

Article

# 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<sub>2</sub> group of *o*-acylanilines to the MeO-connected carbon atom of the heteroaryl ring in an S<sub>N</sub>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.

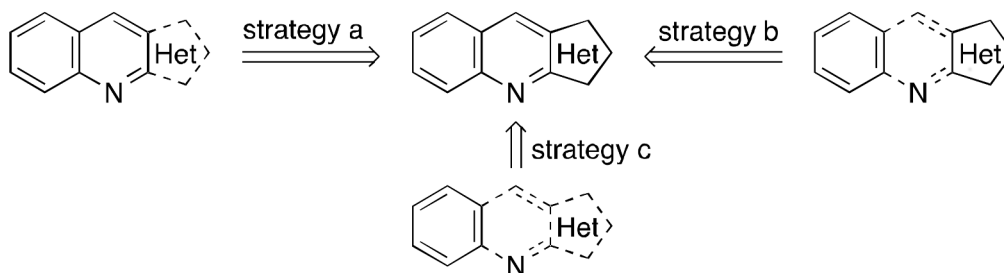
**Keywords:** anti-cancer activity; anti-malarial activity; heteroarenes; indium; Lewis acids; pyridine; one-pot; quindolines; tandem reaction

## 1. Introduction

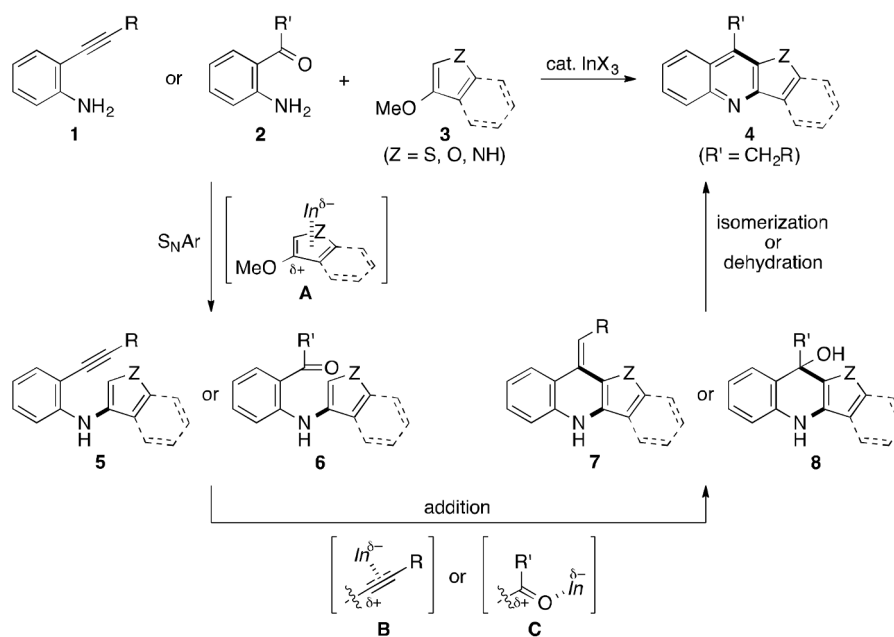
Heteroaryl[*b*]quinolines (HA[*b*]Qs), wherein electron-rich heteroaryl rings are fused to the [*b*] site of quinoline, are important frameworks found in natural products [1–3] and biologically active molecules [1,4–6] as well as functional organic materials [7–9]. Due to their significance, numerous 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<sub>N</sub>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 ( $\text{InX}_3 = \text{In}$ ). The first stage is the  $\text{S}_{\text{N}}\text{Ar}$ -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.

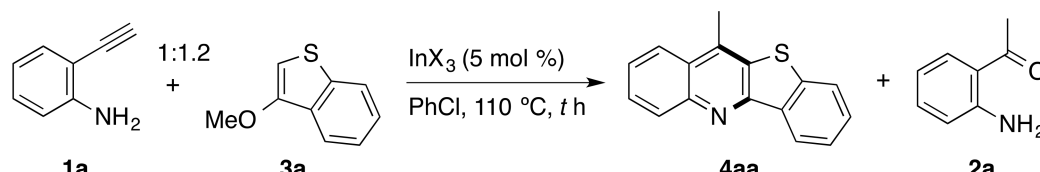


**Scheme 1.** A working hypothesis for the synthesis of HA[b]Qs **4**.  $\text{In} = \text{InX}_3$ .

## 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<sub>2</sub>)<sub>3</sub> (Tf = SO<sub>2</sub>CF<sub>3</sub>) 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)<sub>3</sub> (Nf = SO<sub>2</sub>C<sub>4</sub>F<sub>9</sub>) 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<sub>2</sub>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<sub>2</sub>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 <sup>a</sup>.



