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CuI/I_2-Promoted Electrophilic Tandem Cyclization of 2-Ethynylbenzaldehydes with *ortho*-Benzenediamines: Synthesis of Iodoisoquinoline-Fused Benzimidazoles

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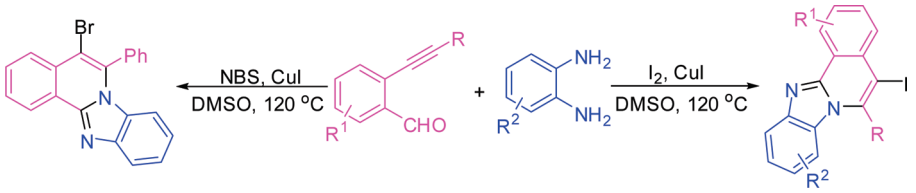

An efficient tandem route to the synthesis of iodoisoquinoline-fused benzimidazole derivatives including an iodocyclization strategy has been developed. In the presence of CuI, a variety of 2-ethynylbenzaldehydes underwent the tandem reaction with benzenediamines and iodine to afford the corresponding iodoisoquinoline-fused benzimidazoles in moderate to good yields.

Introduction

Among the multitude of heterocyclic compounds, isoquinoline-fused benzimidazoles have attracted considerable interest due to their outstanding biological activities, such as anti-HIV-1, anticancer, antimicrobial, and antifungal properties.[1] The importance of isoquinoline-fused benzimidazoles has resulted in the development of two synthetic routes for their preparation: one involves introduction of substituents onto a preexisting benzimidazole ring[2] and the other is the tandem reactions of benzenediamines with 2-ethynylbenzaldehyde[3] or with pyran-2-one derivatives.[4] However, a significant problem for drug discovery is that modification of the benzimidazoisoquinolines prepared by these routes is difficult.

Iodocyclization technology[5−7] has undoubtedly become one of the most powerful methods for the synthesis of iodo-containing cyclic compounds which can be modified easily by introducing diverse functional groups through the cross-coupling reactions. 2-Ethynylbenzaldehyde, an intriguing substrate, has been applied to the synthesis of diverse polycyclic compounds[8] and is a good electrophilic cyclization species for iodocyclization.[7] As a continuing interest in expanding the synthetic application of 2-ethynylbenzaldehydes,[9] we report here an efficient protocol for the synthesis of iodoisoquinoline-fused benzimidazoles by copper-promoted tandem cyclization of 2-ethynylbenzaldehydes with *o*-benzenediamines and iodine (Scheme 1).

Results and Discussion

The reaction between *o*-benzenediamine (**1a**) and 2-(phenylethynyl)benzaldehyde (**2a**) was investigated to optimize the reaction conditions (Table 1). Initially, the reaction between

(1) (a) Rida, S. M.; El-Hawash, S. A. M.; Fahmy, H. T. Y.; Hazzaa, A. A.; El-Meligy, M. M. M. *Arch. Pharmacal. Res.* **2006**, *29*, 826. (b) Deady, L. W.; Rodemann, T.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *Anti-Cancer Drug Des.* **2001**, *15*, 339. (c) Pandey, V. K.; Shukla, A. *Indian J. Chem., Sect B* **1999**, *38B*, 1381. (d) Lu, Z. X.; Quazi, N. H.; Deady, L. W.; Polya, G. M. *Biol. Chem. Hoppe-Seyler* **1996**, *377*, 373. (e) Weinkauf, R. L.; Chen, A. Y.; Yu, C.; Liu, L.; Barrows, L.; LaVoie, E. J. *Bioorg. Med. Chem.* **1994**, *2*, 781.

(2) (a) Pratap, R.; Ram, V. J. *Tetrahedron Lett.* **2007**, *48*, 5039. (b) Kiselyov, A. S. *Tetrahedron Lett.* **2006**, *47*, 2941. (c) Nath, M.; Srivastava, P.; Goel, A.; Ram, V. J. *Eur. J. Org. Chem.* **1998**, 2083.

(3) (a) Dyker, G.; Stirner, W.; Henkel, G. *Eur. J. Org. Chem.* **2000**, *8*, 1433. (b) Okamoto, N.; Sakurai, K.; Ishikur, M.; Takeda, K.; Yanada, R. *Tetrahedron Lett.* **2009**, *50*, 4167. (c) Ohta, Y.; Kubota, Y.; Watabe, T.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 6299.

(4) Hirano, K.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *Chem. Lett.* **2001**, *30*, 1262.

(5) (a) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814. (b) Togo, H.; Iida, S. *Synlett* **2006**, *14*, 2159. (c) da Silva, F. M.; Jones, J., Jr.; de Mattos, M. C. S. *Curr. Org. Synth.* **2005**, *2*, 393. (d) Kitagawa, O.; Inoue, T.; Taguchi, T. *Rev. Heteroatom Chem.* **1996**, *15*, 243. (e) Larock, R. C. *Acetylene Chem.* **2005**, 51. (f) Luo, P.; Tang, R.; Zhong, P.; Li, J. *Chin. J. Org. Chem.* **2009**, *29*, 1924.

