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A Facile Copper-Catalyzed One-Pot Domino Synthesis of 5,12-Dihydroindolo[2,1-*b*]quinazolines

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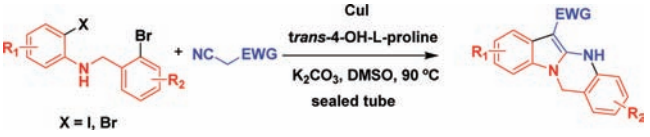
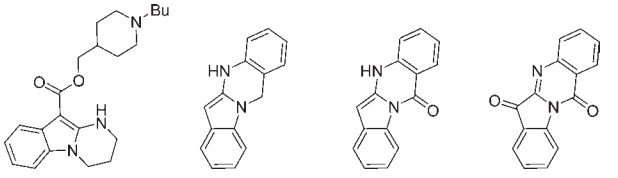
ABSTRACT



A domino synthesis of 5,12-dihydroindolo[2,1-*b*]quinazoline derivatives via copper-catalyzed Ullmann-type intermolecular C−C and intramolecular C−N couplings is reported. Good yields of various 5,12-dihydroindolo[2,1-*b*]quinazoline derivatives were obtained. Reaction scopes, limitations, and the reaction mechanism are discussed.

The 1,2,3,4-tetrahydropyrimido[1,2-*a*]indole and indolo[2,1-*b*]quinazoline skeletons exist in the core structures of several biologically active compounds and natural products such as 5-HT_4 receptor antagonists **A**,[1] antimicrobial active compounds **B**,[2] antimalarial candidates **C**,[3] and anticancer agent tryptanthrin, respectively.[4]



A B C Tryptanthrin

The known methods for the synthesis of 1,2,3,4-tetrahydropyrimido[1,2-*a*]indole and indolo[2,1-*b*]quinazoline have suffered from limitations such as limited availability of starting materials, harsh reaction conditions, and poor overall yield of the multistep synthesis.[5,6] It is highly desirable to develop an efficient synthetic method and expand the structure diversity for current medicinal chemistry needs.

Over the past years, copper-catalyzed coupling reactions in C−C, C−heteroatom bond formation have achieved remarkable progress.[7,8] Many types of heterocycles have

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(1) (a) Gaster, L. M.; Wyman, P. A. WO93/018036, 1993. (b) Gaster, L. M.; Wyman, P. A. US5852014, 1998.

(2) Grandolini, G.; Ambrogi, V.; Perioli, L.; Giannangeli, M.; Jovicevic, L.; Rossi, V. *Farmaco*. **1997**, *52*, 679.

(3) Bhattacharjee, A. K.; Hartell, M. G.; Nichols, D. A.; Hicks, R. P.; Stanton, B.; Van Hamont, J. E.; Milhous, W. K. *Eur. J. Med. Chem.* **2004**, *39*, 59.

(4) (a) Camargo, L. T. F. M.; Sena, M. M.; Camargo, A. J. *SAR QSAR Environ. Res.* **2009**, *20*, 537. (b) Jao, C.-W.; Lin, W.-C.; Wu, Y.-T.; Wu, P.-L. *J. Nat. Prod.* **2008**, *71*, 1275. (c) Sharma, V. M.; Prasanna, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2303.

(5) (a) Portnov, Y. N.; Golubeva, G. A.; Kost, A. N. *Khim. Geterotsikl. Soedin.* **1972**, 61. (b) Portnov, Y. N.; Golubeva, G. A.; Kost, A. N.; Volkov, V. S. *Khim. Geterotsikl. Soedin.* **1973**, 647. (c) Coppola, E. M.; Hardtmann, G. E. *J. Heterocycl. Chem.* **1979**, *16*, 769.

(6) (a) De la Mora, M. A.; Cuevas, E.; Muchowski, J. M. *Tetrahedron Lett.* **2001**, *42*, 5351. (b) Sutherland, J. K. *Chem. Commun.* **1997**, 325. (c) Yang, L.-J.; Yan, S.-J.; Chen, W.; Lin, J. *Synthesis* **2010**, 3536. (d) Xia, Z.; Wang, K.; Zheng, J.; Ma, Z.; Jiang, Z.; Wang, X.; Lv, X. *Org. Biomol. Chem.* **2012**, *10*, 1602.