Entry	InX <sub>3</sub>	t (h)	Yield of <b>4aa</b> (%) <sup>b</sup>	Yield of <b>2a</b> (%) <sup>b</sup>
1	In(NTf <sub>2</sub> ) <sub>3</sub>	24	11	<1
2	In(OTf) <sub>3</sub>	24	9	<1
3	In(ONf) <sub>3</sub>	24	14	2
4	InCl <sub>3</sub>	24	2	<1
5	InBr <sub>3</sub>	24	3	<1
6	InI <sub>3</sub>	24	5	<1
7 <sup>c</sup>	In(ONf) <sub>3</sub>	24	26	30
8 <sup>c</sup>	In(ONf) <sub>3</sub>	36	61 (61) <sup>d</sup>	<1

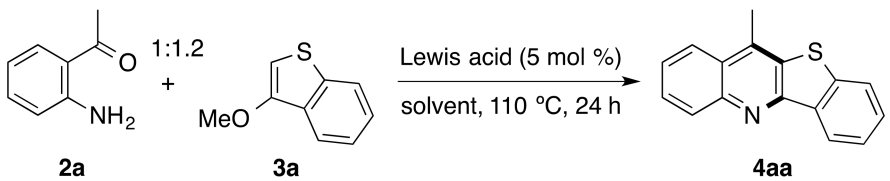
<sup>a</sup> Reagents and conditions (unless otherwise specified): **1a** (0.250 mmol), **3a** (0.300 mmol), InX<sub>3</sub> (12.5 μmol, 5 mol %), PhCl (0.20 mL), and performed under argon (1 atm). <sup>b</sup> Determined by <sup>1</sup>H-NMR using MeNO<sub>2</sub> as an internal standard.

<sup>c</sup> Performed in the presence of H<sub>2</sub>O (1.25 mmol, 5 equiv.). <sup>d</sup> 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)<sub>3</sub> for the same annulation reaction of **2a** with **3a**. Thus, In(OTf)<sub>3</sub> and In(NTf<sub>2</sub>)<sub>3</sub> with the strong electron-withdrawing ligands as In(ONf)<sub>3</sub> also catalyzed the annulation, and the yield of **4aa** increased to 74% in the use of In(NTf<sub>2</sub>)<sub>3</sub> (entries 2 and 3). Among the indium halides examined, InBr<sub>3</sub> and InI<sub>3</sub> 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<sub>3</sub>, 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<sub>3</sub> 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<sub>2</sub>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 be also 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 <sup>a</sup>.



