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Rapid Access to 3-(Aminomethyl)isoquinoline-Fused Polycyclic Compounds by Copper-Catalyzed Four-Component Coupling, Cascade Cyclization, and Oxidation

Yusuke Ohta, Yushi Kubota, Tsuyoshi Watabe, Hiroaki Chiba, Shinya Oishi, Nobutaka Fujii,* and Hiroaki Ohno*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

nfujii@pharm.kyoto-u.ac.jp; hohno@pharm.kyoto-u.ac.jp

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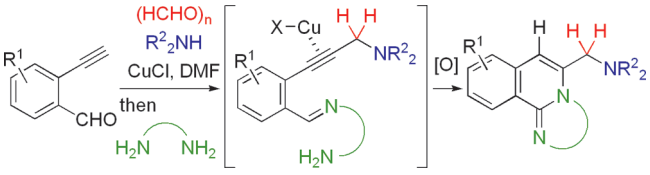
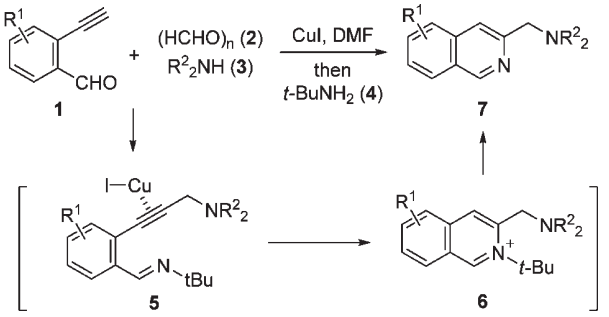


A novel copper-catalyzed synthesis of 3-(aminomethyl) isoquinoline-fused polycyclic compounds, through four-component coupling, cyclization, and oxidation, has been developed. A Mannich-type reaction of 2-ethynylbenzaldehyde with paraformaldehyde and a secondary amine followed by treatment with a diamine component gave tricyclic isoquinolines through cascade cyclization and oxidation. Construction of fused isoquinolines of various ring sizes is also presented.

Cascade reactions[1] and multicomponent reactions[2] in which several bond-forming steps take place in a single reaction vessel play an important role in atom-economical organic chemistry. Recently, considerable attention has been paid to this research area since complex molecules can be produced from readily accessible components in a simple manner.

Isoquinoline-fused polycyclic compounds such as pyrimido[2,1-*a*]isoquinolines and imidazo[2,1-*a*]isoquinolines exert various biological effects[3] including antitumor activity.[4] Considerable efforts have been made to develop efficient methods for the synthesis of this class of compounds, in which stepwise introduction/construction of the desired ring system is generally required.[5] As a part of our ongoing program directed toward development of copper-catalyzed domino multicomponent coupling and cyclization,[6] we reported a novel synthesis of 3-(aminomethyl)isoquinolines by four-component coupling−cyclization (Scheme 1).[7] In this reaction, a copper-catalyzed Mannich-type reaction of a 2-ethynylbenzaldehyde **1** with paraformaldehyde **2** and a secondary amine **3** followed by imine formation with *t*-BuNH$_2$ **4** promotes isoquinoline formation to afford **7** through cleavage of a *tert*-butyl group.

SCHEME 1. Four-Component Synthesis of 3-(Aminomethyl) isoquinoline Using Copper Catalysis



On the basis of this chemistry, we expected that the use of a primary amine containing a tethered nucleophilic group instead of *t*-BuNH$_2$ could bring about an intramolecular

(1) For recent reviews, see: (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581.

(2) For recent reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17–89. (c) Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev.* **2007**, *36*, 484–491. (d) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108.

