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Regioselective Synthesis of Indolo[1,2-*c*]quinazolines and 11*H*-Indolo[3,2-*c*]quinolines via Copper-Catalyzed Cascade Reactions of 2-(2-Bromoaryl)-1*H*-indoles with Aldehydes and Aqueous Ammonia

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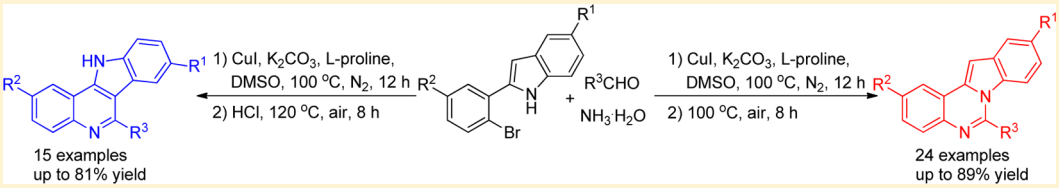
Supporting Information



ABSTRACT: Highly selective and convenient synthesis of indolo[1,2-*c*]quinazolines and 11*H*-indolo[3,2-*c*]quinolines through copper-catalyzed one-pot cascade reactions of 2-(2-bromoaryl)-1*H*-indoles with aldehydes and aqueous ammonia has been achieved. Notably, the regioselectivity was easily controlled by tuning the reaction conditions. Compared with literature methods, the present protocol features easily controlled selectivity, readily available starting materials, good functional group tolerance, and simple operation procedures.

INTRODUCTION

Indoloquinazolines and indoloquinolines have attracted much attention since they are frequently found in natural products and synthetic compounds with a broad spectrum of biological activities (Figure 1).[1] For example, indolo[1,2-*c*]quinazolines exhibit potent antibacterial and antifungal activities.[2] Meanwhile, 11*H*-indolo[3,2-*c*]quinolines have been used as promising antimalarial and anticancer drug candidates,[3] selective protein kinase DYRK1A inhibitors,[4] and DNA intercalator[5] for inhibiting DNA replication, transcription, and/or topoisomerase activities.

In view of their importance, several synthetic routes have been developed for the preparation of indolo[1,2-*c*]quinazoline and 11*H*-indolo[3,2-*c*]quinoline derivatives. For example, the synthesis of indolo[1,2-*c*]quinazolines has been achieved through cyclocondensation of 2-(2-aminoaryl)indoles with aldehydes, acyl cyanides, or nitriles,[2,6] and copper-catalyzed tandem reactions of 2-(2-bromoaryl)indoles with benzylamines, amino acids, or amidines.[7] Meanwhile, palladium-catalyzed isocyanide insertion reactions of 2-(2-aminoaryl)indoles,[8] gold-catalyzed cyclizations of acyclic alkynes,[9] and aza-Wittig reactions of isocyanates with imino-phosphoranes[10] have been utilized for the preparation of 11*H*-indolo[3,2-*c*]quinoline derivatives. Although these existing synthetic routes are quite effective, they are only suitable for the preparation of either indolo[1,2-*c*]quinazolines or 11*H*-indolo[3,2-*c*]quinolines. In addition, most of them still suffer from expensive or difficult-to-obtain starting materials or reagents, a multistep reaction sequence, limited substrate scope, or harsh reaction conditions. Therefore, the development of simple, practical, and general synthetic methods for the selective synthesis of indolo[1,2-*c*]quinazoline and 11*H*-indolo[3,2-*c*]quinoline derivatives from the same starting materials is highly desirable.

On the other hand, copper-catalyzed cross-coupling reaction of aryl halides with amines or aqueous ammonia turned out to be a powerful tool for the construction of aromatic C(sp^2)−N bonds.[11] Recently, by employing copper-catalyzed aromatic C(sp^2)−N bond formation reaction as a key step, we have developed a series of practical and efficient synthetic routes toward various bioactive *N*-fused heterocyclic compounds.[12] As a continuation of our study in this aspect, we disclose herein a convenient synthesis of indolo[1,2-*c*]quinazoline and 11*H*-indolo[3,2-*c*]quinoline derivatives through copper-catalyzed one-pot two-step cascade reactions of 2-(2-bromoaryl)-1*H*-indoles with aldehydes and aqueous ammonia. Interestingly, highly selective synthesis of the above-mentioned two classes of indole-fused heterocycles from the same starting materials was easily accomplished by simply tuning the reaction conditions. Now, we would like to report the details of these transformations.

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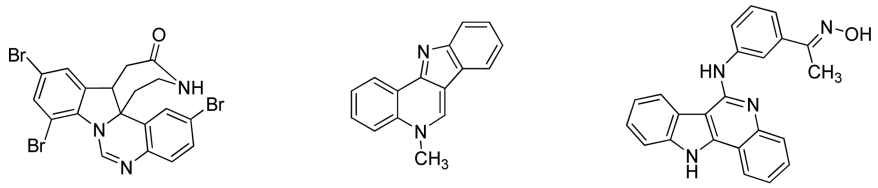
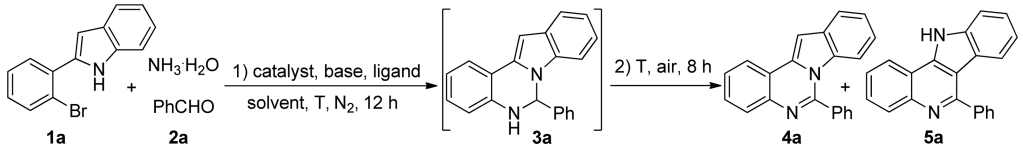


Figure 1. Selective compounds containing a indoloquinazoline or indoloquinoline scaffold.

Table 1. Optimization Study for the Synthesis of 4a[a]



						yield (%)[b]	
entry	catalyst	base	ligand	solvent	T (°C)	**4a**	**5a**
1	CuI	K_2CO_3		DMSO	100	65	5
2	CuCl	K_2CO_3		DMSO	100	52	4
3	CuBr	K_2CO_3		DMSO	100	57	4
4	$Cu(OAc)_2$	K_2CO_3		DMSO	100	56	3
5	$CuCl_2$	K_2CO_3		DMSO	100	62	3
6	CuI	Cs_2CO_3		DMSO	100	50	6
7	CuI	Na_2CO_3		DMSO	100	51	5
8	CuI	K_3PO_4		DMSO	100	56	6
9	CuI	^{t}BuOK		DMSO	100		
10	CuI	DABCO		DMSO	100		
11	CuI	K_2CO_3	L-proline	DMSO	100	75	4
12	CuI	K_2CO_3	DMEDA	DMSO	100	59	4
13	CuI	K_2CO_3	1,10-phen	DMSO	100	59	6
14	CuI	K_2CO_3	DMAP	DMSO	100	66	3
15	CuI	K_2CO_3	L-proline	DMF	100	55	2
16	CuI	K_2CO_3	L-proline	DMAC	100	52	6
17	CuI	K_2CO_3	L-proline	NMP	100	52	6
18	CuI	K_2CO_3	L-proline	1,4-dioxane	100		
19	CuI	K_2CO_3	L-proline	toluene	100		
20	CuI	K_2CO_3	L-proline	DMSO	60	43	6
21	CuI	K_2CO_3	L-proline	DMSO	80	55	3
22	CuI	K_2CO_3	L-proline	DMSO	120	60	8

[a]The reactions were run with (1) **1a** (0.4 mmol), **2a** (0.8 mmol), aqueous ammonia (26%, 0.4 mL), catalyst (0.04 mmol), base (0.8 mmol), ligand (0.08 mmol), solvent (1.5 mL), T (°C), N_2, 12 h; (2) T (°C), air, 8 h. [b]Isolated yield.

