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O-Arylation versus C-Arylation: Copper-Catalyzed Intramolecular Coupling of Aryl Bromides with 1,3-Dicarbonyls

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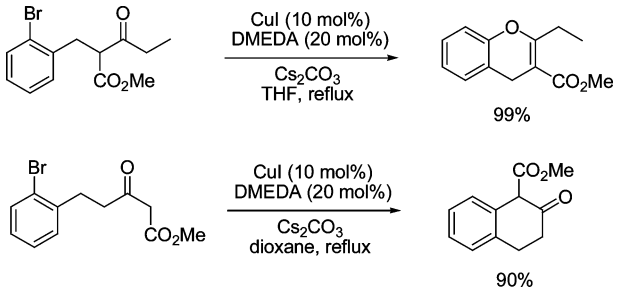

The copper-catalyzed intramolecular coupling of aryl bromides with 1,3-dicarbonyls via a six-membered ring closure was examined. With CuI (10 mol %) as the catalyst, *N*,*N*′-dimethylethylenediamine as the ligand, and Cs_2CO_3 as the base, the reactions of α-(2-bromobenzyl)-*β*-keto esters in THF at refluxing temperature afforded the corresponding substituted 4*H*-1-benzopyrans in high yields via O-arylation. On the other hand, the reactions of *δ*-(2-bromophenyl)-*β*-keto esters in refluxing dioxane led to the formation of 3,4-dihydronaphthalen-2(1*H*)-one derivatives via C-arylation.

Introduction

The formation of aryl C−X bonds (X = O, S, N, etc.) via copper-catalyzed Ullmann coupling between aryl halides and heteroatom-centered nucleophiles has received considerable attention in the past few years.[1] The high stability and low cost of the copper catalysts enable these transformations to be a useful complement to the more extensively investigated palladium-catalyzed processes.[2] By the appropriate combination of copper source, ligand, base, and solvent, these coupling reactions have been developed to include a wide range of substrates under mild conditions.[3] Among them, the O-arylation has been and continues to be the subject of wide interest.[4−10]

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(2) For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negichi, E.-i., Ed.; Wiley: New York, 2002; Vol. 1, p 1051. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (e) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (g) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (h) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

(3) For the latest selected examples, see: (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (b) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Venkanna, G. T.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 9948. (c) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (d) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781. (e) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (f) Fang, Y.; Li, C. *Chem. Commun.* **2005**, 3574.

(4) For examples of O-arylation using a stoichiometric amount of Cu(I) source, see: (a) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T.-Y.; Li, H.; Bräse, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421. (b) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319.

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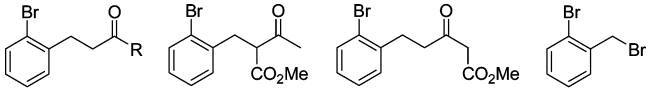
Buchwald et al. reported the first examples of copper-catalyzed synthesis of diaryl ethers from the reaction of aryl bromides or iodides with phenols using $(CuOTf)_2$·PhH as the catalyst and Cs_2CO_3 as the base.[5] With the help of an appropriate ligand, the reaction could be conducted under milder conditions.[6] This was then nicely applied into the total synthesis of the natural product antitumor agent K-13 as reported by Ma et al.[7] In the meantime, O-arylation of aliphatic alcohols could also be performed with high efficiency by the catalysis of Cu(I).[8] More recently, this methodology was extended to the synthesis of substituted benzoxazoles[9] and benzo[*b*]furans[10] via intramolecular O-arylation of amides or ketones.

Of particular interest to us was the use of ketone enolates as nucleophiles in O-arylation, which significantly broadened its scope of application, although so far only the five-membered ring closure leading to benzo[*b*]furans has been successful.[10] We recently reported the first examples of copper-catalyzed intramolecular O-vinylation of carbonyl compounds with vinyl bromides, among which five-, six- and even seven-membered cyclic alkenyl ethers could be efficiently synthesized.[3f] We envisioned that our success in O-vinylation might be extended to O-arylation, which would offer a convenient route to the synthesis of 4*H*-1-benzopyran derivatives via the six-membered ring closure. 4*H*-1-Benzopyrans are an important class of naturally occurring compounds with biological activities.[11] However, unlike 2*H*-1-benzopyrans, no general method has so far been reported for their synthesis.[11,12]