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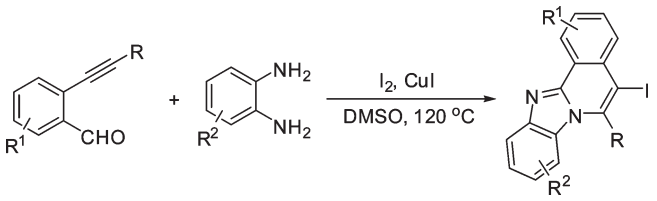
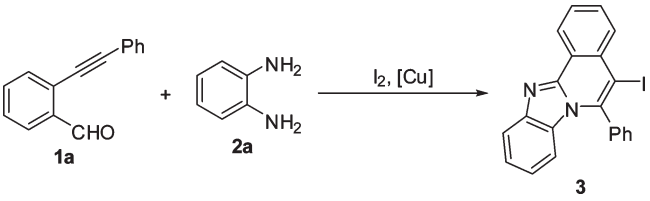
SCHEME 1



aldehyde **1a** and diamine **2a** was tested in the presence of NIS (*N*-iodosuccimide) in DMSO at 80 °C for 20 h; however, only a trace amount of the target product **3** was observed (entry 1). To our delight, the yield was enhanced to 51% when CuI (10 mol %) was added (entry 2). It is noteworthy that the structure of **3** was unambiguously confirmed by X-ray single-crystal diffraction analysis.[10] The effect of the reaction temperature was also examined, and higher temperatures were found to be more effective (entries 2−4). For example, the reaction at 120 °C gave the target product **3** in 60% yield (entry 4). We disclosed that the yield was lowered at a loading of 2 equiv NIS (entry 5). Subsequently, a number of solvents, such as toluene, CH_2ClCH_2Cl, CH_3CN, dioxane, DMF, NMP, and DMA, were investigated in the presence of 10 mol % of CuI and 1 equiv of NIS, but they were inferior to DMSO to some extent in terms of yields (entries 6−12). Two other electrophilic reagents, ICl and I_2, were employed to screen the reaction (entries 13 and 14). The results showed that both ICl and I_2 were also efficient for the reaction catalyzed by CuI at 120 °C in DMSO, giving the product **3** in 58% and 55% yields, respectively. Gratifyingly, the higher yield was obtained when the amount of I_2 was increased: up to 74% yield using 2 equiv of I_2 and 75% yield at 2.5 equiv of I_2 (entries 15−17). Finally, a series of other copper catalysts, such as $Cu(OTf)_2$, $CuCl_2$, CuBr, and Cu_2O, were evaluated (entries 18−21). These copper reagents, when combined with I_2 (2 equiv) and DMSO at 120 °C, were less efficient than CuI on the basis of yields. It is noted that identical results are obtained at 20 mol % CuI (entry 24), and the yield is decreased to 67% at 5 mol % of CuI (entry 22). To our surprise, the reaction could be conducted without Cu catalysts although the yield of the desired product **3** was decreased to some extent (53% yield, entry 23). Notably, the reaction under either air or argon atmosphere afforded the same results (entries 16 and 25).

TABLE 1. Screening Conditions[a]



entry	[Cu] (mol %)	[I] (equiv)	solvent	*T* (°C)	yield (%)
1		NIS (1)	DMSO	80	trace
2	CuI (10)	NIS (1)	DMSO	80	51
3	CuI (10)	NIS (1)	DMSO	100	53
4	CuI (10)	NIS (1)	DMSO	120	60
5	CuI (10)	NIS (2)	DMSO	120	48
6	CuI (10)	NIS (1)	toluene	120	31
7	CuI (10)	NIS (1)	CH_2ClCH_2Cl	120	10
8	CuI (10)	NIS (1)	CH_3CN	120	32
9	CuI (10)	NIS (1)	dioxane	120	47
10	CuI (10)	NIS (1)	DMF	120	50
11	CuI (10)	NIS (1)	NMP	120	56
12	CuI (10)	NIS (1)	DMA	120	55
13	CuI (10)	ICl (1)	DMSO	120	58
14	CuI (10)	I_2 (1)	DMSO	120	55
15	CuI (10)	I_2 (1.5)	DMSO	120	65
16	CuI (10)	I_2 (2)	DMSO	120	74
17	CuI (10)	I_2 (2.5)	DMSO	120	75
18	$Cu(OTf)_2$ (10)	I_2 (2)	DMSO	120	55
19	$CuCl_2$ (10)	I_2 (2)	DMSO	120	60
20	CuBr (10)	I_2 (2)	DMSO	120	69
21	Cu_2O (10)	I_2 (2)	DMSO	120	66
22	CuI (5)	I_2 (2)	DMSO	120	67
23		I_2 (2)	DMSO	120	53
24	CuI (20)	I_2 (2)	DMSO	120	70
25[b]	CuI (10)	I_2 (2)	DMSO	120	74

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), [I], and [Cu] in solvent (2 mL) for 24 h under air atmosphere. [b]Under argon atmosphere.

As shown in Table 2, the scope of both 2-ethynylbenzaldehydes **1** and diamines **2** partners for the tandem cyclization reaction was explored under the standard reaction conditions. We initially investigated the reactions of diamines **2b**−**e** with 2-ethynylbenzaldehyde (**1a**), CuI, and I_2 (entries 1−4). The results demonstrated that electron-donating groups diamines were suitable substrates (entries 1 and 2), but diamines with electron-withdrawing groups displayed