RESULTS AND DISCUSSION

Initially, 2-(2-bromophenyl)-1*H*-indole (**1a**) was treated with benzaldehyde (**2a**) and aqueous ammonia in the presence of CuI and K_2CO_3 in DMSO at 100 °C under a nitrogen atmosphere. TLC analysis showed that **1a** was consumed completely in 12 h to give 6-phenyl-5,6-dihydroindolo[1,2-*c*]quinazoline (**3a**). Subsequent treatment of the resulting mixture at 100 °C for 8 h under air afforded the desired 6-phenylindolo[1,2-*c*]quinazoline (**4a**) in a total yield of 65%. Meanwhile, 6-phenyl-11*H*-indolo[3,2-*c*]quinoline (**5a**) as an unexpected byproduct was also isolated in 5% yield (Table 1, entry 1). To improve the efficiency, we commenced to optimize the reaction parameters (Table 1). First, five different copper catalysts were screened by using K_2CO_3 as base and DMSO as solvent (entries 1−5). Among them, CuI proved to be optimal for the formation of **4a**. With CuI as catalyst, the effect of inorganic and organic bases on this cascade reaction was also investigated. It was found that K_2CO_3 provided the highest yield of **4a** (entries 1 and 6−10). Screening of different ligands revealed that L-proline was the most efficient (entries 1 and 11−14). Next, several solvents, such as DMF, DMAC, NMP, 1,4-dioxane, and toluene, were also tried as the reaction medium, and all of them were found to be less effective than DMSO (entries 11 and 15−19). Moreover, it was observed that decreasing or increasing the reaction temperature from 100 °C resulted in decreased yields of **4a** (entries 11 and 20−22).

With the optimized reaction conditions (Table 1, entry 11) in hand, we then studied the scope and generality of this new method for the preparation of indolo[1,2-*c*]quinazolines (**4**), and the results are shown in Table 2. First, the reactions of different aldehydes (**2**) with 2-(2-bromophenyl)-1*H*-indole (**1a**) and aqueous ammonia were investigated. It was found that aryl-substituted aldehydes with either electron-donating groups including methyl and methoxyl or electron-withdrawing groups such as trifluoromethyl, fluoro, bromo, and chloro on

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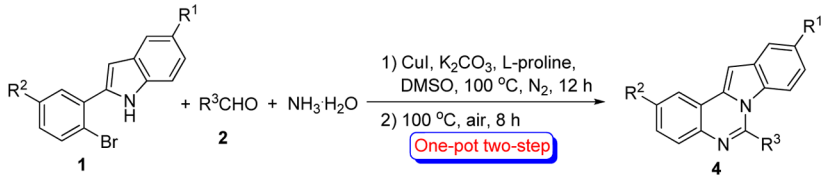
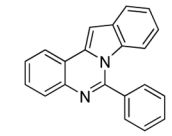
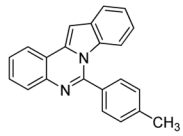
Table 2. Scope for the Synthesis of Indolo[1,2-*c*]quinazolines (4)[a,b]

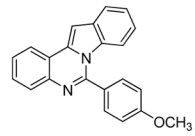


1a: R^1, R^2 = H; **1b**: R^1 = Cl, R^2 = H;
1c: R^1 = H, R^2 = MeO; **1d**: R^1 = H, R^2 = Cl

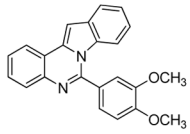

4a, 75%



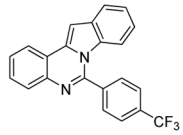
4b, 63%



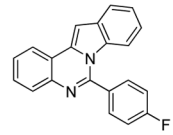
4c, 69%



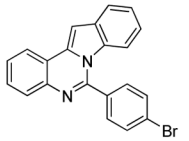
4d, 56%



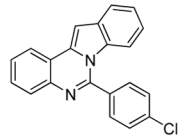
4e, 41%



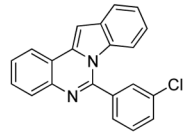
4f, 63%



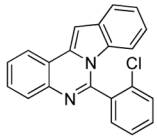
4g, 31%[c]



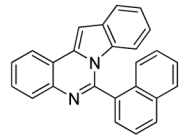
4h, 60%

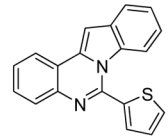


4i, 55%

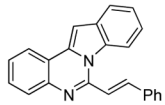


4j, 62%

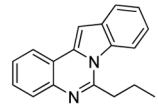

4k, 60%

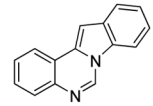


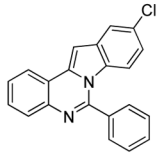
4l, 53%



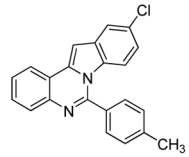
4m, 56%


4n, 35%

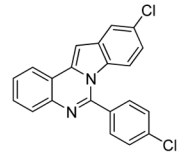

4o, 30%



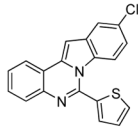
4p, 60%



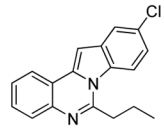
4q, 64%



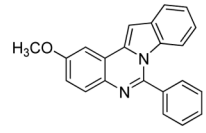
4r, 76%



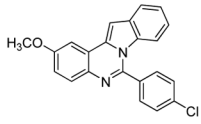
4s, 78%



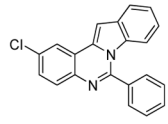
4t, 45%



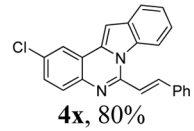
4u, 70%



4v, 89%



4w, 74%



4x, 80%

[a]Reaction conditions: (1) **1** (0.4 mmol), **2** (0.8 mmol), aqueous ammonia (26%, 0.4 mL), CuI (0.04 mmol), K_2CO_3 (0.8 mmol), L-proline (0.08 mmol), DMSO (1.5 mL), 100 °C, N_2, 12 h; (2) 100 °C, air, 8 h. [b]Isolated yields are shown. [c]An unknown byproduct was formed.

the aryl ring at different positions were well tolerated with the reaction conditions to provide the desired 6-aryl substituted indolo[1,2-*c*]quinazolines **4a**−**4j** in moderate to good yields. No obvious electronic and steric effects of these functional

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Scheme 1. One-Pot Two-Step Synthesis of 5a from 1a, 2a, and Aqueous Ammonia

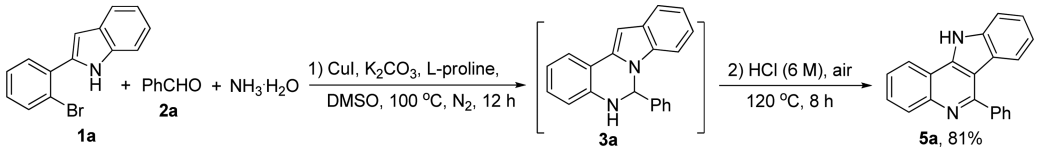
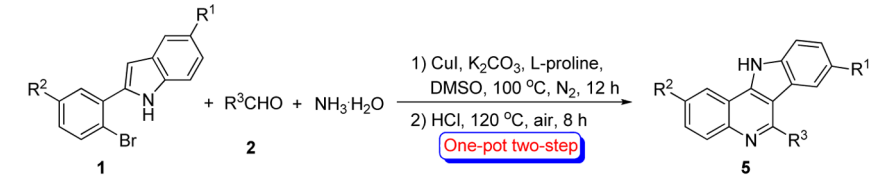
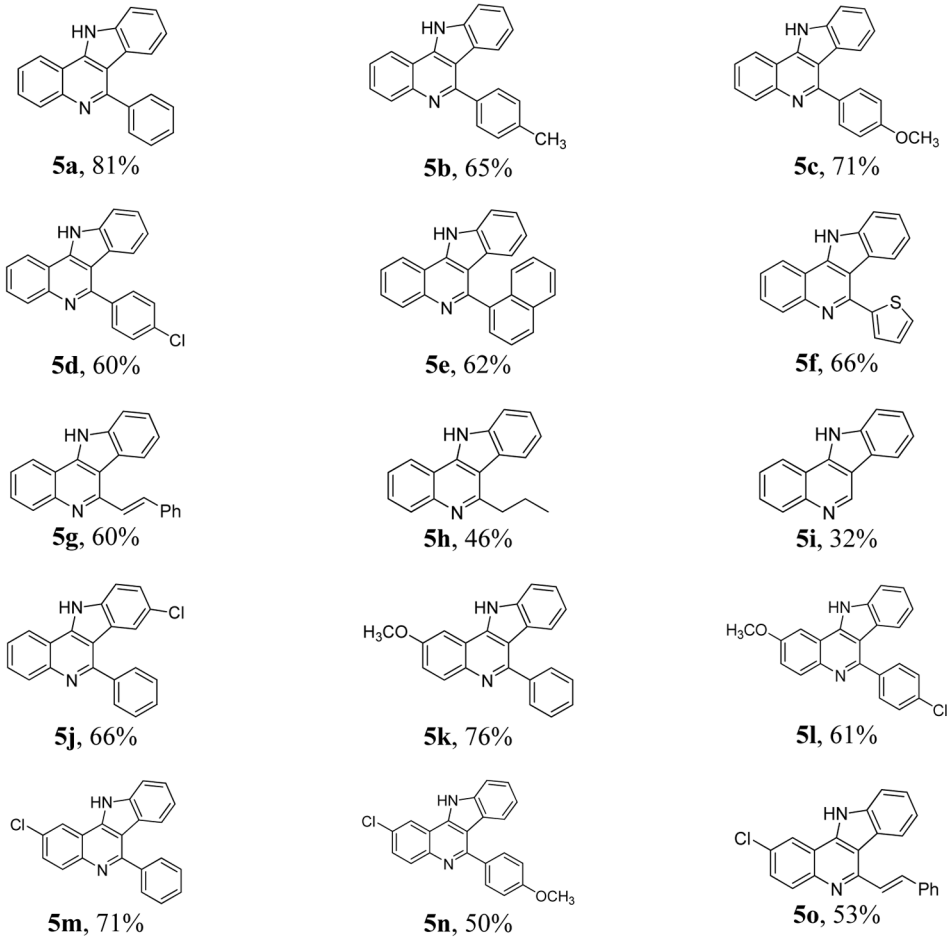