(7) For recent reviews on copper-catalyzed Ullmann-type couplings, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (e) Liu., Y.; Wan, J.-P. *Org. Biomol. Chem.* **2011**, *9*, 6873. (f) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13. (g) Rao, H.; Fu, H. *Synlett* **2011**, *6*, 745. (h) Das, P.; Sharma, D.; Kumar, M.; Singh, B. *Curr. Org. Chem.* **2010**, *14*, 754. (i) Evano, G.; Toumi, M.; Coste, A. *Chem. Commun.* **2009**, *45*, 4166. (j) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Org. Biomol. Chem.* **2011**, *9*, 641.

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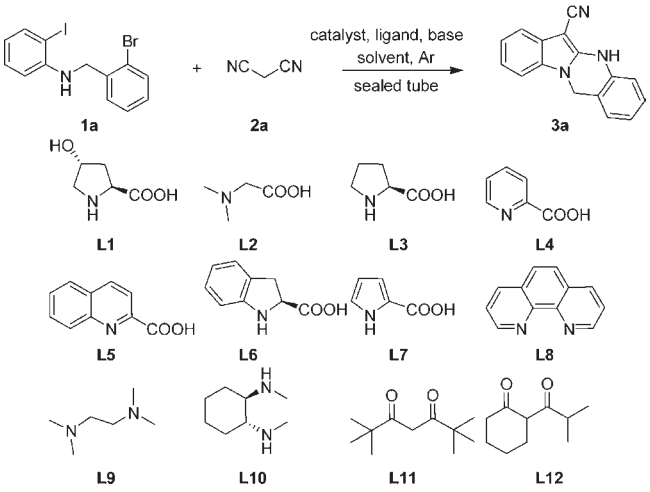
been constructed via copper-catalyzed domino processes; attractively, some tricyclic and tetracyclic systems, e.g. imidazoindolone, pyrrolo[1,2-*a*]quinoxaline, pyrrolo[2,1-*a*]-isoquinoline, pyrido[1,2-*a*]benzimidazole, and 4-oxo-indeno-[1,2-*b*]pyrroles, have also been constructed.[9,10] We are interested in a copper-catalyzed domino process for efficient synthesis of indole fused heterocycles.

For various fused N-heterocycles prepared through Ullmann-type domino coupling precesses,[9] an activating group (carbonyl or its equivalent) was generally employed to speed-up the coupling process.[7c,g,9a−9l] Very recently, Ma's group reported an efficient cascade synthesis of phenothiazine from a nonactivated system.[9m] However, two attempted syntheses for 2-amino indole from a non-activated system failed.[8g,9l] Herein we report a copper-catalyzed domino synthesis of 5,12-dihydroindolo[2,1-*b*]-quinazoline derivatives from nonactivated starting material.

For the model reaction, *N*-(2-bromobenzyl)-2-iodoaniline (**1a**) and malononitrile (**2a**) were adopted, and the reaction was screened by using 10 mol % CuI, 20 mol % ligand, and 3.0 equiv of K_2CO_3 in DMSO at 90 °C under argon. From various ligands (**L1**−**L12**, Table 1) screened, *trans*-4-OH-L-proline (**L1**) which was reported to promote C−C coupling at −45 °C[8a] was identified to be the optimum ligand (entries 1−12, Table 1). A diminished yield was obtained at 70 °C (entry 13, Table 1). Without ligand, the yield was poor (entry 14, Table 1). A low catalyst loading was not effective either (entry 15, Table 1). Other copper sources, e.g. Cu, CuBr, CuCl, and Cu_2O, were found to be less effective (entries 16−19, Table 1).