(6) For selected recent papers on the electrophilic halogenocyclizations of alkynes, see: (a) Stein, A. L.; da Rocha, J.; Menezes, P. He.; Zeni, G. *Eur. J. Org. Chem.* **2010**, 705. (b) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. *Chem. Commun.* **2010**, 4064. (c) Schumacher, R. F.; Rosario, A. R.; Souza, A. C. G.; Menezes, P. H.; Zeni, G. *Org. Lett.* **2010**, *12*, 1952. (d) Huo, Z.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266. (e) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177. (f) Chen, Y.; Cho, C.-H.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802. (g) Manarin, F.; Roehrs, J. A.; Gay, R. M.; Brandao, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153. (h) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141. (i) Ding, Q.; Wang, Z.; Wu, J. *J. Org. Chem.* **2009**, *74*, 921. (j) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (k) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720. (l) Li, P.; Chai, Z.; Zhao, G.; Zhu, S.-Z. *Synlett* **2008**, 2547. (j) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850. (m) Wen, S.-G.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2008**, *73*, 4342. (n) Xie, Y.-X.; Liu, X.-Y.; Wu, L.-Y.; Han, Y.; Zhao, L.-B.; Fan, M.-J.; Liang, Y.-M. *Eur. J. Org. Chem.* **2008**, 1013. (o) Huang, X.; Fu, W.; Miao, M. *Tetrahedron Lett.* **2008**, *49*, 2359. (p) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662. (q) Du, H.-A.; Zhang, X.-G.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 7844. (r) Jiang, T.-S.; Zhang, X.-G.; Li, J.-H. *Synthesis* **2009**, 3029. (s) Crone, B.; Kirsch, S. F.; Umland, K.-D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4661. For special papers, see: (t) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (u) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121. (v) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (w) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140. (x) Barluenga, J.; Palomas, D.; Rubio, E.; Gonzalez, J. M. *Org. Lett.* **2007**, *9*, 2823 and references cited therein. (y) Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 897.

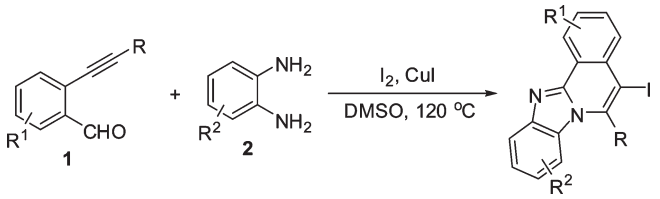
(7) For special papers, see: (a) Barluenga, J; V1zquez-Villa, H.; Merino, I.; Ballesteros, A.; Gonz1lez, J. M. *Chem.—Eur. J.* **2006**, *12*, 5790. (b) Yue, D. W.; Della Cá, N.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381. (c) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121. (d) Yue, D. W.; Della Cà, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.

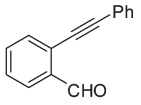
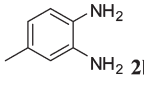
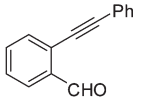
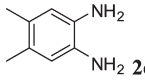
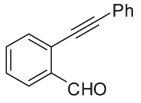
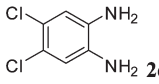
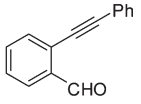
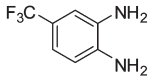
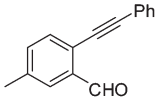
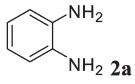
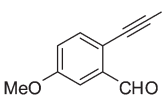
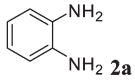
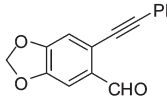
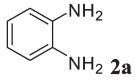
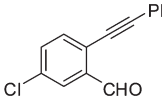
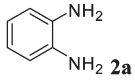
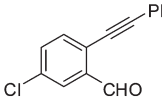
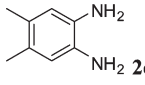
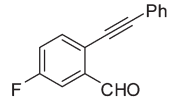
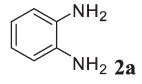
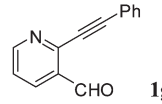
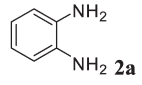
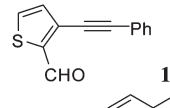
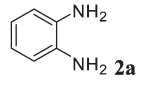
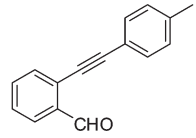
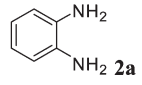
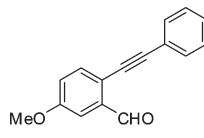
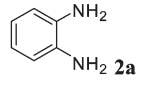
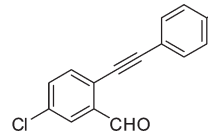
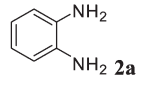
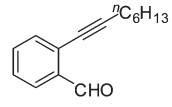
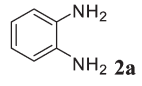
(8) For selected papers, see: (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (c) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504. (d) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (e) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399.

(9) (a) Tang, R.-Y.; Li, J.-H. *Chem.—Eur. J.* **2010**, *16*, 4733. (b) Zhao, X.; Zhang, X.-G.; Tang, R.-Y.; Deng, C.-L.; Li, J.-H. *Eur. J. Org. Chem.* **2010**, 4211.

(10) See the detailed data in the Supporting Information.