Table 3. Scope for the Synthesis of 11*H*-Indolo[3,2-*c*]quinolines (5)[a,b]



1a: R^1, R^2 = H; **1b**: R^1 = Cl, R^2 = H;
1c: R^1 = H, R^2 = MeO; **1d**: R^1 = H, R^2 = Cl



[a]Reaction conditions: (1) **1** (0.4 mmol), **2** (0.8 mmol), aqueous ammonia (26%, 0.4 mL), CuI (0.04 mmol), K_2CO_3 (0.8 mmol), L-proline (0.08 mmol), DMSO (1.5 mL), 100 °C, N_2, 12 h; (2) HCl (6 M), 120 °C, air, 8 h. [b]Isolated yields are shown.

groups were observed. 1-Naphthaldehyde and thiophene-2-carbaldehyde also underwent this cascade reaction smoothly to deliver the corresponding products **4k** and **4l** in 60% and 53% yields, respectively. In addition, with cinnamaldehyde and butyraldehyde, 6-alkenyl and 6-alkyl substituted indolo[1,2-*c*]quinazolines **4m** and **4n** were obtained in 56% and 35% yields. More interestingly, paraformaldehyde proved to be also compatible to generate 6-unsubstituted indolo[1,2-*c*]-quinazoline **4o**, albeit in a lower yield. Second, several 2-(2-bromoaryl)-1*H*-indoles (**1**) were tried, and the results indicated that **1** bearing different R^1 and R^2 groups reacted with various aldehydes (**2**) and aqueous ammonia smoothly to afford **4p**−**4x** in 45%−89% yields.

Having established an efficient synthesis of indolo[1,2-*c*]quinazolines (**4**) from the one-pot cascade reaction of 2-(2-bromoaryl)-1*H*-indoles (**1**) with aldehydes (**2**) and aqueous ammonia, we were then interested in whether 11*H*-indolo[3,2-*c*]quinolines (**5**) could also be preferentially synthesized from

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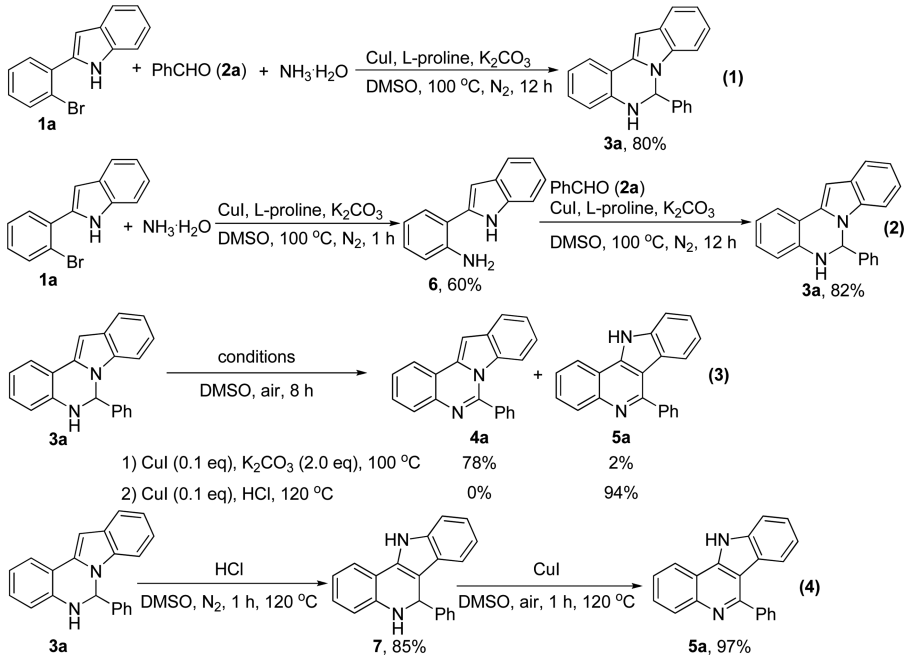
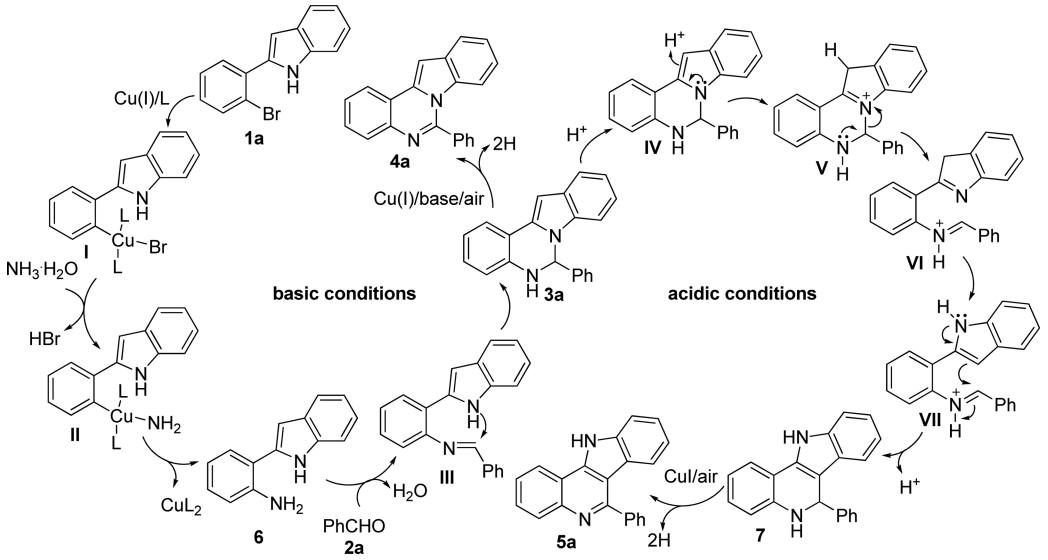
Scheme 2. Control Experiments



Scheme 3. Plausible Mechanisms for Formation of 4a and 5a



the same starting materials under different reaction conditions. For this purpose, 6-phenyl-5,6-dihydroindolo[1,2-*c*]quinazoline (**3a**) was prepared and then subjected to various reaction conditions. After several trials,[13] we were pleased to find that treating **3a** with aqueous HCl and CuI in DMSO at 120 °C under air could afford **5a** in 94% yield. It is worth to be noted that, under these conditions, the formation of **4a** was not observed. These results indicated that the pH value of the reaction system played a vital role in determining the direction of the transformation of **3a**. To be specific, **3a** could be selectively converted into **4a** under basic conditions, as shown in Table 1. In contrast, treating **3a** under acidic conditions could afford **5a** in an exclusive manner. On the basis of these results, we continued our study by exploring the possibility of developing a one-pot two-step synthesis of **5a** directly from **1a**, **2a**, and aqueous ammonia. Thus, **1a** was first treated with **2a** and aqueous ammonia in the presence of CuI, K_2CO_3, and L-proline under N_2 at 100 °C for 12 h. Then, hydrochloric acid was added to the reaction vessel to adjust the pH value of the reaction system to a range of 5−6, and the resulting mixture was stirred at 120 °C for 8 h under air. It was observed that the envisioned one-pot two-step cascade reaction proceeded smoothly to provide **5a** in a total yield of 81% (Scheme 1).