Table 1. Optimization of the Coupling of *N*-(2-Bromobenzyl)-2-iodoaniline with Malononitrile[a]



entry	catalyst	ligand	base	solvent	yield (%)[b]
1	**CuI**	**L1**	**K_2CO_3**	**DMSO**	**71**
2	CuI	**L2**	K_2CO_3	DMSO	41
3	CuI	**L3**	K_2CO_3	DMSO	58
4	CuI	**L4**	K_2CO_3	DMSO	70
5	CuI	**L5**	K_2CO_3	DMSO	52
6	CuI	**L6**	K_2CO_3	DMSO	32
7	CuI	**L7**	K_2CO_3	DMSO	40
8	CuI	**L8**	K_2CO_3	DMSO	42
9	CuI	**L9**	K_2CO_3	DMSO	24
10	CuI	**L10**	K_2CO_3	DMSO	18
11	CuI	**L11**	K_2CO_3	DMSO	49
12	CuI	**L12**	K_2CO_3	DMSO	23
13	CuI	**L1**	K_2CO_3	DMSO	51[c]
14	CuI	–	K2CO3	DMSO	30
15	CuI	**L1**	K_2CO_3	DMSO	20[d]
16	Cu	**L1**	K_2CO_3	DMSO	37
17	CuBr	**L1**	K_2CO_3	DMSO	66
18	CuCl	**L1**	K_2CO_3	DMSO	61
19	Cu_2O	**L1**	K_2CO_3	DMSO	67
20	CuI	**L1**	Cs_2CO_3	DMSO	18
21	CuI	**L1**	K_3PO_4	DMSO	62
22	CuI	**L1**	DBU	DMSO	17
23	CuI	**L1**	K_2CO_3	DMF	22
24	CuI	**L1**	K_2CO_3	DMAc	18
25	CuI	**L1**	K_2CO_3	NMP	0
26	CuI	**L1**	K_2CO_3	Dioxane	0
27	CuI	**L1**	K_2CO_3	DME	trace

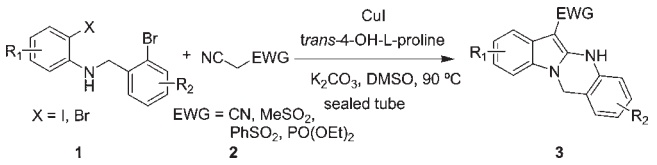
[a] Reaction conditions: *N*-(2-bromobenzyl)-2-iodoaniline (1 mmol), malononitrile (1.2 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (3 mmol), solvent (2 mL), 90 °C, 16 h, under argon in sealed tube. [b] Isolated yield. [c] 70 °C. [d] CuI (0.02 mmol), **L1** (0.04 mmol).