TABLE 2. CuI-Catalyzed Tandem Iodocyclization of 2-Alkynylbenzaldehydes (1) with Diamines (2) and Iodine[a]



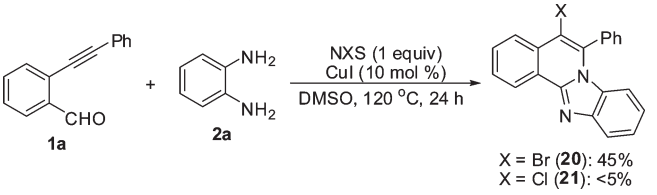
Entry	Substrate 1	Diamine 2	Yield (%)
1[b]	 1a	 2b	62 (**4**)
2	 1a	 2c	64 (**5**)
3	 1a	 2d	56 (**6**)
4[c]	 1a	 2e	35 (**7**)
5	 1b	 2a	71 (**8**)
6	 1c	 2a	68 (**9**)
7	 1d	 2a	65 (**10**)
8	 1e	 2a	72 (**11**)
9	 1e	 2c	48 (**12**)
10	 1f	 2a	70 (**13**)
11	 1g	 2a	35 (**14**)
12	 1h	 2a	57 (**15**)
13	 1i	 2a	63 (**16**)
14	 1j	 2a	63 (**17**)
15	 1k	 2a	56 (**18**)
16	 1l	 2a	58 (**19**)

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), I_2 (2 equiv), and CuI (10 mol %) in DMSO (2 mL) at 120 °C for 24 h under air atmosphere. [b]5-Me/6-Me = 1.3:1. [c]Interestingly, only an isomer was isolated.

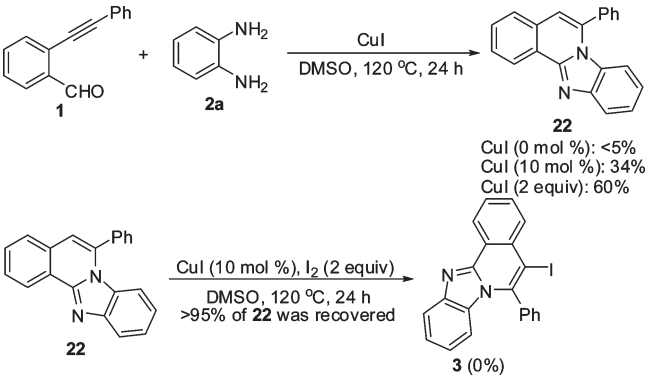
less activity in terms of yields (entries 3 and 4). While 4-methylbenzene-1,2-diamine (**2b**) reacted with 2-ethynylbenzaldehyde (**1a**), CuI, and I_2 to afford the target product **4** in 62% yield (entry 1), CF_3-substituted diamine **2e** gave a low yield under the same conditions (entry 4). Notably, both diamines **2b** and **2e** provided two regioisomers. Subsequently, the reaction between various 2-ethynylbenzaldehydes **1** and *o*-benzenediamines **2** were examined in the presence of I_2 and CuI (entries 5−16). We were pleased to find that several functional groups, such as Me, MeO, OCH_2O, Cl, and F groups, were tolerated (entries 5−10). Substrate **1e** bearing a chloro group, for instance, was reacted with diamines **2a** or **2c**, I_2, and CuI smoothly in 72% and 48% yields, respectively (entries 8 and 9). It was noteworthy that a moderate yield was still achieved from 6-(phenylethynyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (**1d**) (entry 7). To our delight, two heteroaromatic aldehydes **1g** and **1h** could undergo the cyclization reaction, providing two interesting heterocycle-containing products in low to moderate yields (entries 11 and 12). It was found that substrates **1i**−**k**, having a methyl-substituted phenyl group at the terminal alkyne, were suitable for this cyclization reaction under the standard conditions (entries 13−15). Gratifyingly, in the presence of CuI aliphatic alkyne **1l** displayed greater activity to successfully react with diamine **2a** and I_2 leading to a moderate yield (entry 16).

The synthesis of other haloisoquinoline-fused benzimidazoles using *N*-halosuccimide (NXS) was tested (Scheme 2). In the presence of CuI, treatment of 2-ethynylbenzaldehyde (**1a**) with *o*-benzenediamine (**2a**) and NBS (*N*-bromosuccimide)

SCHEME 2. CuI-Catalyzed Tandem Bromocyclization of 2-Ethynylbenzaldehyde (1a) with *o*-Benzenediamine (2a) and *N*-Halosuccimide (NXS)



SCHEME 3. Controlled Experiments



afforded bromoisoquinoline-fused benzimidazole **20** in 45% yield. However, NCS (*N*-chlorosuccimide) has no activity.

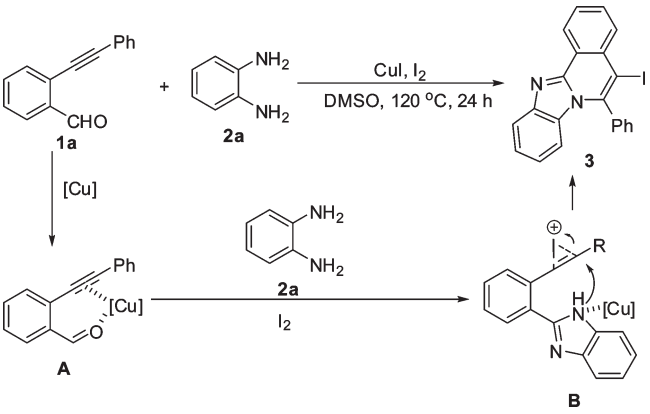
To understand this mechanism, some controlled experiments were carried out (Scheme 3). The reported results demonstrated that without catalysts the reaction could take place although the corresponding isoquinoline-fused benzimidazoles were obtained in low yield using $PhNO_2$ solvent under heat conditions (120 or 150 °C).[3a,b] However, only a trace of isoquinoline-fused benzimidazole **22** was observed in DMSO without catalyst. Gratifyingly, CuI could promote the reaction: product **22** was isolated in 34% yield at 10 mol % of CuI and 60% yield at 2 equiv of CuI. Notably, substrate **22** could not be converted into iodoisoquinoline-fused benzimidazole **3** under the present standard conditions.

