 129.3, 130.8 (q, J = 1.2 Hz), 132.0, 135.1, 135.9, 142.7, 147.3;

19F-NMR (376 MHz, dimethyl sulfoxide-d6) δ –77.3, –53.4. HRMS (FD) Calcd for C17H12F3N2: M+ 301.0947. Found: m/z 301.0936.

Besides a general experimental procedure for the synthesis of compounds 10, details of the reaction conditions, spectral and analytical data (melting point, NMR, and HRMS), and NMR charts for all products 10 in Table 6 are provided in Supplementary Materials.

3.5. An Experimental Procedure for the Synthesis of 11fi by Neutralizing 10fi

Compound 11fi was synthesized based on the literature procedure [82], as follows: 10fi (22.5 mg, 0.0500 mmol) was placed in a 15-mL screw-cap vial. To this, a 5 wt % Na2CO3 aqueous solution (2.0 mL) was added, and the resulting mixture was stirred at 30 °C for 15 min. The aqueous phase was extracted with CHCl3 (4 mL × 4), and the combined organic layer was dried over anhydrous sodium sulfate (Na2SO4). Filtration and evaporation of the solvent followed by column chromatography on silica gel (CHCl3/Et3N = 50/1) gave 5-methyl-11-trifluoromethyl-5H-quindoline (11fi) in 99% yield (14.9 mg) as a dark navy solid [m.p. 251–253 °C (decomp.)]. Compound 11fi was characterized by 1H-, 13C- and 19F-NMR spectroscopy and HRMS, as follows:

1H-NMR (400 MHz, dimethyl sulfoxide-d6) δ 5.02 (s, 3H), 7.12 (ddd, J = 8.4, 6.6, 1.1 Hz, 1H), 7.65 (ddd, J = 8.4, 6.8, 1.1 Hz, 1H), 7.72 (dd, J = 8.6, 0.8 Hz, 1H), 8.86 (ddd, J = 8.6, 6.8, 1.0 Hz, 1H), 7.96 (ddd, J = 8.9, 6.9, 1.1 Hz, 1H), 8.47–8.52 (m, 1H), 8.55 (dd, J = 8.5, 0.7 Hz, 1H), 8.70 (d, J = 8.9 Hz, 1H); 13C-NMR (100 MHz, dimethyl sulfoxide-d6) δ 40.3, 113.6, 116.1 (q, J = 29.2 Hz), 117.4, 117.9, 119.5, 120.1 (q, J = 1.4 Hz), 124.0 (q, J = 3.8 Hz), 125.0 (q, J = 277.3 Hz), 125.7, 125.9, 127.8, 131.6, 132.7, 142.3, 143.8, 162.9; 19F-NMR (471 MHz, dimethyl sulfoxide-d6) δ –50.8. HRMS (FD) Calcd for C17H11F3N2: M, 300.0874. Found: m/z 300.0870.

4. Conclusions

We disclosed here that the indium-catalyzed tandem N–C and C–C bond-forming reaction of o-acylanilines with MeO–heteroarenes is a practical methodology to synthesize a range of HA[b]Qs with tricyclic and tetracyclic [2,3-b] and [3,2-b] skeletons fused with sulfur-, oxygen-, and nitrogen-based five-membered heteroaryl rings. Indolo[3,2-b]quinolines, which are also the frameworks constructed by our method, were readily converted to cryptolepine derivatives that have not yet been prepared. Mechanistic investigations revealed that the central pyridyl ring is constructed by the sequence of the intermolecular N–C bond-formation, followed by the C–C bond-forming ring closure.
Supplementary Materials: Supplementary materials are available online: experimental details for the synthesis of each product as well as 1H-, 13C- and 19F-NMR spectra and HRMS data. References [53,82] are cited in the supplementary materials.

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Author Contributions: T.T. conceived the idea of this study and designed the experiments; K.Y., M.S. and Y.Y. performed the experiments; K.Y., M.S. and Y.Y. analyzed the data; T.T. contributed reagents/materials/analysis tools; K.Y. with the assistance of T.T. wrote the paper and prepared the Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

References and Notes


72. For the synthesis of HA[β]Qs with one type of a heteroaryl ring, see: References 10–16, 18–21, 25–28, 30–36, 38, 40–50, 52 and 53.

73. For the synthesis of HA[β]Qs with two types of heteroaryl rings, see: References 17, 22, 37, 39 and 51.

74. For the synthesis of HA[β]Qs with three types of heteroaryl rings, see: References 24 and 29. The synthesis of HA[β]Qs with three types of heteroaryl rings is also achieved in references 4 and 23 but uses the same synthetic method as in reference 42 cited within reference 72.


Sample Availability: Sample Availability: Not available.