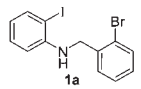
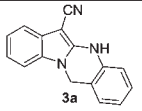
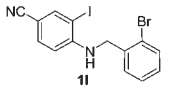
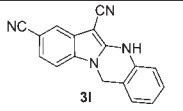
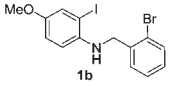
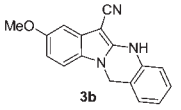
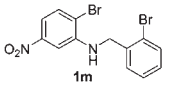
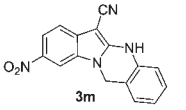
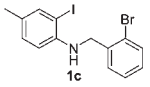
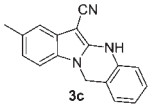
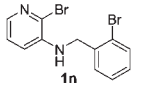
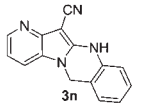
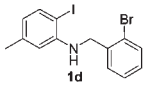
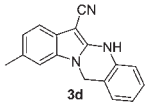
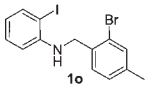
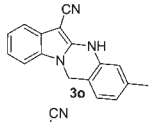
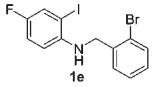
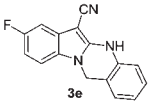
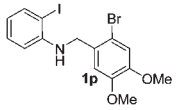
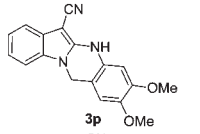
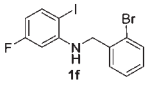
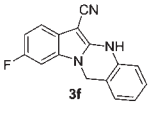
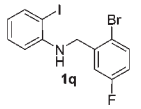
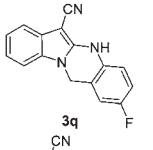
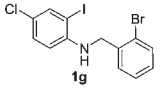
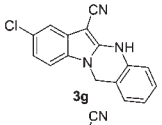
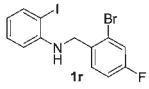
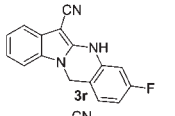
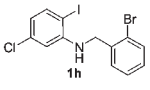
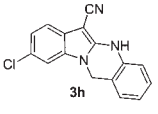
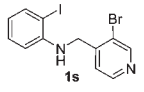
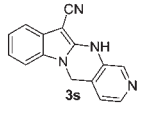
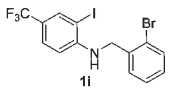
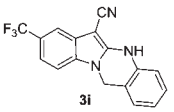
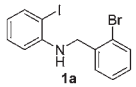
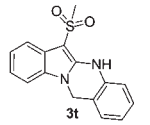
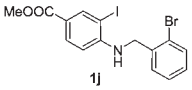
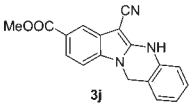
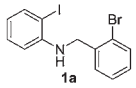
(8) For copper-catalyzed Ullman-type C−C and C−N bond formation: (a) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050. (b) Yip, S. F.; Cheung, H. Y.; Zhou, Z.; Kwong, F. Y. *Org. Lett.* **2007**, *9*, 3469. (c) Xie, X.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 4693. (d) Mino, T.; Yagishita, F.; Shibuya, M.; Kajiwara, K.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2009**, *15*, 2457. (e) Jiang, Y.; Wu, N.; Wu, H.; He, M. *Synlett* **2005**, *18*, 2731. (f) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606. (g) Yang, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2010**, *352*, 1033. (h) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469. (i) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625. (j) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761. (k) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742. (l) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (m) Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5167. (n) Wang, D.; Ding, K. *Chem. Commun.* **2009**, *45*, 1891. (o) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (p) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609. (q) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (r) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (s) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. (t) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379. (u) Chen, D.; Wang, Z.; Bao, W. *J. Org. Chem.* **2010**, *75*, 5768.

(9) Recent examples for N-heterocycles construction via copper-catalyzed domino process: (a) Diao, X.; Xu, L.; Zhu, W.; Jiang, Y.; Wang, H.; Guo, Y.; Ma, D. *Org. Lett.* **2011**, *13*, 6422. (b) Xu, H.; Fu, H. *Chem.—Eur. J.* **2012**, *18*, 1180. (c) Liu, T.; Wang, R.; Yang, H.; Fu, H. *Chem.—Eur. J.* **2011**, *17*, 6765. (d) Xu, S.; Lu, J.; Fu, H. *Chem. Commun.* **2011**, *47*, 5596. (e) Lu, J.; Gong, X.; Yang, H.; Fu, H. *Chem. Commun.* **2010**, *46*, 4172. (f) Cai, Q.; Li, Z.; Wei, J.; Fu, L.; Ha, C.; Pei, D.; Ding, K. *Org. Lett.* **2010**, *12*, 1500. (g) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274. (h) Lu, J.; Fu, H. *J. Org. Chem.* **2011**, *76*, 4600. (i) Vaillard, V. A.; Rossi, R. A.; Martin, S. E. *Org. Biomol. Chem.* **2011**, *9*, 4927. (j) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598. (k) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (l) Kobayashi, K.; Komatsu, T.; Yokoi, Y.; Konishi, H. *Synthesis* **2011**, 764. (m) Ma, D.; Geng, Q.; Zhang, H.; Jiang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 1291.