The reactions of substrate **1a** with CuI or I_2 were conducted without diamines after 15 min, and then determined by ^{13}C NMR analysis.[10] The results showed that the presence of CuI could affect the chemical shift to some extent in the ^{13}C NMR spectra. Interestingly, in the presence of I_2 some intermediates besides substrate **1a** were observed: one is an iodonium ion.

Therefore, a possible mechanism as outlined in Scheme 4 was proposed on the base of the present results and the reported mechanism.[3,5−7,11] Initially, complexation of 2-ethynylbenzaldehyde (**1**) with CuI gives intermediate **A**. copper/iodine-catalyzed oxidative cyclization of intermediate **A** with *o*-benzenediamine (**2**) takes place,[3,11] followed by I_2 added to a triple bond leading to intermediate **B**.[5−7] Finally, intermediate **B** undergoes the electrophilic cyclization to afford the target cyclization product.

It was found that the iodocyclization reaction could take place without Cu catalysts; however, the presence of CuI could improve the yield of product **3** from 53% to 74% (entries 16 and 23 in Table 1). We also found that CuI plays a crucial role among the cyclization using NIS (entries 1 and 4 in Table 1). Based on the controlled experiments and the possible mechanism, we deduce that CuI has some important roles including: (1) catalyst or/and promoter for the catalytic oxidation cyclization of intermediate **A** leading to intermediate **B** and (2) complexation of the carbon−carbon triple bond to activate it.

SCHEME 4. Possible Mechanism



As shown in Scheme 5, the reactions of the product **3** with phenylboronic acid, phenylacetylene or 1-methyl-4-vinylbenzene were examined under the previously reported reaction conditions.[12−14] To our delight, substrate **3** smoothly underwent the Suzuki,[12] Sonogashira,[13] and Heck[14] coupling reactions, respectively, in excellent yields.

In summary, we have developed a new electrophilic tandem cyclization protocol for the synthesis of haloisoquinoline-fused benzimidazoles *via* CuI-promoted tandem cyclization of 2-ethynylbenzaldehydes with *o*-benzenediamines and iodine. This protocol allows the formation of two heterocyclic rings in a one-pot reaction through the electrophilic annulation. Most importantly, these isoquinoline-fused benzimidazoles with a halo group would be useful introduction of various functional groups, which should be significant for drug discovery.

Experimental Section

Typical Experimental Procedure for the Cu-Catalyzed Electrophilic Tandem Cyclization. 2-Ethynylbenzaldehyde **1** (0.2 mmol), *o*-benzenediamine **2** (0.2 mmol), I_2 (2 equiv), CuI (10 mol %), and DMSO (2 mL) were added to a two-neck flask in turn. Then the solution was stirred at 120 °C for 24 h until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction was finished, the mixture was washed with saturated $Na_2S_2O_3$ solution, extracted with EtOAc, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether) to afford the desired product.

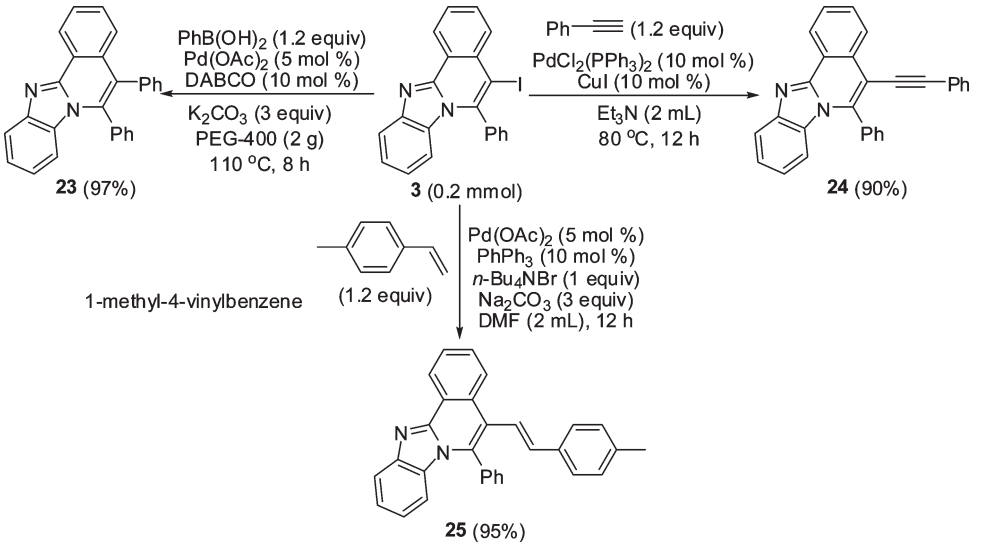
(11) (a) Balogh-Hergovich, É; Bodnár, G.; Speier, G. *Acta Chim. Acad. Sci. Hung.* **1981**, *108*, 37. (b) Speier, G.; Párkányi, L. *J. Org. Chem.* **1986**, *51*, 218.

(12) Li, J.-H.; Liu, W.-J.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 5409.

(13) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *44*, 4467. (b) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259. (c) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253.

(14) (a) Grasa, A. G.; Singh, R.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2003**, *687*, 269. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113. (c) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031.