(3) (a) Handley, D. A.; Van Valen, R. G.; Melden, M. K.; Houlihan, W. J.; Saunders, R. N. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 617–623. (b) Houlihan, W. J.; Cheon, S. H.; Parrino, V. A.; Handley, D. A.; Larson, D. A. *J. Med. Chem.* **1993**, *36*, 3098–3102. (c) Scholz, D.; Schmidt, H.; Prieschl, E. E.; Csonga, R.; Scheirer, W.; Weber, V.; Lembachner, A.; Seidl, G.; Werner, G.; Mayer, P.; Baumruker, T. *J. Med. Chem.* **1998**, *41*, 1050–1059. (d) Griffin, R. J.; Fontana, G.; Golding, B. T.; Guiard, S.; Hardcastle, I. R.; Leahy, J. J. J.; Martin, N; Richadson, C.; Rigoreau, L.; Stockley, M.; Smith, G. C. M. *J. Med. Chem.* **2005**, *48*, 569–585.

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(5) (a) Chaykovsky, M.; Benjamin, L.; Ian Fryer, R.; Metlesics, W. *J. Org. Chem.* **1970**, *35*, 1178–1180. (b) Houlihan, W. J.; Parrino, V. A. *J. Org. Chem.* **1982**, *47*, 5177–5180. (c) Loones, K. T. J.; Maes, B. U. W.; Dommisse, R. A.; Lemière, G. L. F. *Chem. Commun.* **2004**, 2466–2467. (d) Parenty, A. D. C.; Smith, L. V.; Pickering, A. L.; Long, D.-L.; Cronin, L. *J. Org. Chem.* **2004**, *69*, 5934–5946. (e) Sharon, A.; Pratap, R.; Maulik, P. R.; Ram, V. J. *Tetrahedron* **2005**, *61*, 3781–3787. (f) Kiselyov, A. S. *Tetrahedron Lett.* **2005**, *46*, 4487–4490. (g) Parenty, A. D. C.; Guthrie, K. M.; Song, Y.-F.; Smith, L. V.; Burkholder, E.; Cronin, L. *Chem. Commun.* **2006**, 1194–1196. (h) Loones, K. T. J.; Maes, B. U. W.; Herrebout, W. A.; Dommisse, R. A.; Lemière, G. L. F.; Van der Veken, B. J. *Tetrahedron* **2007**, *63*, 3818–3825. (i) Hubbard, J. W.; Piegols, A. M.; Söderberg, B. C. G. *Tetrahedron* **2007**, *63*, 7077–7085. (j) Parenty, A. D. C.; Cronin, L. *Synthesis* **2008**, 155–160.

(6) (a) Ohno, H.; Ohta, Y.; Oishi, S.; Fujii, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2295–2298. (b) Ohta, Y.; Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 3535–3838.

(7) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2008**, 835–837.

(8) For a related two-component reaction using 1,2-diaminobenzene, see: (a) Dyker, G.; Stirner, W.; Henkel, G. *Eur. J. Org. Chem.* **2000**, 1433–1441. For a related synthesis of pyroroisoquinolines through 1,3-dipolar cycloaddition, see: (b) Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744–7745.

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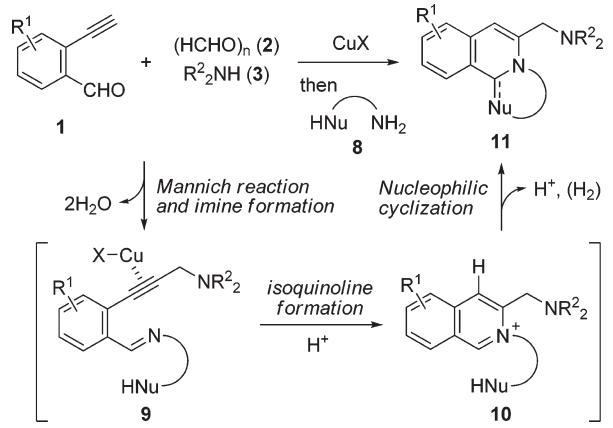
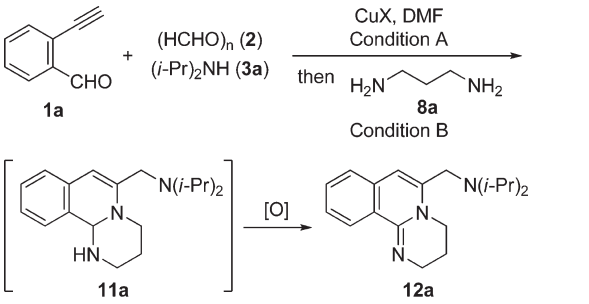
SCHEME 2. Four-Component Construction of an Isoquinoline-Fused Tricyclic Ring System