(10) Recent examples for copper-catalyzed polycyclic systems construction: (a) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1972. (b) Cai, Q.; Zhou, F.; Xu, T.; Fu, L.; Ding, K. *Org. Lett.* **2011**, *13*, 340. (c) Barange, D. K.; Tu, Y.-C.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Adv. Synth. Catal.* **2011**, *353*, 41. (d) Wu, Z.; Huang, Q.; Zhou, X.; Yu, L.; Li, Z.; Wu, D. *Eur. J. Org. Chem.* **2011**, 5242. (e) Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. *Org. Lett.* **2010**, *12*, 3034. (f) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138. (g) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

Table 2. Copper-Catalyzed Domino Synthesis of 5,12-Dihydroindolo[2,1-*b*]quinazoline Derivatives[a]



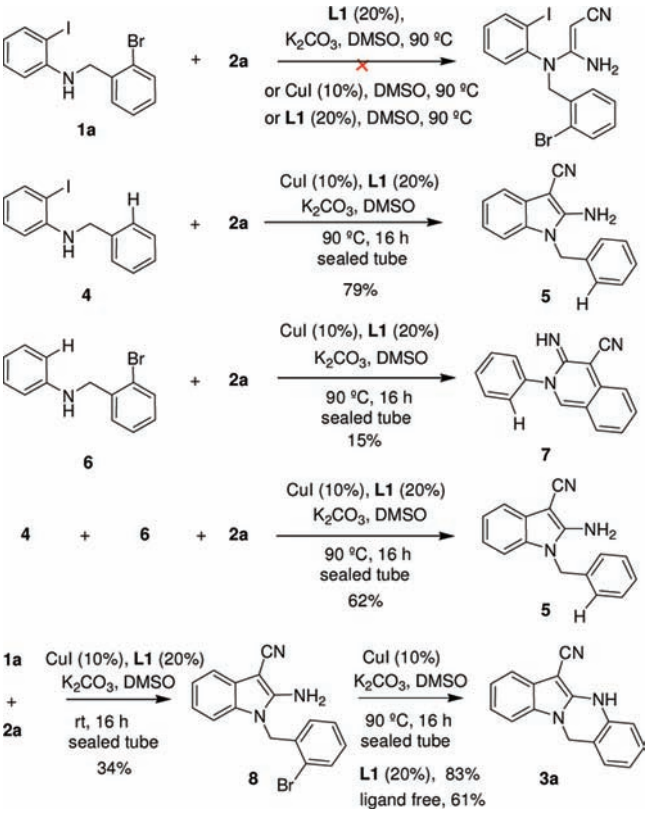
entry	substrate **1**	product	yield (%)[b]	entry	substrate **1**	product	yield (%)[b]
1	 **1a**	 **3a**	71	12	 **1l**	 **3l**	75
2	 **1b**	 **3b**	72	13	 **1m**	 **3m**	67
3	 **1c**	 **3c**	80	14	 **1n**	 **3n**	44
4	 **1d**	 **3d**	64	15	 **1o**	 **3o**	62
5	 **1e**	 **3e**	52	16	 **1p**	 **3p**	62
6	 **1f**	 **3f**	63	17	 **1q**	 **3q**	73
7	 **1g**	 **3g**	63	18	 **1r**	 **3r**	66
8	 **1h**	 **3h**	61	19	 **1s**	 **3s**	52
9	 **1i**	 **3i**	62	20	 **1a**	 **3t**	70[c]
10	 **1j**	 **3j**	76	21	 **1a**	**3u**	51[d]
11	**1k**	**3k**	75	22	**1a**	**3v**	23[e]

[a] Reaction conditions: **1** (1 mmol), malononitrile (1.2 mmol), CuI (0.1 mmol), *trans*-4-OH-L-Proline (0.2 mmol), K_2CO_3 (3 mmol), DMSO (2 mL), 90 °C, 16 h, under argon, sealed tube. [b] Isolated yield. [c] 2-(Methylsulfonyl)acetonitrile. [d] 2-(Phenylsulfonyl)acetonitrile. [e] Diethyl cyanomethylphosphonate.

Among the base selected, K_2CO_3 was the best (compare entry 1 with entries 20−22, Table 1). For solvent selection, DMSO was found to be much better than DMF and DMAc (entries 23 and 24, Table 1). NMP, 1,4-dioxane, or DME was not suitable (entries 25−27, Table 1).

The reaction scope was then examined under the optimized conditions, and the results are summarized in Table 2.