SCHEME 5. Applications in Organic Synthesis



Compound 3: red solid; mp 199.5−201.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 7.5 Hz, 1H), 8.15 (m, J = 8.0 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.75−7.67 (m, 6H), 7.48−7.45 (m, 2H), 7.33 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 143.6, 139.6, 138.5, 132.5, 132.4, 131.0, 130.8, 130.3, 129.9, 129.6, 128.7, 125.2, 124.5, 122.4, 121.7, 119.5, 114.0, 87.0; LRMS (EI, 70 eV) m/z 420 (M^+, 100), 292 (52); HRMS (EI) for $C_{21}H_{13}IN_2$ (M^+) calcd 420.0123, found 420.0126.

Compound 4: 5-Me/6-Me = 1.3:1; yellow solid; mp 232.2−233.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88−8.86 (m, 2H), 8.21 (d, J = 7.5 Hz, 1H), 8.15−8.13 (m, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.76−7.68 (m, 10H), 7.51−7.46 (m, 4H), 7.18 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.67 (d, J = 8.4 Hz, 0.56H), 5.52 (s, 0.44H), 2.44 (s, 1.7H), 2.18 (s, 1.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 147.0, 143.5, 141.4, 139.6, 138.5, 138.4, 132.7, 132.4, 132.3, 132.2, 131.5, 130.9, 130.8, 130.3, 130.2, 130.0, 129.9, 129.5, 129.4, 128.8, 128.7, 128.2, 126.2, 125.2, 125.0, 123.5, 123.2, 122.4, 122.2, 119.0, 118.8, 114.0, 113.4, 86.8, 21.9, 21.5; LRMS (EI, 70 eV) m/z 434 (M^+, 100), 305 (20); HRMS (EI) for $C_{22}H_{15}IN_2$ (M^+) calcd 434.0280, found 434.0285.

Compound 5: yellow solid; mp 248.2−249.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (d, J = 7.2 Hz, 1H), 8.20−8.13 (m, 1H), 7.75−7.67 (m, 6H), 7.57−7.46 (m, 2H), 5.50 (s, 1H), 2.34 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 142.4, 139.7, 138.7, 132.2, 130.8, 130.7, 130.6, 130.5, 130.1, 130.0, 129.5, 129.4, 128.6, 125.0, 122.7, 119.4, 114.1, 86.1, 20.7, 20.3; LRMS (EI, 70 eV) m/z 448 (M^+, 100); HRMS (EI) for $C_{23}H_{17}IN_2$ (M^+) calcd 448.0436, found 448.0439.

Compound 6: yellow solid; mp 292.2−292.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, J = 7.9 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.02 (s 1H), 7.84−7.73 (m, 5H), 7.48 (d, J = 7.0 Hz, 2H), 5.78 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 142.2, 139.1, 137.6, 132.8, 132.7, 132.2, 130.9, 130.0, 129.8, 129.6, 129.3, 129.1, 125.7, 125.6, 121.7, 120.1, 115.6, 88.2; LRMS (EI, 70 eV) m/z 488 (M^+, 100), 326 (42); HRMS (EI) for $C_{21}H_{11}Cl_2IN_2$ (M^+) calcd 487.9344, found 487.9349.

Compound 7: yellow solid mp 273.2−274.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, J = 8.1 Hz, 1H), 8.22−8.20 (m, 2H), 7.85−7.71 (m, 5H), 7.52−7.28 (m, 2H), 7.19 (d, J = 8.7 Hz, 1H), 5.87 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.1, 143.3, 139.4, 138.2, 132.7, 132.6, 131.7, 130.7, 129.9, 129.8, 129.1, 126.8 (q, $^2J_{C-F}$ = 32.5 Hz, 1C), 125.4, 124.5 (q, $^1J_{C-F}$ = 273.5 Hz, 1C), 122.3, 118.3, 117.2, 114.5, 88.1; LRMS (EI, 70 eV) m/z 488 (M^+, 100), 360 (33); HRMS (EI) for $C_{22}H_{12}F_3IN_2$ (M^+) calcd 487.9997, found 487.9998.

Compound 8: yellow solid; mp 228.6−230.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J = 8.1 Hz, 1H), 7.95−7.90 (m, 2H), 7.69−7.68 (m, 3H), 7.54 (d, J = 8.1 Hz, 1H), 7.48−7.46 (m, 2H), 7.34 (t, J = 7.5, 1H), 6.92 (t, J = 7.5 Hz, 1H), 5.81 (d, J = 8.7 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 143.9, 141.6, 139.7, 138.7, 132.5, 132.3, 131.0, 130.3, 130.2, 130.0, 129.6, 125.2, 124.4, 121.4, 120.3, 119.5, 114.0, 86.9, 22.0; LRMS (EI, 70 eV) m/z 434 (M^+, 100), 306 (30); HRMS (EI) for $C_{22}H_{15}IN_2$ (M^+) calcd 434.0280, found 434.0284.

Compound 9: brown solid; mp 223.7−226.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.69−7.67 (m, 3H), 7.49−7.45 (m, 2H), 7.35−7.30 (m, 2H), 6.94 (t, J = 7.7 Hz, 1H), 5.83 (d, J = 8.7 Hz, 1H), 4.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 147.4, 143.7, 138.6, 137.4, 134.6, 133.1, 130.3, 129.6, 128.8, 127.7, 126.6, 123.6, 121.7, 121.4, 119.6, 114.1, 105.2, 86.7, 56.1; LRMS (EI, 70 eV) m/z 450 (M^+, 26), 105 (100); HRMS (EI) for $C_{22}H_{15}IN_2O$ (M^+) calcd 450.0229, found 450.0231.