Results and Discussion

We chose ketones **1a**,**b** and *β*-keto esters **2a** and **3a** as the model substrates to explore the possible formation of 4*H*-1-benzopyrans. These four compounds were readily prepared from the common starting material 2-bromobenzyl bromide **4** according to the conventional methods.[13] We first tested ketones **1a** and **1b** according to Chen's procedure.[10a] However, no reaction occurred. Changing the base from K_3PO_4 to the much stronger NaO^{t}Bu did not show any improvement. We then screened various bases (Na_2CO_3, Cs_2CO_3, NaO^{t}Bu, Et_3N), ligands (*N*,*N*′-dimethylethylenediamine (DMEDA), L-proline, 1,-10-phenanthroline, and PPh_3), and copper sources (Cu, CuI, CuCl, CuOAc) in different solvents (THF, dioxane, toluene, and DMF) at refluxing temperature. To our disappointment, under all the experimental conditions screened, no expected cyclization products could be obtained while, in most cases, the starting materials simply remained unchanged.



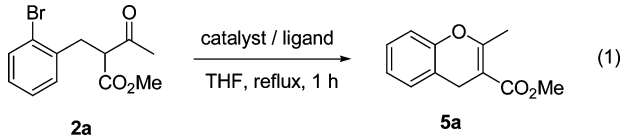
1a (R = Me)
1b (R = Ph)
2a **3a** **4**

Apparently the six-membered ring closure was much more difficult than the five-membered ring closure. Although steric factors could play an important role in the two types of cyclizations, the above different reactivities might also be attributed to the much easier enolization of the deoxybenzoins in the five-membered ring closure cases. We envisioned that, by changing the substrates from simple ketones to the more readily enolizable 1,3-dicarbonyls, such as **2a** or **3a**, the formation of 4*H*-1-benzopyrans might be possible as a similar situation was observed in our O-vinylation cases.[3f] Thus, *β*-keto ester **2a** was subjected to the treatment of CuI (0.1 equiv), DMEDA (0.2 equiv), and K_2CO_3 (2 equiv) in THF at refluxing temperature for 1 h. To our delight, the corresponding cyclization product 4*H*-1-benzopyran **5a** was isolated in 40% yield. We then used *β*-keto ester **2a** as the model compound to optimize the reaction conditions (eq 1), and the results are summarized in Table 1.

TABLE 1. Optimization of Reaction Conditions in the Synthesis of 5a

entry	copper source	base	ligand[b]	yield (%)[c]
1		Cs_2CO_3	**A**	0
2	Cu	Cs_2CO_3	**A**	trace
3	CuCl	Cs_2CO_3	**A**	30
4	$CuCl_2$	Cs_2CO_3	**A**	10
5	CuI	Cs_2CO_3	**A**	99
6	CuI	K_2CO_3	**A**	40
7	CuI	DABCO	**A**	0
8	CuI	NaO^{t}Bu	**A**	0
9	CuI		**A**	0
10	CuI	Cs_2CO_3	**B**	<5
11	CuI	Cs_2CO_3	**C**	15
12	CuI	Cs_2CO_3	**D**	<5
13	CuI	Cs_2CO_3		26

[a] Reaction conditions: **2a** (0.1 M in THF), copper catalyst (10 mol %), ligand (20 mol %), reflux, 1 h. [b] **A**: *N*,*N*′-dimethylethylenediamine (DMEDA). **B**: 1,10-phenanthroline. **C**: L-proline, **D**: PPh_3. [c] Isolated yield based on **2a**.



2a **5a** (1)

As can be seen in Table 1, the careful choice of copper source was critical for the high yield of product in a short time. As expected, no coupling took place when the reaction was carried out in the absence of the metal catalyst (entry 1, Table 1). Among the readily available copper compounds screened, including Cu, CuCl, $CuCl_2$, and CuI, the air-stable CuI had the best performance (entries 2−5, Table 1). In addition to a copper source, bases were also found to have a dramatic influence on the reaction outcome. For example, the reaction was much faster with Cs_2CO_3 as the base (entry 5, Table 1) than with K_2CO_3 (entry 6, Table 1). An organic base, such as DABCO or NaO^{t}Bu, completely inhibited the reaction (entries 7 and 8, Table 1), while no reaction occurred in the absence of a base (entry 9, Table 1). A brief study of the effect of the ligand was also carried out. Dramatic differences in the yield of **5a** were observed when DMEDA (99%), 1,10-phenanthroline (<5%), L-proline (15%), PPh_3 (<5%), or no ligand (26%) was used (entries 5 and 10−13, Table 1).