Next, the substrate scope for the synthesis of 11*H*-indolo[3,2-*c*]quinolines (**5**) was studied in detail. As demonstrated in Table 3, various aldehydes **2** and indoles **1** took part in this cascade reaction to give the desired 11*H*-indolo[3,2-*c*]quinolines **5a**−**5o** in modest to good yields. For aldehydes **2**, it was found that aryl- and alkenyl-substituted aldehydes usually gave the corresponding products in yields higher than alkyl-substituted aldehydes. Moreover, it is worth noting that 6-unsubstituted 11*H*-indolo[3,2-*c*]quinoline **5i**, which can be

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successfully utilized in the synthesis of the alkaloid *isocryptolepine* (Figure 1) by regioselective *N*-methylation reaction,[3a,c,14] could also be obtained by using paraformaldehyde as a substrate. For indoles **1**, different R^1 and R^2 groups showed a slight influence on the outcome of this cascade reaction.

To explore the reaction mechanism for the regioselective synthesis of indole-fused heterocycles **4** and **5**, several control experiments were performed, and the results are shown in Scheme 2. First, treatment of a mixture of **1a**, **2a**, and aqueous ammonia by using CuI as catalyst, L-proline as ligand, and K_2CO_3 as base under N_2 afforded the key intermediate **3a** in 80% yield (Scheme 2, eq 1). Second, copper-catalyzed cross-coupling reaction of **1a** with aqueous ammonia at 100 °C under a nitrogen atmosphere gave 2-(2-aminophenyl)-1*H*-indole (**6**) in 60% yield. The following cyclocondensation of **6** with benzaldehyde (**2a**) under N_2 afforded **3a** in 82% yield (Scheme 2, eq 2). Third, treating a mixture of **3a**, CuI, and K_2CO_3 at 100 °C for 8 h under air could afford **4a** (78%) together with **5a** (2%). On the other hand, treatment of **3a** with CuI and HCl at 120 °C for 8 h under air gave rise to **5a** in 94% yield (Scheme 2, eq 3). Finally, treatment of **3a** with HCl at 120 °C for 1 h under N_2 afforded intermediate **7** in 85% yield. Next, **7** was oxidized by air under the catalysis of CuI to deliver **5a** in 97% yield (Scheme 2, eq 4).

Based on the above results and previous studies,[12] plausible mechanisms for the formation of **4a** and **5a** are illustrated in Scheme 3. First, copper-catalyzed amination of 2-(2-bromophenyl)-1*H*-indole (**1a**) with aqueous ammonia via intermediates **I** and **II** affords 2-(2-aminophenyl)-1*H*-indole (**6**). Subsequent condensation of **6** with benzaldehyde (**2a**) gives rise to an imine intermediate **III**, which then undergoes an intramolecular *N*-nucleophilic addition under basic conditions to deliver the key intermediate **3a**. With the promotion of CuI and K_2CO_3, **3a** could be oxidized by air to afford **4a** as a major product. As for the formation of **5a**, it is proposed that, under acidic conditions, an addition of H^+ to the 3-position of the indole-ring of **3a** affords intermediate **V**, which then undergoes a ring-opening process to deliver **VI**. Rearomatization of **VI**, followed by intramolecular *C*-nucleophilic addition, gives intermediate **7**. Subsequent oxidative aromatization of **7** in the presence of air and CuI generates **5a**.

CONCLUSION

In conclusion, we have developed an efficient and general strategy for the selective synthesis of indolo[1,2-*c*]quinazoline and 11*H*-indolo[3,2-*c*]quinoline derivatives via copper-catalyzed one-pot sequential reactions of 2-(2-bromoaryl)-1*H*-indoles, aldehydes, and aqueous ammonia. In addition, plausible reaction mechanisms for the formation of indolo[1,2-*c*]quinazolines and 11*H*-indolo[3,2-*c*]quinolines are suggested based on the control experimental results. Compared with the literature procedures, the present synthetic route exhibits high efficiency and regioselectivity, readily obtainable starting materials, and operational simplicity. Further application of this novel method in the synthesis of bioactive compounds embedding the indolo[1,2-*c*]quinazoline or 11*H*-indolo[3,2-*c*]quinoline skeleton is currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. 2-(2-Bromoaryl)-1*H*-indoles **1** were prepared by the Fischer indole synthesis.[15] Other reagents and solvents were purchased from commercial sources and used as received. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. High-resolution mass spectra (HRMS) were collected in ESI mode by using a MicrOTOF mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm), and components were visualized by observation under UV light (254 and 365 nm).

General Procedure for the Synthesis of Indolo[1,2-*c*]-quinazolines 4. To a tube containing a solution of 2-(2-bromoaryl)-1*H*-indole **1** (0.4 mmol) in DMSO (1.5 mL) were added K_2CO_3 (0.8 mmol), CuI (0.04 mmol), L-proline (0.08 mmol), aldehyde **2** (0.8 mmol), and 26% aqueous ammonia (0.4 mL) under a nitrogen atmosphere. Then, the tube was sealed, and the mixture was stirred at 100 °C for 12 h. Next, the resulting mixture was opened to air and stirred at 100 °C for another 8 h. After being cooled to room temperature, the reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to afford the desired indolo[1,2-*c*]quinazoline **4**.

*6-Phenylindolo[1,2-c]quinazoline (**4a**).*[7c] Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (88 mg, 75%), mp 195−197 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.48 (d, J = 8.8 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.49−7.58 (m, 2H), 7.62−7.70 (m, 5H), 7.78 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 6.8 Hz, 1H), 8.11 (dd, J = 0.8, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.8, 115.0, 120.55, 120.60, 121.6, 122.8, 123.5, 127.5, 127.9, 128.3, 129.2, 129.4, 130.4, 130.5, 131.7, 135.2, 135.9, 139.2, 149.4. MS (ESI) m/z 295 $[M + H]^+$.

*6-p-Tolylindolo[1,2-c]quinazoline (**4b**).*[7c] Petroleum ether/ethyl acetate (20:1) as eluent; yellow solid (78 mg, 63%), mp 157−159 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 6.61 (d, J = 8.8 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 7.26 (s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.47−7.55 (m, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 95.8, 115.1, 120.5, 120.6, 121.5, 122.7, 123.5, 127.3, 127.9, 128.2, 129.1, 129.9, 130.4, 131.8, 133.1, 135.3, 139.3, 140.6, 149.6. MS (ESI) m/z 309 $[M + H]^+$.

*6-(4-Methoxyphenyl)indolo[1,2-c]quinazoline (**4c**).*[16a] Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (90 mg, 69%), mp 174−176 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.95 (s, 3H), 6.65 (d, J = 8.0 Hz, 1H), 7.01−7.05 (m, 1H), 7.11−7.14 (m, 2H), 7.26 (s, 1H), 7.30−7.34 (m, 1H), 7.47−7.56 (m, 2H), 7.61−7.64 (m, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.85 (dd, J = 0.8, 7.6 Hz, 1H), 8.10 (dd, J = 1.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5, 95.8, 114.6, 115.1, 120.5, 121.5, 122.7, 123.5, 127.3, 127.7, 128.2, 129.1, 129.9, 130.4, 131.8, 135.4, 139.2, 149.4, 161.2 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{22}H_{17}N_2O$ $[M + H]^+$ 325.1335, found 325.1347.