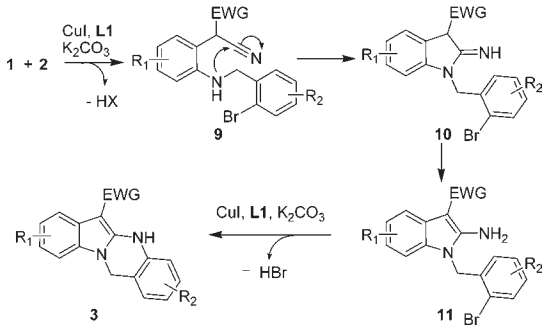
Scheme 1. Reaction Passway Identification



For *ortho*-iodo aniline substrates, electron-donating *para*-methoxy and methyl groups afforded good isolated yields of the desired products (entries 2 and 3, Table 2); however, *meta*-methyl substitution provided a diminished yield (entry 4, Table 2). The substitution of fluoro, chloro, or trifluoromethyl only resulted in moderate yields (entries 5–9, Table 2). In comparison, an electron-withdrawing ester group and cyano substituent led to good production of the desired compounds (entries 10–12, Table 2). For a strong electron-withdrawing counterpart, even *ortho*-bromo aniline is active enough for the cascade reaction. While nitro substitution resulted in a good yield of product, the pyridine system only gave an acceptable yield of the desired compound (entries 13 and 14, Table 2). For the substituents at the *ortho*-bromide benzyl moiety, it is noteworthy that both electron-withdrawing and -donating groups led to good yields of the desired products (entries 15–18, Table 2). However, a pyridine species gave a lower yield (entry 19, Table 2). Furthermore, other types of acetonitrile substituted with electron-withdrawing groups of $-CO_2Me$, $-SO_2Me$, $-SO_2Ph$, and $-PO(OEt)_2$ were also investigated in such a copper-catalyzed domino process (entries 20–22, Table 2). While $-SO_2Me$ provided a good yield of the product, $-SO_2Ph$ and $-PO(OEt)_2$ substitutions led to less satisfied results. Unfortunately, $-CO_2Me$ failed to afford the target product under the same conditions (not shown in Table 2).

For mechanistic studies, control experiments were carried out under standard conditions as shown in Scheme 1.

Scheme 2. Proposed Reaction Mechanism



Direct condensation of amine (**1a**) to **2a** did not seem to happen under various conditions. Reaction of *N*-benzyl-2-iodoaniline (**4**) with **2a** produced 2-amino-1-benzyl-1*H*-indole-3-carbonitrile (**5**) in 79% yield. Meanwhile, reaction of *N*-(2-bromobenzyl)aniline (**6**) with **2a** presumably generated product **7** in 15% yield. The combination of *N*-benzyl-2-iodoaniline (**4**) with *N*-(2-bromobenzyl)aniline (**6**) and **2a** (**4:6:2a** = 1:1:1.2) gave product **5** as the only isolated product in 62% yield. These results suggest that insertion of Cu into the C–I bond plays a major role in the reaction. Reaction of *N*-(2-bromobenzyl)-2-iodoaniline (**1a**) and **2a** at room temperature for 16 h allowed us to isolate the corresponding intermediate **8** in 34% yield and recover 60% of **1a** via flash chromatography, which clearly suggests that the reaction initially takes place through Cu insertion into the C–I bond. Intermediate **8** was heated to 90 °C for 16 h under standard conditions, targeting product **3a**, which was obtained in 83% yield after purification. Based on the above discussions, a reaction mechanism is proposed as shown in Scheme 2. Copper-catalyzed Ullmann-type intermolecular C–C coupling produces **9**, and then base-promoted intramolecular nucleophilic attack generates **10** which tautomerizes to give **11**. Copper-catalyzed intramolecular C–N coupling provides the target products **3**.

In summary, we have developed a facile and efficient one-pot domino synthesis of 5,12-dihydroindolo[2,1-*b*]quinazoline derivatives via copper-catalyzed Ullmann-type intermolecular C–C and intramolecular C–N couplings under mild conditions. The protocol displays a wide functional group compatibility and provides economical and practical advantages over the previous methods.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.