nucleophilic attack onto the isoquinolinium ion **10** without causing cleavage (Scheme 2).[8−10] In this paper, we describe a novel approach to 3-(aminomethyl)isoquinoline-fused polycyclic compounds utilizing four-component coupling and cascade cyclization in the presence of a copper catalyst. To the best of our knowledge, this is the first example of multicomponent sequential construction of an isoquinoline-fused heterocyclic ring system including imidazo[2,1-*a*]isoquinolines and pyrimido[2,1-*a*]isoquinolines.

We envisioned that 1,3-diaminopropane would be an appropriate primary amine as it has an additional nucleophilic group that could sequentially form isoquinoline and pyrimidine rings.[11] Thus, our attempts to construct the pyrimido[2,1-*a*]isoquinoline framework were initiated with 2-ethynylbenzaldehyde **1a**, paraformaldehyde **2**, diisopropylamine **3a**, and 1,3-diaminopropane **8a** (Table 1). Coexistence of two amines with two aldehydes in one portion of the reaction would hamper the effective Mannich-type reaction of **1a**, **2**, and **3a** and subsequent imine formation with **8a** in the desired order. Therefore, the copper-catalyzed Mannich-type reaction of **1a**, **2** (2 equiv), and **3a** (2 equiv) in DMF was completed and monitored by TLC, and then the reaction mixture was treated with **8a** (3 equiv) at 120 °C to afford the expected product of the oxidized form **12a** in 38% yield (entry 1).[12] The elevated reaction temperature (200 °C) under microwave irradiation in the ring formation step led to a lower yield of **12a** (29%, entry 2). When other copper salts such as CuBr, $CuBr_2$, $CuCl_2$, CuF_2, $Cu(OAc)_2$, and CuCl (entries 3−8) were used in the reaction, it was revealed that CuCl was the most effective catalyst for this transformation (43% yield, entry 8). Use of MS 4 Å slightly improved the yield of **12a** (52%, entry 9). Further optimization demonstrated that the cyclization reaction under an oxygen atmosphere, which would facilitate the oxidation step, realized rapid formation of **12a** in 72% yield (entry 10).

TABLE 1. Optimization of Reaction Conditions Using 1,3-Diaminopropane[a]



entry	CuX	condition A	condition B	yield[d] (%)
1	CuI	rt, 0.5 h	120 °C, 15 h	38
2	CuI	rt, 0.5 h	MW, 200 °C, 0.33 h	29
3	CuBr	rt, 1.5 h	120 °C, 15 h	42
4	$CuBr_2$	rt, 1.0 h	120 °C, 15 h	38
5	$CuCl_2$	rt, 2.3 h	120 °C, 10 h	42
6	CuF_2	100 °C, 0.5 h	120 °C, 16 h	27
7	$Cu(OAc)_2$	rt, 2.5 h	120 °C, 12 h	20
8	CuCl	rt, 1.5 h	120 °C, 12 h	43
9[b]	CuCl	rt, 1.5 h	120 °C, 20 h	52
10[b,c]	CuCl	rt, 1.5 h	120 °C, 1 h	72

[a]After the Mannich-type reaction of **1a**, **2** (2 equiv), and **3a** (2 equiv) in the presence of copper salt (10 mol %) was completed under conditions A (monitored by TLC), **8a** (3 equiv) was added. The reaction mixture was stirred under conditions B. [b]**8a** with MS 4 Å was added. [c]Under oxygen atmosphere. [d]Isolated yields.