Compound 10: yellow solid; mp 258.6−259.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.70−7.63 (m, 4H), 7.47−7.44 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 6.91 (t, J = 8.4 Hz, 1H), 6.17 (s, 2H), 5.80 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1, 148.9, 147.5, 143.8, 138.7, 138.3, 130.8, 130.3, 130.0, 129.6, 129.4, 124.5, 121.1, 119.2, 118.0, 114.0, 111.3, 103.1, 102.2, 86.2; LRMS (EI, 70 eV) m/z 464 (M^+, 100), 336 (23); HRMS (EI) for $C_{22}H_{13}IN_2O_2$ (M^+) calcd 464.0022, found 464.0025.

Compound 11: brown solid; mp 224.2−225.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.70−7.61 (m, 4H), 7.49−7.47 (m, 2H), 7.33 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.5, 1H), 5.79 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 142.6, 138.9, 137.2, 133.9, 130.1, 129.9, 129.5, 128.8, 128.6, 123.7, 123.3, 122.3, 121.0, 118.7, 113.0, 84.5; LRMS (EI, 70 eV) m/z 454 (M^+, 100), 326 (31); HRMS (EI) for $C_{21}H_{12}ClIN_2$ (M^+) calcd 453.9734, found 453.9737.

Compound 12: yellow solid; mp 285.5−291.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.19 (d, J = 7.5 Hz, 1H), 7.72−7.70 (m, 3H), 7.65−7.64 (m, 2H), 7.46−7.47 (m, 2H), 5.49 (s, 1H), 2.33 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 141.3, 138.9, 137.5, 133.8, 133.1, 133.0, 130.3, 129.7, 129.6, 129.3, 129.1, 128.9, 128.5, 127.9, 123.2, 118.5, 113.1, 83.8, 19.5, 19.3; LRMS (EI, 70 eV) m/z 482 (M^+, 100), 356

(26); HRMS (EI) for $C_{23}H_{16}ClIN_2$ (M^+) calcd 482.0047, found 482.0050.

Compound 13: brown solid; mp 206.2−207.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, J = 8.7 Hz, 1H), 8.19−8.15 (m, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.70−7.69 (m, 3H), 7.49−7.45 (m, 3H), 7.36 (t, J = 7.8 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 5.82 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5 (d, $^1J_{C-F}$ = 248.7 Hz, 1C), 146.7 (d, $^4J_{C-F}$ = 3.8 Hz, 1C), 143.6, 139.0, 138.3, 135.2 (d, $^3J_{C-F}$ = 8.8 Hz, 1C), 130.9, 130.4, 129.9, 129.6, 129.0, 124.7, 123.7 (d, $^3J_{C-F}$ = 8.8 Hz, 1C), 122.3, 119.8, 119.4 (d, $^2J_{C-F}$ = 23.8 Hz, 1C), 114.0, 110.3 (d, $^2J_{C-F}$ = 23.8 Hz, 1C), 85.6; LRMS (EI, 70 eV) m/z 438 (M^+, 100), 310 (43), 155 (25); HRMS (EI) for $C_{21}H_{12}FIN_2$ (M^+) calcd 438.0029, found 438.0031.

Compound 14: brown solid; mp 237.1−237.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14−9.07 (m, 2H), 7.94 (d, J = 8.1 Hz, 1H), 7.74−7.72 (m, 3H), 7.67−7.64 (m, 1H), 7.53−7.51 (m, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 5.89 (d, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 147.1, 146.8, 144.1, 143.3, 137.8, 133.2, 130.8, 130.7, 130.6, 129.8, 129.6, 125.0, 123.4, 122.4, 119.8, 118.4, 114.2, 90.3; LRMS (EI, 70 eV) m/z 421 (M^+, 100), 293 (20); HRMS (EI) for $C_{20}H_{12}IN_3$ (M^+) calcd 421.0076, found 421.0080.

Compound 15: yellow solid; mp 254.9−256.6 °C; IR (KBr, cm^{-1}) 1522, 1445, 1416, 1267, 753, 708; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.70−7.57 (m, 5H), 7.47−7.45 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.7 Hz, 1H), 5.90 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 144.1, 141.5, 138.8, 137.2, 130.4, 130.3, 130.1, 129.9, 129.7, 129.0, 125.0, 124.2, 121.2, 119.4, 114.2; LRMS (EI, 70 eV) m/z 426 (M^+, 100), 298 (31); HRMS (EI) for $C_{19}H_{11}IN_2S$ (M^+) calcd 425.9688, found 425.9695.

Compound 16: brown solid; mp 229.9−231.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, J = 7.2 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.75−7.70 (m, 2H), 7.50−7.47 (m, 2H), 7.38−7.34 (m, 3H), 6.96 (t, J = 8.0 Hz, 1H), 5.92 (d, J = 8.4 Hz,1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 143.8, 140.5, 139.9, 135.7, 132.5, 132.4, 131.0, 130.9, 130.3, 129.7, 128.6, 125.2, 124.5, 122.6, 121.6, 119.6, 114.2, 87.2, 21.7; LRMS (EI, 70 eV) m/z 434 (M^+, 100), 306 (33); HRMS (EI) for $C_{22}H_{15}IN_2$ (M^+) calcd 434.0280, found 434.0285.