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

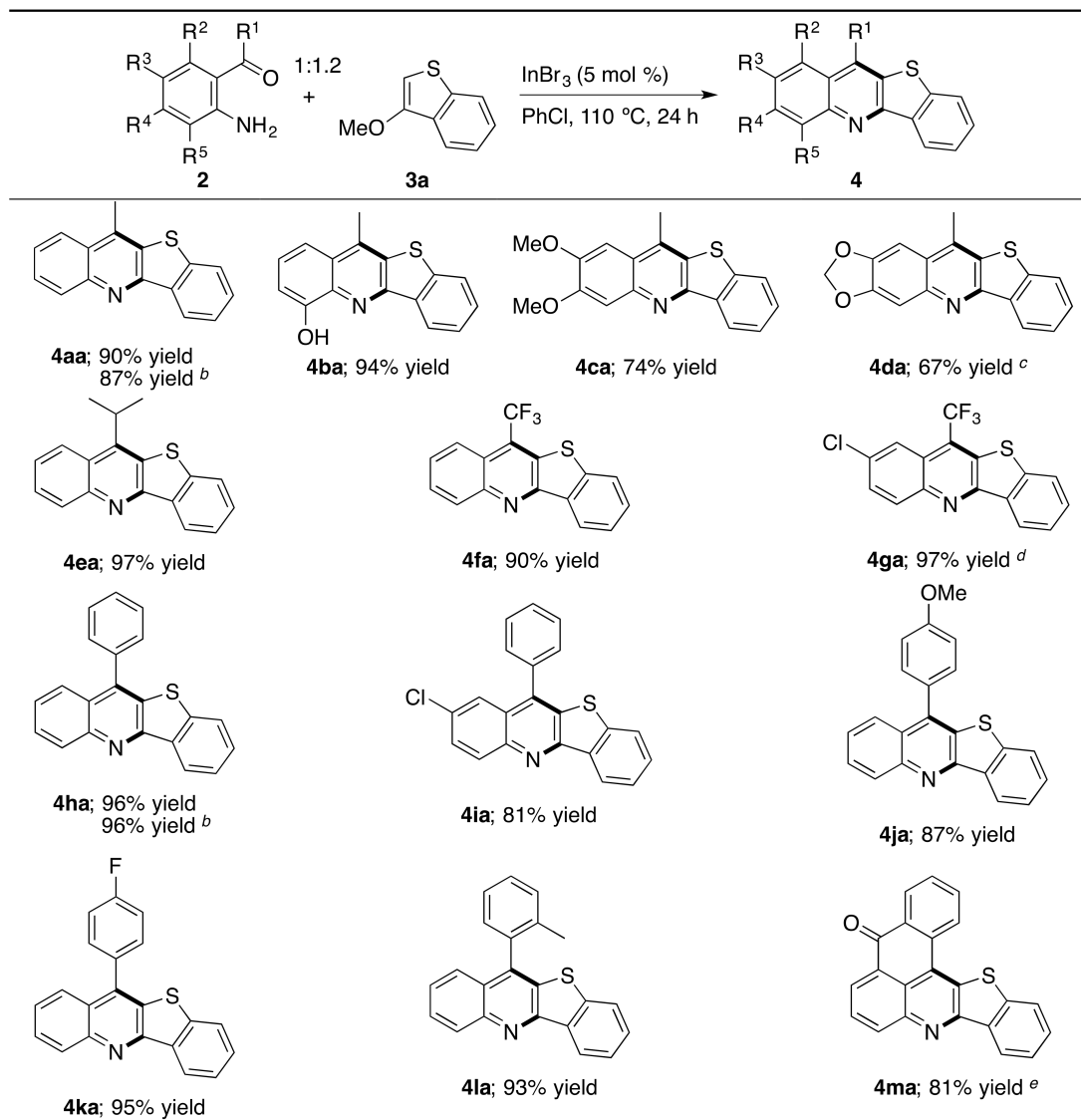
<sup>a</sup> Reagents and conditions (unless otherwise specified): **2a** (0.250 mmol), **3a** (0.300 mmol), Lewis acid (12.5 μmol, 5 mol %), solvent (0.20 mL), and performed under argon (1 atm). <sup>b</sup> Determined by GC using *n*-dodecane as an internal standard. <sup>c</sup> Determined by <sup>1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

With the proper reaction conditions in hand, we next examined the scope of the *o*-acylaniline 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<sub>2</sub> group does. No undesired ring fragmentation of the acetal moiety in **4da** was observed, even under the Lewis acidic conditions [78]. The bulkier