*6-(3,4-Dimethoxyphenyl)indolo[1,2-c]quinazoline (**4d**).* Petroleum ether/ethyl acetate (5:1) as eluent; yellow solid (79 mg, 56%), mp 183−185 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 3H), 4.02 (s, 3H), 6.63 (d, J = 8.8 Hz, 1H), 7.01−7.05 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.25−7.26 (m, 1H), 7.27 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.48−7.56 (m, 2H), 7.77 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 8.10 (dd, J = 1.2, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.1, 56.2, 95.9, 111.2, 111.6, 115.2, 120.50, 120.52, 121.2, 121.6, 122.7, 123.5, 127.4, 127.7, 128.2, 129.1, 130.4, 131.7, 135.3, 139.1, 149.2, 149.6, 150.7. HRMS (ESI) calcd for $C_{23}H_{19}N_2O_2$ $[M + H]^+$ 355.1441, found 355.1459.

*6-(4-(Trifluoromethyl)phenyl)indolo[1,2-c]quinazoline (**4e**).* Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (59 mg, 41%), mp 202−204 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.52 (d, J = 8.4 Hz, 1H), 7.03−7.07 (m, 1H), 7.28 (s, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.51−7.59 (m, 2H), 7.79−7.85 (m, 4H), 7.90 (d, J = 8.0 Hz, 2H), 8.09−8.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.2, 114.5, 120.6, 120.8, 121.9, 122.8, 123.8, 123.9 (q, J = 270.3 Hz, 1C), 126.3 (q, J = 3.3 Hz, 2C), 127.87, 127.91, 129.0, 129.3, 130.5, 131.3, 132.5 (q, J = 33 Hz, 1C), 135.1, 138.9, 139.3, 147.8. HRMS (ESI) calcd for $C_{22}H_{14}F_3N_2$ $[M + H]^+$ 363.1104, found 363.1105.

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*6-(4-Fluorophenyl)indolo[1,2-c]quinazoline (**4f**).*[7c] Petroleum ether/ethyl acetate (30:1) as eluent; yellow solid (79 mg, 63%), mp 217−219 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.54 (d, J = 8.8 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.29−7.35 (m, 3H), 7.47−7.56 (m, 2H), 7.65−7.68 (m, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.0, 114.8, 116.5 (d, J = 22.1 Hz, 2C), 120.5, 120.7, 121.6, 122.8, 123.6, 127.6, 127.8, 129.2, 130.5, 130.6 (d, J = 8.4 Hz, 2C), 131.6, 132.1 (d, J = 3.8 Hz, 1C), 135.2, 139.0, 148.4, 163.9 (d, J = 249.2 Hz, 1C). MS (ESI) m/z 313 $[M + H]^+$.

*6-(4-Bromophenyl)indolo[1,2-c]quinazoline (**4g**).* Petroleum ether/ethyl acetate (40:1) as eluent; yellow solid (47 mg, 31%), mp 204−206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.61 (d, J = 8.8 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.26 (s, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.49−7.58 (m, 4H), 7.75−7.83 (m, 4H), 8.09 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.0, 114.7, 120.6, 120.7, 121.7, 122.8, 123.7, 124.9, 127.7, 127.9, 129.2, 130.1, 130.4, 131.4, 132.5, 134.8, 135.2, 139.0, 148.2. HRMS (ESI) calcd for $C_{21}H_{14}BrN_2$ $[M + H]^+$ 373.0335, found 373.0364.

*6-(4-Chlorophenyl)indolo[1,2-c]quinazoline (**4h**).*[7b] Petroleum ether/ethyl acetate (40:1) as eluent; yellow solid (79 mg, 60%), mp 201−203 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.60 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 7.23 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.47−7.56 (m, 2H), 7.58−7.63 (m, 4H), 7.77 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.0, 114.8, 120.5, 120.7, 121.7, 122.8, 123.7, 127.6, 127.9, 129.2, 129.6, 129.9, 130.4, 131.4, 134.3, 135.2, 136.6, 139.0, 148.2. MS (ESI) m/z 329 $[M + H]^+$.

*6-(3-Chlorophenyl)indolo[1,2-c]quinazoline (**4i**).* Petroleum ether/ethyl acetate (40:1) as eluent; yellow solid (73 mg, 55%), mp 167−169 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (d, J = 8.8 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.25 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.49−7.56 (m, 4H), 7.65 (s, 1H), 7.71 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.1, 114.7, 120.6, 120.7, 121.8, 122.8, 123.7, 126.6, 127.7, 127.9, 128.6, 129.2, 130.4, 130.6, 130.7, 131.4, 135.1, 135.4, 137.4, 138.9, 147.8. HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$ 329.0840, found 329.0862.

*6-(2-Chlorophenyl)indolo[1,2-c]quinazoline (**4j**).* Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (82 mg, 62%), mp 119−121 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.37 (d, J = 8.0 Hz, 1H), 7.05 (t, J = 8.0 Hz, 1H), 7.31 (s, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.52−7.66 (m, 6H), 7.80 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.0, 113.4, 120.7, 120.8, 122.3, 122.9, 123.7, 127.8, 128.0, 129.2, 130.31, 130.32, 130.4, 131.3, 131.7, 133.4, 134.7, 135.2, 139.0, 146.7 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$ 329.0840, found 329.0862.

*6-(Naphthalen-1-yl)indolo[1,2-c]quinazoline (**4k**).* Petroleum ether/ethyl acetate (20:1) as eluent; yellow solid (83 mg, 60%), mp 148−150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.99 (d, J = 8.8 Hz, 1H), 6.79 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.33−7.37 (m, 2H), 7.51−7.64 (m, 4H), 7.71−7.80 (m, 3H), 7.95−7.97 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 8.16−8.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.0, 114.6, 120.5, 120.8, 121.9, 122.9, 123.5, 124.7, 125.9, 126.7, 126.9, 127.6, 127.7, 128.1, 128.6, 129.2, 130.4, 130.6, 131.0, 131.3, 133.4, 133.8, 135.0, 139.3, 148.5. HRMS (ESI) calcd for $C_{25}H_{17}N_2$ $[M + H]^+$ 345.1386, found 345.1389.

*6-(Thiophen-2-yl)indolo[1,2-c]quinazoline (**4l**).*[7b] Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (64 mg, 53%), mp 163−164 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72−6.74 (m, 1H), 7.07−7.11 (m, 1H), 7.26−7.29 (m, 2H), 7.33−7.37 (m, 1H), 7.49−7.57 (m, 3H), 7.65−7.66 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.83−7.86 (m, 1H), 8.09−8.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.0, 114.8, 120.6, 120.7, 121.7, 122.7, 123.6, 127.5, 127.8, 128.0, 128.3, 129.1, 129.2, 130.4, 131.6, 135.3, 136.0, 139.0, 143.5. MS (ESI) m/z 301 $[M + H]^+$.

*(E)-6-Styrylindolo[1,2-c]quinazoline (**4m**).*[16a] Petroleum ether/ethyl acetate (40:1) as eluent; yellow solid (72 mg, 56%), mp 182−184 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 1H), 7.34−7.38 (m, 1H), 7.41−7.56 (m, 6H), 7.68−7.74 (m, 3H), 7.83 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 16.0 Hz, 1H), 8.05 (t, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.6, 115.0, 120.3, 120.9, 121.2, 122.2, 122.7, 123.6, 127.1, 127.4, 127.8, 129.06, 129.13, 129.7, 130.6, 131.6, 135.1, 135.6, 138.9, 139.8, 147.7. MS (ESI) m/z 321 $[M + H]^+$.

*6-Propylindolo[1,2-c]quinazoline (**4n**).*[7b] Petroleum ether/ethyl acetate (20:1) as eluent; yellow solid (36 mg, 35%), mp 95−97 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, J = 7.6 Hz, 3H), 2.04−2.11 (m, 2H), 3.40 (t, J = 7.6 Hz, 2H), 7.23 (s, 1H), 7.38−7.48 (m, 3H), 7.53 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.99 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 19.6, 38.6, 95.6, 115.0, 120.3, 120.8, 122.2, 122.6, 123.3, 126.8, 127.0, 129.0, 130.6, 131.2, 135.2, 138.6, 151.6. MS (ESI) m/z 261 $[M + H]^+$.