Compound 17: red solid; mp 226.3−227.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.36−7.29 (m, 4H), 6.96 (t, J = 8.0 Hz, 1H), 5.92 (d, J = 8.4 Hz, 1H), 4.06 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 147.2, 143.6, 140.3, 137.5, 135.7, 134.3, 131.1, 130.2, 130.0, 126.6, 124.5, 123.4, 121.6, 121.3, 119.4, 114.3, 105.1, 87.0, 56.1, 21.7; LRMS (EI, 70 eV) m/z 464 (M^+, 100); HRMS (EI) for $C_{23}H_{17}IN_2O$ (M^+) calcd 464.0386, found 464.0389.

Compound 18: brown solid; mp 243.5−245.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.36−7.26 (m, 3H), 6.96 (t, J = 8.7 Hz, 1H), 5.89 (d, J = 8.4 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 143.7, 140.6, 140.1, 135.4, 134.8, 134.1, 131.1, 130.9, 130.8, 130.3, 129.6, 124.7, 124.3, 123.3, 122.0, 119.7, 114.2, 85.8, 21.7; LRMS (EI, 70 eV) m/z 468 (M^+, 100), 340 (29); HRMS (EI) for $C_{22}H_{14}ClIN_2$ (M^+) calcd 467.9890, found 467.9895.

Compound 19: red oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 3.64 (t, J = 8.0 Hz, 2H), 1.83−1.77 (m, 2H), 1.62−1.59 (m, 2H), 1.36−1.30 (m, 2H), 1.22−1.18 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 143.2, 140.5, 132.7, 132.2, 131.3, 130.5, 128.2, 125.4, 125.0, 122.6, 121.4, 120.0, 114.5, 87.2, 38.3, 31.4, 28.9, 26.7, 22.6, 14.0; LRMS (EI, 70 eV) m/z 428 (M^+, 21), 301 (38), 231 (100); HRMS (EI) for $C_{21}H_{21}IN_2$ (M^+) calcd 428.0749, found 428.0746.

Compound 20: yellow solid; mp 205.5−206.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 8.1 Hz, 1H), 8.21 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.78−7.66 (m, 5H), 7.53−7.51 (m, 2H), 7.38−7.33 (m, 1H), 6.92 (t, J = 8.1 Hz, 1H), 5.92 (d, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 143.8, 136.2, 134.8, 130.9, 130.7, 130.5, 130.3, 129.9, 129.5, 128.7, 127.3, 125.2, 124.5, 123.0, 121.4, 119.7, 113.8, 108.5; LRMS (EI, 70 eV) m/z 374 ($M^+ + 2$, 97), 373 (57), 372 (M^+, 100), 292 (42); HRMS (EI) for $C_{21}H_{13}BrN_2$ (M^+) calcd 372.0262, found 372.0265.

Compound 22:[3a,b] yellow solid; mp 173.2−174.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92−8.90 (m, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.73−7.68 (m, 3H), 7.65−7.60 (m, 5H), 7.40 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.92 (s, 1H), 6.49 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 144.0, 137.4, 134.6, 131.6, 130.2, 129.9, 129.4, 129.0, 128.0, 126.6, 125.2, 124.3, 121.3, 119.6, 114.1, 112.7; LRMS (EI, 70 eV) m/z 294 (M^+, 100).

Compound 23: yellow solid; mp 265.4−266.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.68−7.66 (m, 1H), 7.60−7.57 (m, 2H), 7.38−7.33 (m, 7H), 7.25−7.22 (m, 4H), 6.94−6.91 (m, 1H), 6.00 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 144.2, 133.7, 132.7, 131.5, 130.7, 129.9, 129.2, 128.8, 128.0, 127.8, 127.3, 126.4, 125.1, 124.2, 121.3, 119.6, 114.1, 112.6; LRMS (EI, 70 Ev) m/z 370 (M^+, 100); HRMS (EI) for $C_{27}H_{18}N_2$ (M^+) calcd 370.1470, found 370.1465.

Compound 24: yellow solid; mp 232.1−233.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, J = 8.0 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.80−7.66 (m, 7H), 7.38 (t, J = 7.5 Hz, 1H), 7.28−7.22 (m, 5H), 6.99 (t, J = 7.5 Hz, 1H), 6.28 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3, 144.3, 140.6, 133.9, 131.2, 130.8, 130.4, 130.1, 130.0, 129.1, 128.4, 128.3, 125.9, 125.1, 124.6, 123.0, 121.7, 119.7, 114.1, 106.7, 97.1, 84.3; LRMS (EI, 70 eV) m/z 394 (M^+, 100); HRMS (EI) for $C_{29}H_{18}N_2$ (M^+) calcd 394.1469, found 394.14696.

Compound 25: yellow solid; mp 241.7−243.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99−8.97 (m, 1H), 8.16−8.14 (m, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.70−7.69 (m, 2H), 7.59−7.57 (m, 3H), 7.50−7.49 (m, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.19−7.18 (m, 2H), 7.11−7.10 (m, 2H), 6.92−6.91 (m, 1H), 6.83 (d, J = 17.0 Hz, 1H), 6.50 (d, J = 16.5 Hz, 1H), 6.02 (d, J = 8.0 Hz, 1H), 2.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 144.1, 137.8, 136.6, 134.3, 130.5, 130.0, 129.7, 129.3, 127.8, 126.2, 125.5, 125.4, 124.1, 121.5, 121.2, 119.5, 114.1, 21.2; LRMS (EI, 70 eV) m/z 410 (M^+, 100); HRMS (EI) for $C_{30}H_{22}N_2$ (M^+) calcd 410.1783, found 410.1781.

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Supporting Information Available: Copies of spectra and the crystallographic data of product **3**. This material is available free of charge via the Internet at http://pubs.acs.org.