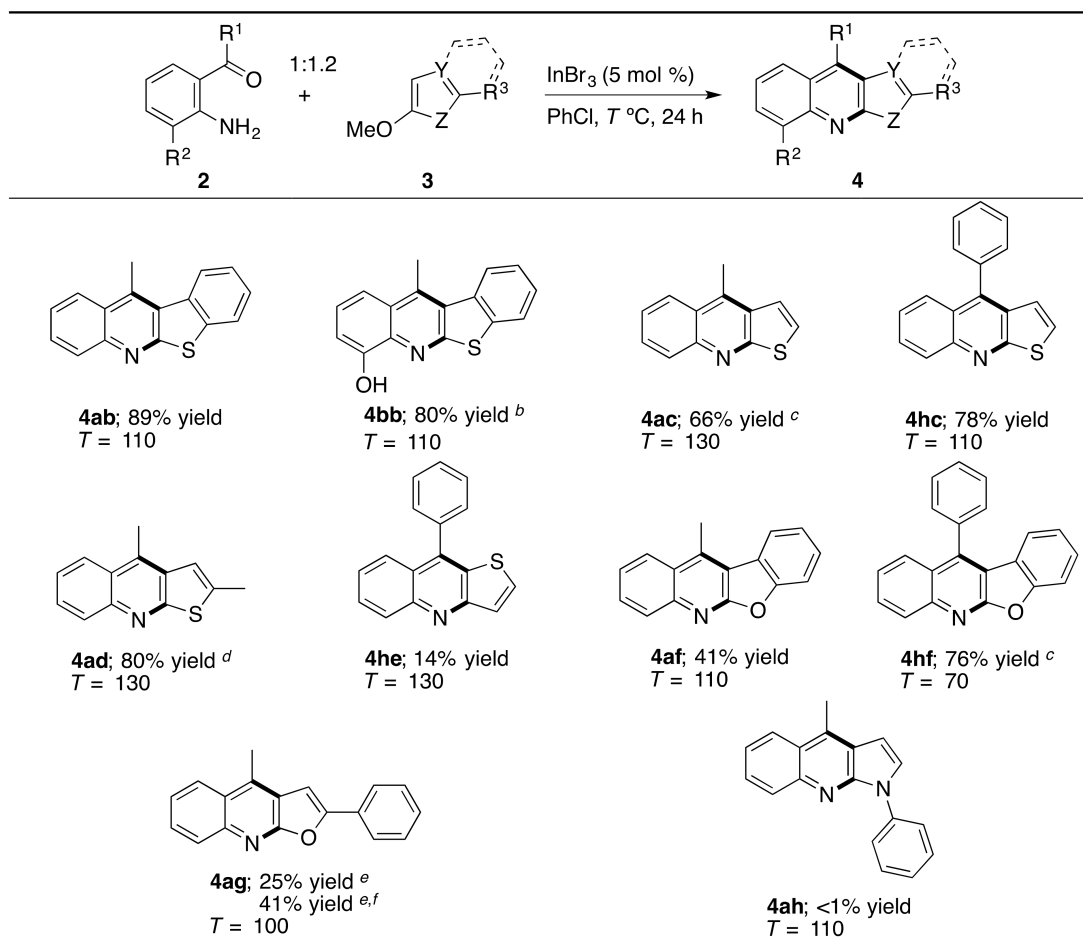
isopropyl group on the carbonyl carbon atom does not affect the efficiency of the annulation, giving **4ea** in 97% yield. A CF<sub>3</sub> group, the C–F bond of which is known to increase metabolic stability and membrane permeability, thus leading to improvement in bioavailability [79], can be also 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*-MeOC<sub>6</sub>H<sub>4</sub> for **4ja**, *p*-FC<sub>6</sub>H<sub>4</sub> for **4ka**, *o*-MeC<sub>6</sub>H<sub>4</sub> for **4la**, and *o*-fused-aroylC<sub>6</sub>H<sub>4</sub> 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 NH<sub>2</sub> 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 S<sub>N</sub>Ar 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 S<sub>N</sub>Ar 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 S<sub>N</sub>Ar 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**, InI<sub>3</sub> worked as a catalyst more efficiently than InBr<sub>3</sub>. 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.

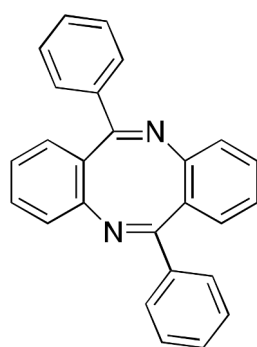
As collected separately in Table 5, we successively present the result of constructing the framework of the indolo[3,2-*b*]quinoline, which is alternatively named quindoline, having been known to show cytotoxic activity against human cancer cell lines [81]. As in our preceding S<sub>N</sub>Ar amination [54], commercially unavailable 3-methoxyindole was not required, but rather commercially available 3-acetyloxyindole (**3i**) can be used here again as a substrate. Thus, mixing **2a**, **3i**, and InBr<sub>3</sub> (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–H<sub>2</sub>O with 3-methoxybenzothiophene (**3a**) (see **4ga** in Table 3), the pre-removal of HCl and H<sub>2</sub>O from **2g**–HCl–H<sub>2</sub>O as a commercial source is required here to obtain **4gi** in reasonable yield. With **2g**–HCl–H<sub>2</sub>O 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 <sup>a</sup>.

<sup>a</sup> Reagents and conditions (unless otherwise specified): **2** (0.250 mmol), **3a** (0.300 mmol), InBr<sub>3</sub> (12.5 μmol, 5 mol %), PhCl (0.20 mL), and performed under argon (1 atm). Yields of isolated **4** based on **2** are shown here. <sup>b</sup> Yields when performed under air (1 atm). <sup>c</sup> Performed in PhCl (0.40 mL) for 36 h. <sup>d</sup> Performed with a HCl–H<sub>2</sub>O adduct of **2g**. <sup>e</sup> Performed in PhCl (0.50 mL) at 130 °C.