*Indolo[1,2-c]quinazoline (**4o**).*[7b] Petroleum ether/ethyl acetate (10:1) as eluent; yellow solid (26 mg, 30%), mp 199−200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (s, 1H), 7.40−7.47 (m, 2H), 7.50−7.58 (m, 2H), 7.82−7.84 (m, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 94.9, 109.9, 121.0, 121.3, 122.4, 123.2, 124.2, 127.8, 128.0, 129.2, 129.8, 130.4, 132.8, 137.2, 139.1. MS (ESI) m/z 219 $[M + H]^+$.

*10-Chloro-6-phenylindolo[1,2-c]quinazoline (**4p**).*[7b] Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (79 mg, 60%), mp 205−207 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.34 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 7.19 (s, 1H), 7.51−7.58 (m, 2H), 7.60−7.65 (m, 5H), 7.71 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.2, 115.9, 119.7, 120.2, 121.8, 122.9, 127.7, 127.9, 128.2, 129.3, 129.5, 129.6, 130.0, 130.7, 131.5, 135.4, 136.5, 139.1, 149.0. MS (ESI) m/z 329 $[M + H]^+$.

*10-Chloro-6-p-tolylindolo[1,2-c]quinazoline (**4q**).* Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (87 mg, 64%), mp 212−214 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53 (s, 3H), 6.45 (d, J = 9.2 Hz, 1H), 6.94 (d, J = 9.2 Hz, 1H), 7.15 (s, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.48−7.57 (m, 4H), 7.69 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 95.1, 116.0, 119.6, 120.1, 121.7, 122.8, 127.5, 127.9, 128.1, 129.2, 129.5, 130.0, 131.5, 132.6, 136.5, 139.3, 140.8, 149.1 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{22}H_{16}ClN_2$ $[M + H]^+$ 343.0997, found 343.1018.

*10-Chloro-6-(4-chlorophenyl)indolo[1,2-c]quinazoline (**4r**).*[7b] Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (110 mg, 76%), mp 244−246 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.49 (d, J = 9.2 Hz, 1H), 6.99 (d, J = 9.6 Hz, 1H), 7.20 (s, 1H), 7.51−7.62 (m, 6H), 7.73 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.4, 115.6, 119.9, 120.2, 121.9, 122.9, 127.9, 128.0, 129.5, 129.67, 129.73, 129.78, 129.82, 131.5, 133.8, 136.5, 136.9, 139.0, 147.8. MS (ESI) m/z 364 $[M + H]^+$.

*10-Chloro-6-(thiophen-2-yl)indolo[1,2-c]quinazoline (**4s**).*[7b] Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (104 mg, 78%), mp 234−236 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.59 (d, J = 9.2 Hz, 1H), 7.12 (dd, J = 1.6, 9.2 Hz, 1H), 7.35 (t, J = 4.0 Hz, 1H), 7.55 (s, 1H), 7.58−7.63 (m, 3H), 7.75 (d, J = 7.2 Hz, 1H), 7.87 (s, 1H), 7.98 (d, J = 4.8 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 96.3, 116.1, 120.1, 120.3, 121.9, 123.9, 128.0, 128.2, 128.6, 128.7, 130.0, 130.3, 130.4, 131.6, 135.3, 136.7, 139.1, 143.3 (one ^{13}C signal was not observed). MS (ESI) m/z 335 $[M + H]^+$.

*10-Chloro-6-propylindolo[1,2-c]quinazoline (**4t**).* Petroleum ether/ethyl acetate (20:1) as eluent; yellow solid (53 mg, 45%), mp 124−126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, J = 7.6 Hz, 3H), 2.00−2.10 (m, 2H), 3.30 (t, J = 7.6 Hz, 2H), 7.10 (s, 1H), 7.31 (d, J = 9.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.75 (m, 2H), 7.86 (d, J = 9.6 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 19.4, 38.6, 94.8, 115.9, 119.9, 120.0, 122.2, 122.7, 127.0, 127.3, 129.0, 129.3, 129.5, 131.6, 136.5, 138.9, 150.8. HRMS (ESI) calcd for $C_{18}H_{16}ClN_2$ $[M + H]^+$ 295.0997, found 295.1025.

*2-Methoxy-6-phenylindolo[1,2-c]quinazoline (**4u**).* Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (91 mg, 70%), mp

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184−186 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (s, 3H), 6.48 (d, J = 8.8 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 7.15 (dd, J = 2.4, 8.8 Hz, 1H), 7.25 (s, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 2.8 Hz, 1H), 7.59−7.68 (m, 5H), 7.77−7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.7, 95.6, 104.9, 115.0, 117.3, 120.5, 121.45, 121.50, 123.3, 128.4, 129.3, 129.4, 130.2, 130.3, 131.7, 133.7, 135.2, 136.1, 147.3, 158.8. HRMS (ESI) calcd for $C_{22}H_{17}N_2O$ $[M + H]^+$ 325.1335, found 325.1365.

6-(4-Chlorophenyl)-2-methoxyindolo[1,2-c]quinazoline (**4v**). Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (127 mg, 89%), mp 220−222 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.99 (s, 3H), 6.61 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 7.15 (dd, J = 2.4, 8.8 Hz, 1H), 7.26 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.60−7.66 (m, 4H), 7.76−7.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.7, 95.8, 104.9, 114.8, 117.4, 120.7, 121.5, 121.6, 123.5, 129.4, 129.6, 130.0, 130.3, 131.5, 133.5, 134.5, 135.1, 136.4, 146.1, 158.9. HRMS (ESI) calcd for $C_{22}H_{16}ClN_2O$ $[M + H]^+$ 359.0946, found 359.0978.

2-Chloro-6-phenylindolo[1,2-c]quinazoline (**4w**). Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (97 mg, 74%), mp 243−245 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.29 (d, J = 8.8 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.59 (dd, J = 2.0, 8.4 Hz, 1H), 7.64−7.73 (m, 7H), 7.82 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 97.9, 114.8, 121.3, 122.2, 122.4, 123.1, 124.0, 128.6, 129.6, 129.69, 129.74, 130.3, 131.0, 131.6, 132.3, 133.9, 135.9, 137.9, 149.6. HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$ 329.0840, found 329.0861.

(E)-2-Chloro-6-styrylindolo[1,2-c]quinazoline (**4x**). Petroleum ether/ethyl acetate (15:1) as eluent; yellow solid (113 mg, 80%), mp 222−224 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 1H), 7.36−7.51 (m, 6H), 7.69−7.75 (m, 4H), 7.84 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 15.6 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 96.2, 115.0, 121.1, 121.4, 121.6, 122.2, 122.6, 123.7, 127.8, 129.0, 129.1, 129.3, 129.7, 130.4, 131.6, 132.4, 133.9, 135.5, 137.8, 139.7, 147.7. HRMS (ESI) calcd for $C_{23}H_{16}ClN_2$ $[M + H]^+$ 355.0997, found 355.1009.

Typical Procedure for the Synthesis of the Intermediate 3a. To a tube containing a solution of 2-(2-bromophenyl)-1*H*-indole **1a** (109 mg, 0.4 mmol) in DMSO (1.5 mL) were added K_2CO_3 (110 mg, 0.8 mmol), CuI (7.6 mg, 0.04 mmol), L-proline (9.2 mg, 0.08 mmol), benzaldehyde **2a** (81 μL, 0.8 mmol), and 26% aqueous ammonia (0.4 mL) under a nitrogen atmosphere. Then, the tube was sealed, and the mixture was stirred at 100 °C for 12 h. After being cooled to room temperature, the reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (15:1), to afford **3a** (95 mg) as a yellow solid in 80% yield (mp: 205−206 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.55 (br s, 1H), 6.65−6.68 (m, 2H), 6.85−6.93 (m, 3H), 7.00−7.12 (m, 3H), 7.21 (m, 2H), 7.26−7.29 (m, 3H), 7.63 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.7, 95.9, 110.0, 115.5, 116.2, 120.0, 120.3, 120.5, 121.6, 124.2, 126.1, 128.7, 129.0, 129.5, 133.7, 135.3, 138.8, 140.7 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{21}H_{16}N_2Na$ $[M + Na]^+$ 319.1206, found 319.1205.