Several substituted 2-ethynylbenzaldehydes were then applied to this copper-catalyzed four-component synthesis of 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline under optimized conditions (Table 1, entry 10). The results are summarized in Table 2. The substitution by a fluorine atom at the *para*-position to the formyl group slightly decreased the yield of **12b** (55%, entry 1). The reaction with 2-ethynylbenzaldehydes **1c** and **1d** containing a fluorine atom at the *meta*-position or methyl group at the *para*-position to the formyl group showed a good conversion to yield the desired tricyclic compounds **12c** and **12d** (74 and 71%, respectively, entries 2 and 3). The use of 2-ethynyl-5-methoxybenzaldehyde **1e** also gave tricyclic compound **12e** (55%, entry 4). Overall, this four-component construction of 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline having an aminomethyl group was found to be applicable to 2-ethynylbenzaldehydes containing an electron-donating or electron-withdrawing group.

(9) For related three-component monocyclizations, see: (a) Asao, N.; Iso, K.; Yudha, S., S. *Org. Lett.* **2006**, *8*, 4149–4151. (b) Ding, Q.; Wang, B.; Wu, J. *Tetrahedron* **2007**, *63*, 12166–12171. (c) Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959–4962. (d) Gao, K.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8611–8613. (e) Ye, Y.; Ding, Q.; Wu, J. *Tetrahedron* **2008**, *64*, 1378–1382.

(10) For related two-component monocyclizations using aldimines, see: (a) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339–7341. (b) Asao, N.; Yudha, S.; Nogami, S.; Yamamoto, T. *Angew. Chem. Int. Ed* **2005**, *44*, 5526–5528. (c) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822–3825. (d) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462–4468.

(11) The reaction using 3-aminopropanol as the amine component **8** showed a promising result. However, the main product of this reaction was unstable and decomposed during purification.

(12) The unambiguous structure assignment for **12a** was made by X-ray analysis (for CIF, see the Supporting Information).

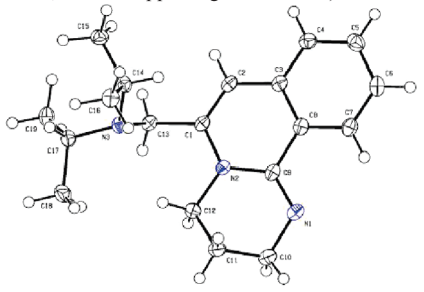
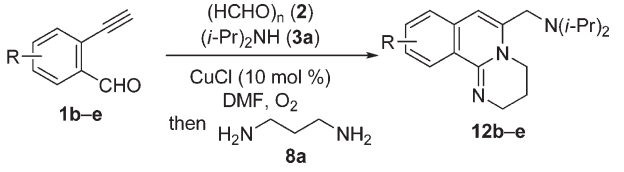
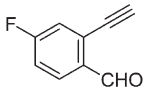
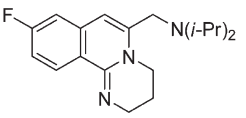
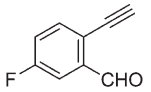
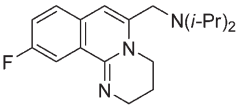
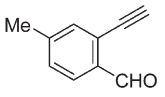
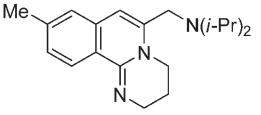
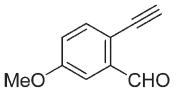
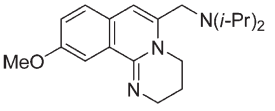


TABLE 2. Reaction with Substituted 2-Ethynylbenzaldehydes[a]