**Table 4.** Indium-catalyzed annulation of *o*-acylanilines with methoxyheteroarenes <sup>a</sup>.

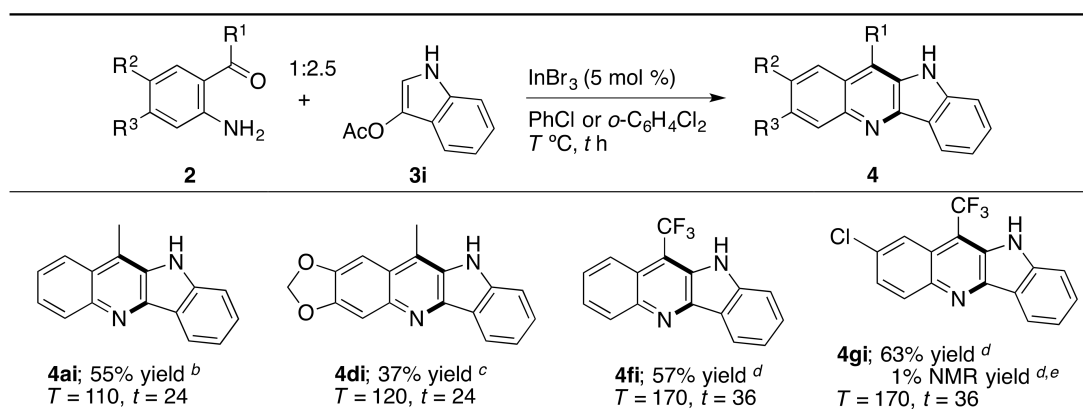
<sup>a</sup> Reagents and conditions (unless otherwise specified): **2** (0.250 mmol), **3** (0.300 mmol), InBr<sub>3</sub> (12.5 μmol, 5 mol %), PhCl (0.20 mL), and performed under argon (1 atm). Yields of isolated **4** based on **2** are shown here. <sup>b</sup> Performed with a 1.2:1 mixture of **2b**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



**9**; 58% NMR yield  
**(2h; 81% NMR conversion)**

**Figure 2.** A major byproduct formed in the reaction of **2h** with **3e**.



**Table 5.** Indium-catalyzed annulation of *o*-acylanilines with 3-acetyloxyindole <sup>a</sup>.

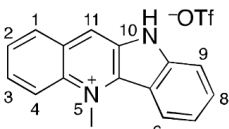
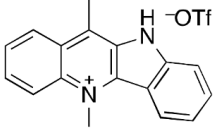
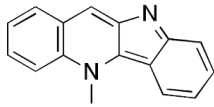
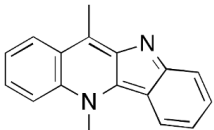
<sup>a</sup> Reagents and conditions (unless otherwise specified): **2** (0.250 mmol), **3i** (0.625 mmol), InBr<sub>3</sub> (12.5 μmol, 5 mol %), PhCl or *o*-C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub> as a solvent, and performed under argon (1 atm). Yields of isolated **4** based on **2** are shown here.

<sup>b</sup> Performed on the following larger scale in the presence of H<sub>2</sub>O: **2a** (2.20 mmol), **3i** (5.50 mmol), H<sub>2</sub>O (11.0 mmol), InBr<sub>3</sub> (110 μmol, 5 mol %), PhCl (1.7 mL). <sup>c</sup> Performed in PhCl (0.30 mL). <sup>d</sup> Performed in *o*-C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub> (0.20 mL). <sup>e</sup> Performed with **2g**-HCl-H<sub>2</sub>O as a commercial source instead of **2g**.

As previously demonstrated, the HOTf adduct of the 11-methylated cryptolepine (**11-Me-10**) shows higher anti-malarial and antitrypanosomal 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 quinoline 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<sub>3</sub> group instead of the 11-CH<sub>3</sub> group in **11-Me-10**, might be expected to be promising in view of anti-malarial and antitrypanosomal 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<sub>2</sub>CO<sub>3</sub> aqueous solution provides **11fi** with no TfOH in quantitative yield (Scheme 2).

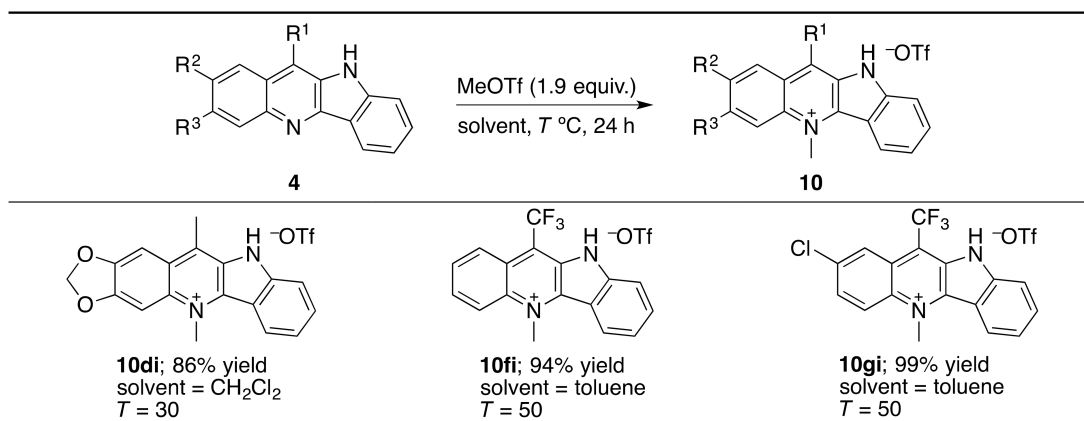
In order to get insight into the reaction pathway of the present annulation reaction, some experiments were performed (Scheme 3). At first, upon treating **2e** with **3a** at room temperature rather than the standard heating temperature, only the S<sub>N</sub>Ar-based intermolecular N–C bond-forming 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<sub>2</sub>-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<sub>2</sub>-12ea**. As a result, **Me<sub>2</sub>-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<sub>N</sub>Ar-based intermolecular N–C bond formation, followed by the S<sub>E</sub>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.