General Procedure for the Synthesis of 11*H*-Indolo[3,2-*c*]quinolines 5. To a tube containing a solution of 2-(2-bromoaryl)-1*H*-indole **1** (0.4 mmol) in DMSO (1.5 mL) were added K_2CO_3 (0.8 mmol), CuI (0.04 mmol), L-proline (0.08 mmol), aldehyde **2** (0.8 mmol), and 26% aqueous ammonia (0.4 mL) under a nitrogen atmosphere. Then, the tube was sealed, and the mixture was stirred at 100 °C for 12 h. After the pH value of the resulting mixture was adjusted to a range of 5−6 by addition of HCl (6 M, ca. 0.7 mL), the tube was opened to air and the reaction mixture was stirred at 120 °C for another 8 h. Upon completion, the reaction was quenched with saturated $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel to afford the desired 11*H*-indolo[3,2-*c*]quinoline **5**.

6-Phenyl-11H-indolo[3,2-c]quinoline (**5a**).[9a] Petroleum ether/ethyl acetate (2:1) as eluent; white solid (95 mg, 81%), mp 248−250 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.10−7.13 (m, 1H), 7.41−7.45 (m, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.58−7.64 (m, 3H), 7.66−7.76 (m, 3H), 7.83 (dd, J = 1.2, 7.6 Hz, 2H), 8.13−8.15 (m, 1H), 8.59 (dd, J = 1.2, 8.0 Hz, 1H), 12.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.38, 112.43, 116.7, 120.7, 121.5, 122.2, 122.4, 125.8, 126.0, 128.8, 128.9, 129.28, 129.31, 129.8, 139.5, 141.2, 141.5, 145.4, 155.9. MS (ESI) m/z 295 $[M + H]^+$.

6-p-Tolyl-11H-indolo[3,2-c]quinoline (**5b**).[9b] Petroleum ether/ethyl acetate (2:1) as eluent; white solid (80 mg, 65%), mp 282−284 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.44 (s, 3H), 7.12 (t, J = 8.0 Hz, 1H), 7.39−7.44 (m, 3H), 7.59 (d, J = 7.6 Hz, 1H), 7.65−7.74 (m, 5H), 8.12 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 12.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.5, 112.3, 112.4, 116.7, 120.6, 121.6, 122.2, 122.4, 125.7, 125.9, 128.8, 129.29, 129.33, 129.8, 138.4, 138.7, 139.5, 141.5, 145.5, 156.0. MS (ESI) m/z 309 $[M + H]^+$.

6-(4-Methoxyphenyl)-11H-indolo[3,2-c]quinoline (**5c**).[9a] Petroleum ether/ethyl acetate (1:1) as eluent; white solid (92 mg, 71%), mp 278−280 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.89 (s, 3H), 7.15−7.21 (m, 3H), 7.46 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.69−7.83 (m, 5H), 8.13 (d, J = 8.4 Hz, 1H), 8.60 (d, J = 7.6 Hz, 1H), 13.17 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.8, 112.5, 114.3, 116.7, 120.8, 121.7, 122.4, 122.5, 125.9, 126.0, 129.0, 129.8, 130.9, 133.6, 139.6, 141.6, 145.6, 155.8, 160.4 (one ^{13}C signal was not observed). MS (ESI) m/z 325 $[M + H]^+$.

6-(4-Chlorophenyl)-11H-indolo[3,2-c]quinoline (**5d**).[9b] Petroleum ether/ethyl acetate (2:1) as eluent; white solid (79 mg, 60%), mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.15 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.65−7.75 (m, 5H), 7.85 (d, J = 8.4 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 8.56−8.58 (m, 1H), 12.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.2, 112.4, 116.7, 120.8, 121.4, 121.9, 122.4, 125.9, 126.2, 128.9, 129.0, 129.8, 131.2, 134.1, 139.5, 140.0, 141.5, 145.4, 154.5. MS (ESI) m/z 329 $[M + H]^+$.

6-(Naphthalen-1-yl)-11H-indolo[3,2-c]quinoline (**5e**). Petroleum ether/ethyl acetate (2:1) as eluent; white solid (85 mg, 62%), mp 298−300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.40 (d, J = 8.0 Hz, 1H), 6.79−6.83 (m, 1H), 7.23−7.32 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 7.46−7.51 (m, 1H), 7.66−7.79 (m, 5H), 8.06 (d, J = 8.4 Hz, 1H), 8.13−8.16 (m, 2H), 8.61 (dd, J = 1.2, 8.0 Hz, 1H), 13.00 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.3, 114.1, 116.9, 120.7, 120.9, 122.0, 122.5, 125.67, 125.74, 126.1, 126.3, 126.6, 126.8, 126.9, 128.8, 129.0, 129.1, 129.8, 131.4, 133.6, 138.5, 139.5, 140.9, 145.5, 155.0. HRMS (ESI) calcd for $C_{25}H_{17}N_2$ $[M + H]^+$ 345.1386, found 345.1389.

6-(Thiophen-2-yl)-11H-indolo[3,2-c]quinoline (**5f**). Petroleum ether/ethyl acetate (3:1) as eluent; white solid (80 mg, 66%), mp 245−246 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.21−7.25 (m, 1H), 7.32−7.35 (m, 1H), 7.46−7.50 (m, 1H), 7.65−7.69 (m, 1H), 7.72−7.76 (m, 2H), 7.81−7.85 (m, 2H), 8.09 (d, J = 8.4 Hz, 2H), 8.55−8.58 (m, 1H), 12.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.0, 112.5, 116.7, 120.8, 121.6, 121.9, 122.4, 126.0, 126.1, 127.9, 128.5, 128.8, 129.1, 129.5, 139.6, 141.8, 143.9, 145.1, 149.3. HRMS (ESI) calcd for $C_{19}H_{13}N_2S$ $[M + H]^+$ 301.0794, found 301.0798.

(E)-6-Styryl-11H-indolo[3,2-c]quinoline (**5g**). Petroleum ether/ethyl acetate (2:1) as eluent; white solid (77 mg, 60%), mp 206−208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.37−7.43 (m, 2H), 7.46−7.54 (m, 3H), 7.63 (t, J = 7.6 Hz, 1H), 7.71−7.76 (m, 2H), 7.92 (d, J = 7.6 Hz, 2H), 8.14−8.26 (m, 3H), 8.47−8.53 (m, 2H), 12.83 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.4, 113.1, 116.8, 121.3, 122.1, 122.4, 122.7, 125.6, 125.7, 125.8, 128.1, 129.0, 129.2, 129.4, 129.6, 135.5, 136.8, 139.5, 141.4, 145.5, 151.1. HRMS (ESI) calcd for $C_{23}H_{17}N_2$ $[M + H]^+$ 321.1386, found 321.1391.

6-Propyl-11H-indolo[3,2-c]quinoline (**5h**). Petroleum ether/ethyl acetate (1:1) as eluent; white solid (48 mg, 46%), mp 206−208 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.08 (t, J = 7.2 Hz, 3H), 1.87−1.96 (m, 2H), 3.36 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.67−7.74 (m, 2H), 8.05 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 8.49 (d, J = 8.0 Hz, 1H), 12.80

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(br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 14.5, 21.6, 39.4, 112.4, 112.8, 116.6, 121.2, 121.9, 122.2, 122.3, 125.4, 125.5, 128.6, 128.9, 139.3, 140.8, 144.9, 158.3. HRMS (ESI) calcd for $C_{18}H_{17}N_2$ $[M + H]^+$ 261.1386, found 261.1386.

*11H-Indolo[3,2-c]quinoline (**5i**).*[9a] Petroleum ether/ethyl acetate (1:1) as eluent; white solid (28 mg, 32%), mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.34 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.68−7.77 (m, 3H), 8.15 (d, J = 8.0 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.55 (d, J = 7.2 Hz, 1H), 9.62 (s, 1H), 12.85 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.4, 114.7, 117.5, 120.6, 121.1, 122.3, 122.7, 126.1, 126.3, 128.6, 129.7, 139.3, 140.4, 145.1, 145.5. MS (ESI) m/z 219 $[M + H]^+$.