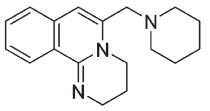
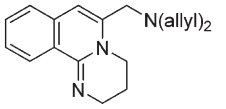
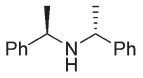
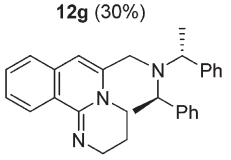
entry	2-ethynylbenzaldehyde	product (yield)[b]
1	 **1b**	 **12b** (55%)
2	 **1c**	 **12c** (74%)
3	 **1d**	 **12d** (71%)
4	 **1e**	 **12e** (55%)

[a]After the Mannich-type reaction of **1**, **2** (2 equiv), and **3a** (2 equiv) in the presence of CuCl (10 mol %) in DMF under O_2 was completed (rt, within 1.5 h, monitored by TLC), **8a** (2 equiv) and MS 4 Å were added and the reaction mixture was stirred at 120 °C for 1 h. [b]Isolated yields.

Next, investigation with several secondary amines **3** was conducted (Table 3). A one-portion Mannich-type reaction with 2-ethynylbenzaldehyde **1a**, paraformaldehyde **2**, and piperidine **3b** was very sluggish. Therefore, a mixture of **2** and **3b** in DMF was allowed to react at rt for 1 h in the presence of CuCl before successive addition of **1a** and 1,3-diaminopropane **8a**. This stepwise addition was successful to give the desired 3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline **12f** in 61% yield (entry 1). Diallylamine **3c** and bis(1-phenylethyl) amine **3d** showed relatively low reactivity to give **12g** and **12h** in 30 and 38% respective yields (entries 2 and 3).

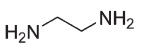
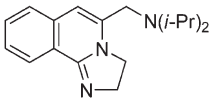
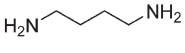
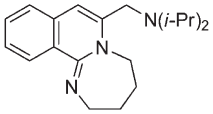
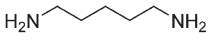
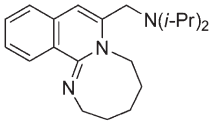
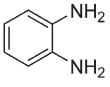
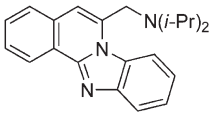
Finally, we examined preparation of 3-(aminomethyl)isoquinolines fused with various heterocycles by changing the carbon tether of the diamine component **8** (Table 4). Use of 1,2-diaminoethane **8b** in the reaction of 2-ethynylbenzaldehyde **1a**, paraformaldehyde **2**, and diisopropylamine **3a** in the presence of CuCl under an oxygen atmosphere gave the desired 2,3-dihydroimidazo[2,1-*a*]isoquinoline **13** in 56% yield (entry 1). The reaction using 1,4-diaminobutane **8c** afforded the tricyclic compound **14** with a tetrahydro[1,3]-diazepine structure in 50% yield (entry 3). The limitation of this reaction can be seen in the reaction with 1,5-diaminopentane **8d**, which produced 1,3-diazocine-fused isoquinoline **15** in only 12% yield (entry 5). This strategy was also

TABLE 3. Reaction with Secondary Amines 3b–d[a]

entry	secondary amine	product (yield)[b]
1[c]	 **3b**	 **12f** (61%)
2[c]	$allyl_2NH$ **3c**	 **12g** (30%)
3[d]	 **3d**	 **12h** (38%)

[a]The reactions were conducted as described in Table 2. [b]Isolated yields. [c]Before addition of **1a**, a mixture of **2** and **3b** or **3c** in DMF was stirred at rt for 1 h in the presence of CuCl. [d]One-portion Mannich-type reaction of **1a**, **2**, and **3d** was conducted at 100 °C for 1 h.