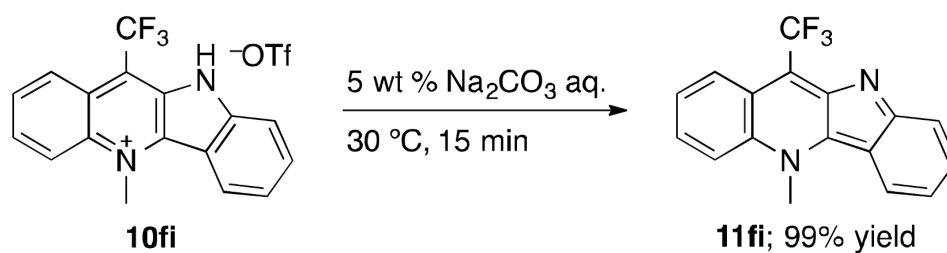
anti-malarial activity antitrypanosomal activity		
	<	
cryptolepine•HOTf ( <b>10</b> )		11-methylcryptolepine•HOTf ( <b>11-Me-10</b> )
activity against malaria parasites ( <i>P. falciparum</i> K1 strain) [IC <sub>50</sub> (μM)]	0.33 ± 0.05	0.062 ± 0.023
activity against trypanosoma parasites ( <i>T. cruzi</i> epimastigotes) [IC <sub>50</sub> (μM)]	1.3 ± 0.2	0.30 ± 0.05
anti-cancer activity		
	<	
cryptolepine ( <b>11</b> )		11-methylcryptolepine ( <b>11-Me-11</b> )
cytotoxicity against cancer cells (KB) [IC <sub>50</sub> (μM)]	1.5 ± 0.5	0.53 ± 0.07

**Figure 3.** Anti-malarial, antitrypanosomal and anti-cancer activities of cryptolepine, 11-methylcryptolepine, and their HOTf adducts [82].

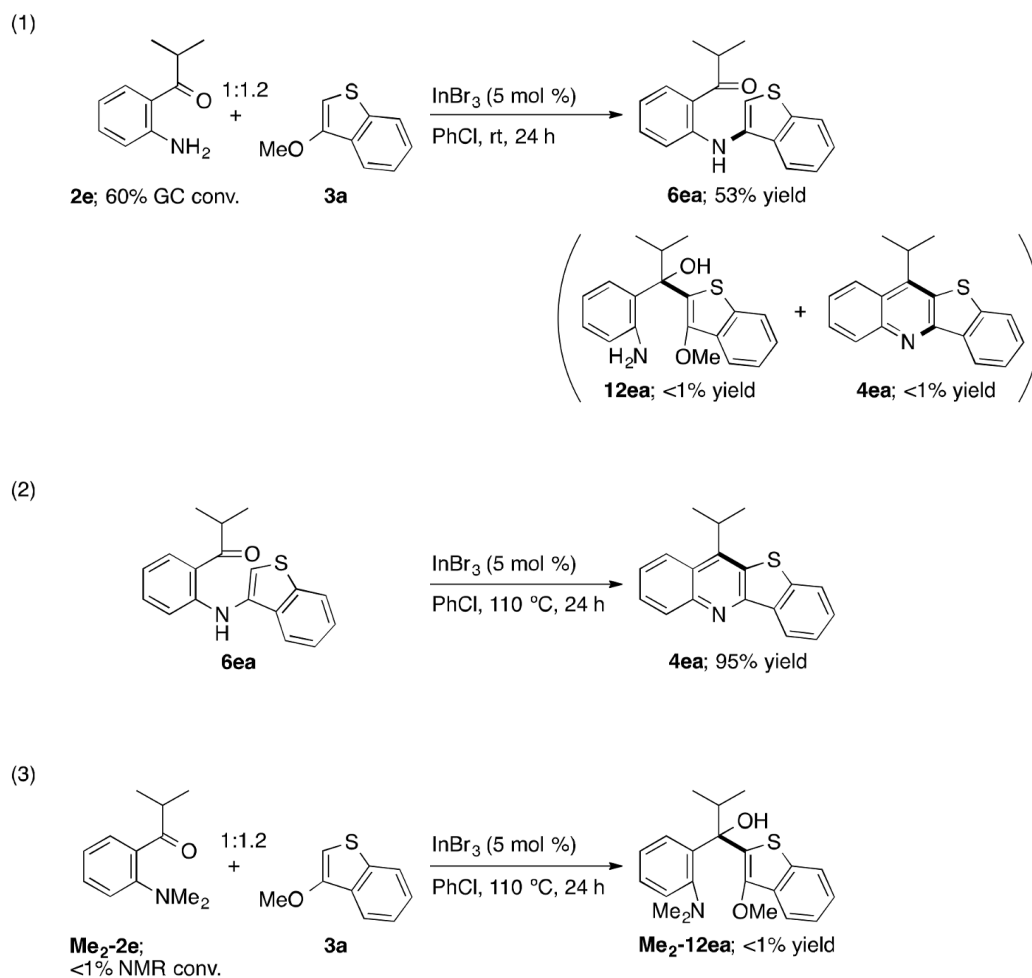
**Table 6.** *N*-Methylation of indolo[3,2-*b*]quinolines with MeOTf<sup>a</sup>.