*8-Chloro-6-phenyl-11H-indolo[3,2-c]quinoline (**5j**).* Petroleum ether/ethyl acetate (3:1) as eluent; white solid (87 mg, 66%); mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.37−7.42 (m, 2H), 7.61−7.63 (m, 3H), 7.66−7.70 (m, 2H), 7.73−7.79 (m, 3H), 8.11 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 7.6 Hz, 1H), 13.04 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.7, 113.9, 116.6, 120.6, 122.4, 123.4, 124.9, 125.6, 126.3, 128.9, 129.2, 129.3, 129.5, 129.8, 137.9, 140.8, 142.2, 145.6, 155.8. HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$ 329.0840, found 329.0840.

*2-Methoxy-6-phenyl-11H-indolo[3,2-c]quinoline (**5k**).* Petroleum ether/ethyl acetate (2:1) as eluent; white solid (98 mg, 76%), mp 249−252 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.99 (s, 3H), 7.08−7.12 (m, 1H), 7.37 (dd, J = 2.8, 9.2 Hz, 1H), 7.42 (t, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.56−7.62 (m, 3H), 7.71 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 8.00−8.04 (m, 2H), 12.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 56.0, 101.5, 112.3, 112.4, 117.3, 120.3, 120.5, 121.5, 122.1, 125.8, 128.8, 129.1, 129.3, 131.3, 139.5, 140.9, 141.1, 141.3, 153.4, 157.4. HRMS (ESI) calcd for $C_{22}H_{17}N_2O$ $[M + H]^+$ 325.1335, found 325.1323.

*6-(4-Chlorophenyl)-2-methoxy-11H-indolo[3,2-c]quinoline (**5l**).* Petroleum ether/ethyl acetate (3:1) as eluent; white solid (88 mg, 61%), mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.98 (s, 3H), 7.12−7.16 (m, 1H), 7.37 (dd, J = 2.8, 9.2 Hz, 1H), 7.41−7.45 (m, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.64−7.66 (m, 2H), 7.72 (d, J = 8.4 Hz, 1H), 7.82−7.84 (m, 2H), 7.99−8.03 (m, 2H), 12.77 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 56.0, 101.5, 112.2, 112.4, 117.4, 120.4, 120.7, 121.5, 121.9, 125.9, 128.9, 131.2, 131.3, 133.9, 139.5, 140.0, 140.9, 141.1, 152.0, 157.5. HRMS (ESI) calcd for $C_{22}H_{16}ClN_2O$ $[M + H]^+$ 359.0946, found 359.0935.

*2-Chloro-6-phenyl-11H-indolo[3,2-c]quinoline (**5m**).* Petroleum ether/ethyl acetate (3:1) as eluent; white solid (93 mg, 71%), mp > 300 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.13 (t, J = 7.2 Hz, 1H), 7.43−7.50 (m, 2H), 7.61−7.62 (m, 3H), 7.71−7.74 (m, 2H), 7.79−7.81 (m, 2H), 8.11 (d, J = 8.8 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H), 12.94 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.5, 113.0, 117.5, 120.9, 121.6, 121.8, 126.2, 128.9, 129.2, 129.3, 129.5, 130.2, 131.9, 139.5, 140.5, 140.8, 143.8, 156.3 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ $[M + H]^+$ 329.0840, found 329.0833.

*2-Chloro-6-(4-methoxyphenyl)-11H-indolo[3,2-c]quinoline (**5n**).* Petroleum ether/ethyl acetate (1:1) as eluent; white solid (72 mg, 50%), mp 230−232 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.88 (s, 3H), 7.14−7.18 (m, 3H), 7.43−7.47 (m, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.71−7.74 (m, 2H), 7.76−7.80 (m, 2H), 8.09 (d, J = 8.8 Hz, 1H), 8.65 (d, J = 2.4 Hz, 1H), 12.91 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.7, 112.5, 112.9, 114.2, 117.4, 120.9, 121.4, 121.7, 121.9, 126.2, 129.1, 130.0, 130.8, 131.7, 133.0, 139.5, 140.5, 143.7, 156.1, 160.4. HRMS (ESI) calcd for $C_{22}H_{16}ClN_2O$ $[M + H]^+$ 359.0946, found 359.0946.

*(E)-2-Chloro-6-styryl-11H-indolo[3,2-c]quinoline (**5o**).* Petroleum ether/ethyl acetate (2:1) as eluent; white solid (75 mg, 53%), mp 286−288 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.40−7.54 (m, 5H), 7.66−7.73 (m, 2H), 7.89 (d, J = 8.0 Hz, 2H), 8.07−8.14 (m, 3H), 8.43 (d, J = 8.4 Hz, 1H), 8.57 (s, 1H), 12.81 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 112.5, 113.5, 117.5, 121.48, 121.51, 121.8, 122.8, 125.3, 126.1, 128.1, 129.2, 129.36, 129.39, 129.7, 131.5, 135.9, 136.6, 139.5, 140.4, 143.7, 151.4. HRMS (ESI) calcd for $C_{23}H_{16}ClN_2$ $[M + H]^+$ 355.0997, found 355.0988.

Typical Procedure for the Synthesis of Compound 6. To a tube containing a solution of 2-(2-bromophenyl)-1*H*-indole **1a** (109 mg, 0.4 mmol) in DMSO (1.5 mL) were added K_2CO_3 (110 mg, 0.8 mmol), CuI (7.6 mg, 0.04 mmol), L-proline (9.2 mg, 0.08 mmol), and 26% aqueous ammonia (0.4 mL) under a nitrogen atmosphere. Then, the tube was sealed, and the mixture was stirred at 100 °C for 1 h. After being cooled to room temperature, the reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (8:1), to afford **6** (50 mg) as a brown solid in 60% yield (mp: 146−148 °C): ^{1}H NMR ($CDCl_3$, 400 MHz)[16b] δ 4.12 (br s, 2H), 6.75 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 7.15−7.25 (m, 3H), 7.42 (t, J = 7.6 Hz, 2H), 7.67 (d, J = 8.0 Hz, 1H), 8.49 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 101.6, 110.9, 116.6, 118.8, 119.1, 120.2, 120.5, 122.2, 128.9, 129.1, 129.3, 135.9, 136.2, 144.1. MS (ESI) m/z 209 $[M + H]^+$.

Typical Procedure for the Selective Synthesis of Compound 5a from 3a. To a solution of compound **3a** (89 mg, 0.3 mmol) in DMSO (1 mL) were added CuI (5.7 mg, 0.03 mmol) and HCl (0.04 mL, 0.5 M) under air, and then the mixture was stirred at 120 °C for 8 h. Next, brine and $CHCl_3$ were added into the reaction mixture. After extraction, the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (2:1), to afford **5a** (83 mg) as a white solid in 94% yield.

Typical Procedure for the Synthesis of Intermediate 7 from 3a. To a tube containing a solution of compound **3a** (89 mg, 0.3 mmol) in DMSO (1 mL) was added HCl (0.04 mL, 0.5 M) under a nitrogen atmosphere. Then, the tube was sealed, and the mixture was stirred at 120 °C for 1 h. Next, brine and $CHCl_3$ were added into the reaction mixture. After extraction, the combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by *flash chromatography* on silica gel, eluting with petroleum ether/dichloromethane (1:1), to afford **7** (75.3 mg) as a light yellow solid in 85% yield (mp: 209−210 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.35 (s, 1H), 6.23 (s, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.74 (dt, J = 0.8, 7.6 Hz, 1H), 6.92−6.98 (m, 2H), 7.04−7.08 (m, 1H), 7.10−7.15 (m, 1H), 7.27−7.32 (m, 2H), 7.33−7.37 (m, 3H), 7.49−7.52 (m, 2H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 57.7, 109.5, 110.8, 113.1, 113.6, 117.3, 118.8, 120.0, 120.1, 122.2, 126.1, 127.4, 127.9, 128.70, 128.73, 130.6, 137.2, 143.2, 144.8. HRMS (ESI) calcd for $C_{21}H_{17}N_2$ $[M + H]^+$ 297.1386, found 297.1367.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02076.

Table S1 and ^{1}H and ^{13}C NMR spectra of compounds **4a−4x**, **3a**, **5a−5o**, **6**, and **7** (PDF)

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Notes

The authors declare no competing financial interest.

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