TABLE 4. Synthesis of (Aminomethyl)isoquinoline-Fused Polycyclic Compounds[a]

entry	diamine	atmosphere[b]	product (yield)[c]
			
1	**8b**	O_2	**13** (56%)
2	**8b**	Ar	**13** (53%)
			
3	**8c**	O_2	**14** (50%)
4	**8c**	Ar	**14** (63%)
			
5	**8d**	O_2	**15** (12%)
6	**8d**	Ar	**15** (5%)
			
7	**8e**	O_2	**16** (44%)
8	**8e**	Ar	**16** (58%)

[a]The reactions were conducted as described in Table 2. [b]The reaction under argon required 15 h for the cyclization/oxidation step. [c]Isolated yields.

applicable to the synthesis of tetracyclic benzimidazo[2,1-*a*]-isoquinoline **16** (entry 7).[8a] In the case of entries 4 and 8, the increased yields of **14** and **16** were observed under an argon

atmosphere, although a prolonged reaction time was required (15 h for the cyclization/oxidation step).[13]

In conclusion, we have developed a novel route to isoquinoline-fused polycyclic compounds by a four-component coupling and cascade cyclization strategy. In this reaction, the cyclization/oxidation step can be accelerated by use of an oxygen atmosphere, giving rise to improved yields of the cyclized products in many cases. Because this four-component reaction catalytically forms one carbon−carbon and four carbon−nitrogen bonds producing only H_2O and H_2 as the theoretical waste products, it would be useful for diversity-oriented synthesis of various isoquinolines in an atom-economical manner.

Experimental Section

General Procedure for Synthesis of 3-(Aminomethyl)isoquinoline-Fused Polycyclic Compounds by Domino Mannich-Type Reaction and Cascade Cyclization: Synthesis of 6-[(*N*,*N*-Diisopropylamino) methyl]-3,4-dihydro-2*H*-pyrimido[2,1-*a*]isoquinoline (12a) (Table 1, Entry 10). A mixture of 2-ethynylbenzaldehyde **1a** (25.0 mg, 0.19 mmol), paraformaldehye **2** (11.5 mg, 0.38 mmol), diisopropylamine **3a** (53.8 μL, 0.38 mmol), and CuCl (1.9 mg, 0.019 mmol) in DMF (1.5 mL) was stirred under O_2 at rt for 1.5 h. After the Mannich-type reaction was completed and monitored by TLC, propanediamine **8a** (48.1 μL, 0.58 mmol) and MS 4 Å (37.5 mg) were added, and the mixture was additionally stirred at 120 °C for 1 h. The mixture was concentrated in vacuo and purified by column chromatography over alumina with $CHCl_3/CH_3OH$ (15:1) as the eluent to give **12a** (41.3 mg, 72%) as a colorless solid: mp 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.6 Hz, 12H, 4 × CH_3), 1.91−1.96 (m, 2H, 3-CH_2), 3.06−3.16 (m, 2H, 2 × C*H*(CH_3)$_2$), 3.49 (s, 2H, NCH_2), 3.64 (t, J = 5.6 Hz, 2H, NCH_2), 4.13 (t, J = 5.9 Hz, 2H, NCH_2), 6.05 (s, 1H, 7-H), 7.19 (d, J = 7.8 Hz, 1H, Ar), 7.23−7.27 (m, 1H, Ar), 7.36−7.40 (m, 1H, Ar), 8.26 (d, J = 8.0 Hz, 1H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3 (4C), 21.0, 43.5, 44.4, 47.2 (2C), 48.0, 105.3, 124.9, 125.6, 126.1, 127.2, 130.2, 134.0, 140.7, 149.9; MS (FAB) m/z 298 (MH^+, 100); HRMS (FAB) calcd for $C_{19}H_{28}N_3$ (MH^+) 298.2284, found 298.2285.

(13) The exact reason for the increased yields of **14** and **16** under argon atmosphere is unclear. One plausible explanation is instability of **14** and **16** under the oxidative reaction conditions, which would decrease their yields under O_2 in the presence of a copper salt.

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Supporting Information Available: Experimental procedures, full characterization, and ^{1}H and ^{13}C NMR charts of the 2-ethynylbenzaldehydes and cyclization products and a crystallographic information file for **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.