<sup>a</sup> Reagents: **4** (0.100 mmol), MeOTf (0.190 mmol), solvent [CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) or toluene (0.60 mL)]. Yields of isolated **10** based on **4** are shown here.

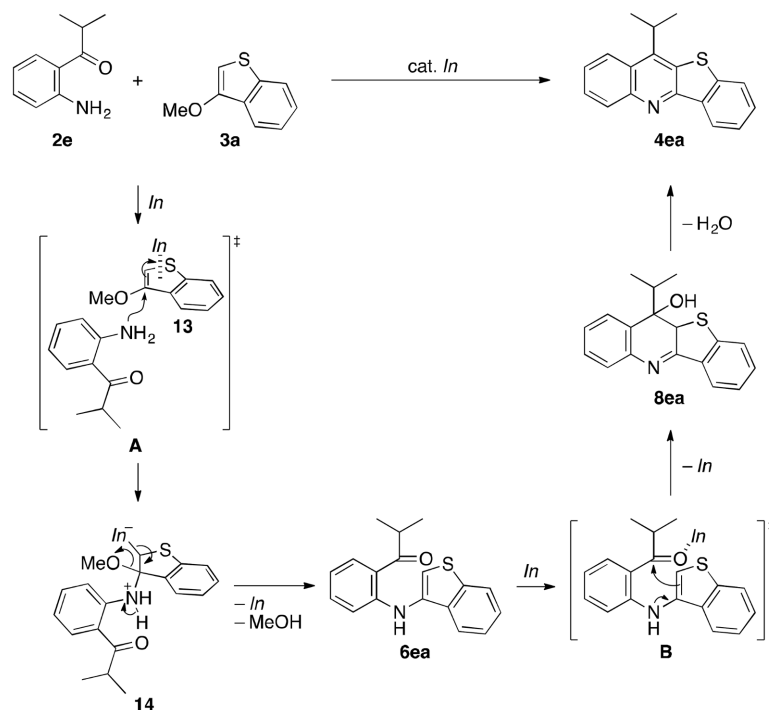


**Scheme 2.** Neutralization of **10fi**.



**Scheme 3.** Control experiments for mechanistic studies.

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  $S_NAr$ -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.



Scheme 4. A proposed reaction mechanism.

### 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 (<sup>1</sup>H, 400 MHz; <sup>13</sup>C, 100 MHz; <sup>19</sup>F, 376 MHz) or JEOL JMN-ECA 500 (<sup>1</sup>H, 500 MHz; <sup>13</sup>C, 125 MHz; <sup>19</sup>F, 471 MHz) spectrometer (JEOL, Tokyo, Japan) using tetramethylsilane (<sup>1</sup>H and <sup>13</sup>C) or trichlorofluoromethane (<sup>19</sup>F) 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 (CH<sub>2</sub>Cl<sub>2</sub>) were distilled under argon from CaCl<sub>2</sub> just prior to use. Dibutyl ether (Bu<sub>2</sub>O) and 1,4-dioxane were distilled under argon from sodium just prior to use. 1,2-Diethoxyethane, nitromethane (MeNO<sub>2</sub>), butanol (BuOH) and *o*-dichlorobenzene (*o*-C<sub>6</sub>H<sub>4</sub>Cl<sub>2</sub>) were stored over molecular sieves 4 Å (MS 4 Å) under argon. Butyronitrile (PrCN) was distilled under argon from P<sub>2</sub>O<sub>5</sub> just prior to use. MeOH was stored over molecular sieves 3 Å (MS 3 Å) under argon. The following indium salts and substrates were synthesized according to the respective literature methods: In(NTf<sub>2</sub>)<sub>3</sub> [83,84], In(ONf)<sub>3</sub> [56,85], 1-(2-aminophenyl)-2-methyl-1-propanone (2e) [86], 1-(2-aminophenyl)-2,2,2-trifluoroethanone (2f) [87], (2-aminophenyl)(4-methoxyphenyl)methanone (2j) [88], (2-aminophenyl)(2-methylphenyl)methanone (2i) [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-1*H*-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 H<sub>2</sub>O from **2g**-HCl-H<sub>2</sub>O

A hydrochloride-hydrate adduct of **2g** (407 mg, 1.46 mmol) was placed in a 15-mL screw-cap vial. To this, a saturated NaHCO<sub>3</sub> 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 (Na<sub>2</sub>SO<sub>4</sub>). 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 <sup>1</sup>H-NMR data are provided here. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 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 (**Me<sub>2</sub>-2e**)

On the basis of the literature procedure that has been used when dimethylating closely related 1-(2-aminophenyl)ethanone derivatives [90], **Me<sub>2</sub>-2e** was prepared using the following reagents and conditions: **2e** (163 mg, 1.00 mmol), MeI (426 mg, 3.00 mmol), K<sub>2</sub>CO<sub>3</sub> (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 **Me<sub>2</sub>-2e** has already appeared in the literature [91], and its spectral and analytical data are in good agreement with those reported. Accordingly, only the <sup>1</sup>H-NMR data are provided here. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) 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*-Acyylanilines with Alkoxyheteroarenes: An Experimental Procedure Exemplified by the Synthesis of **4aa**

InBr<sub>3</sub> (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 NaHCO<sub>3</sub> 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 (Na<sub>2</sub>SO<sub>4</sub>). 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 <sup>1</sup>H- and <sup>13</sup>C-NMR spectroscopy and HRMS, as follows: <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 17.4, 122.8, 123.0, 124.0, 125.1, 125.9, 126.1, 128.5, 129.8, 130.1, 132.0, 135.1, 137.2, 140.7, 146.7, 153.3. HRMS (FD) Calcd for C<sub>16</sub>H<sub>11</sub>NS: 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.

### 3.4. N-Methylation of Indolo[3,2-*b*]quinolines with MeOTf: An Experimental Procedure Exemplified by the Synthesis of **10fi**

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 Et<sub>2</sub>O (5 mL). The filtrate was concentrated, and the residue was filtered and then washed with Et<sub>2</sub>O (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 <sup>1</sup>H-, <sup>13</sup>C- and <sup>19</sup>F-NMR spectroscopy and HRMS, as follows: <sup>1</sup>H-NMR (500 MHz, dimethyl sulfoxide-*d*<sub>6</sub>) 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), 8.97 (d, J = 9.2 Hz, 1H), 12.71 (s, 1H); <sup>13</sup>C-NMR (125 MHz, dimethyl sulfoxide-*d*<sub>6</sub>) 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; <sup>19</sup>F-NMR (376 MHz, dimethyl sulfoxide-*d*<sub>6</sub>) δ -77.3, -53.4. HRMS (FD) Calcd for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>: M<sup>+</sup>, 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 % Na<sub>2</sub>CO<sub>3</sub> 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 CHCl<sub>3</sub> (4 mL × 4), and the combined organic layer was dried over anhydrous sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>). Filtration and evaporation of the solvent followed by column chromatography on silica gel (CHCl<sub>3</sub>/Et<sub>3</sub>N = 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 <sup>1</sup>H-, <sup>13</sup>C- and <sup>19</sup>F-NMR spectroscopy and HRMS, as follows: <sup>1</sup>H-NMR (400 MHz, dimethyl sulfoxide-*d*<sub>6</sub>) 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); <sup>13</sup>C-NMR (100 MHz, dimethyl sulfoxide-*d*<sub>6</sub>) 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; <sup>19</sup>F-NMR (471 MHz, dimethyl sulfoxide-*d*<sub>6</sub>) δ -50.8. HRMS (FD) Calcd for C<sub>17</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>: 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  $^1\text{H}$ -,  $^{13}\text{C}$ - and  $^{19}\text{F}$ -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.

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