On the basis of the above results, we concluded that the optimized conditions were CuI (10 mol %) as the catalyst, DMEDA (20 mol %) as the ligand, Cs_2CO_3 (2 equiv) as the base, and THF as the solvent. We then prepared a variety of

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(12) For recent examples on the synthesis of 4*H*-1-benzopyran derivatives, see: (a) Yavari, I.; Anary-Abbasinejad, M.; Alizadeh, A.; Hossaini, Z. *Tetrahedron* **2003**, *59*, 1289. (b) Yavari, I.; Djahaniani, H.; Nasiri, F. *Tetrahedron* **2003**, *59*, 9409. (c) Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765. (d) Kumar, P.; Bodas, M. S. *Org. Lett.* **2000**, *2*, 3821.

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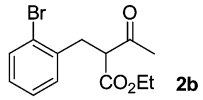
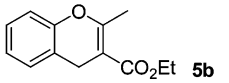
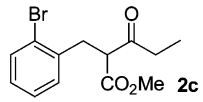
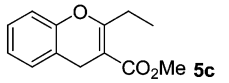
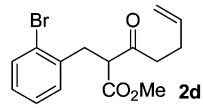
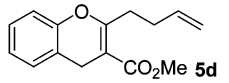
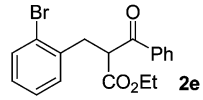
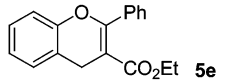
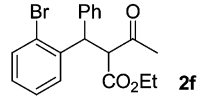
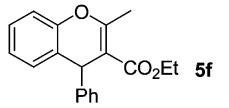
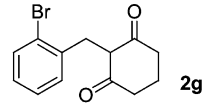
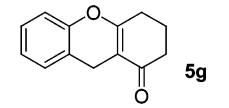
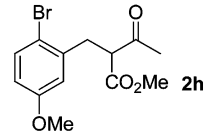
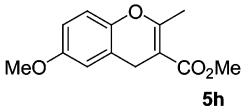
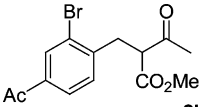
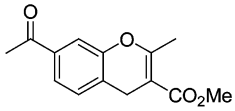
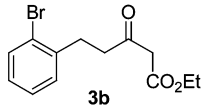
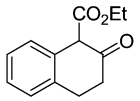
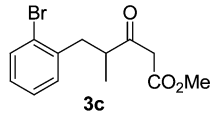
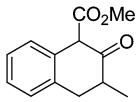
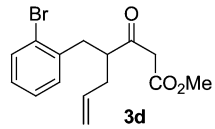
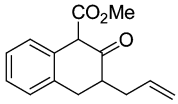
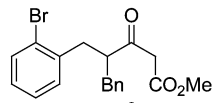
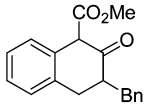
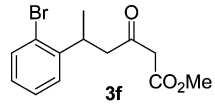
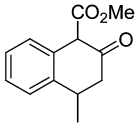
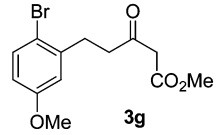
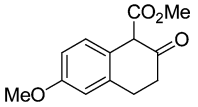
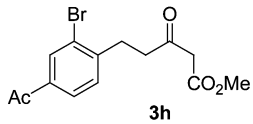
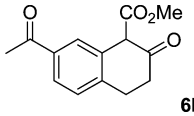
TABLE 2. Synthesis of 4*H*-1-Benzopyrans 5

entry	substrate	time (h)	product	yield (%)[a]
1	 **2b**	1	 **5b**	99
2	 **2c**	3	 **5c**	99
3	 **2d**	2	 **5d**	92
4	 **2e**	21	 **5e**	80[b]
5	 **2f**	5	 **5f**	80
6	 **2g**	2	 **5g**	89
7	 **2h**	16	 **5h**	90
8	 **2i**	21	 **5i**	90[b]

[a] Isolated yield based on **2**. [b] The reaction was run in dioxane at refluxing temperature.

TABLE 3. Synthesis of 3,4-Dihydronaphthalen-2(1*H*)-ones 6

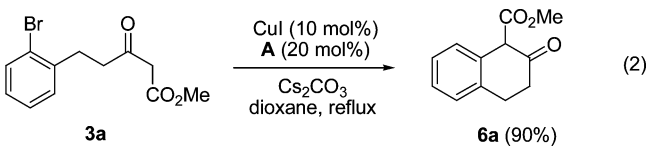
entry	substrate	time (h)	product	yield (%)[a]
1	 **3b**	20	 **6b**	84
2	 **3c**	2	 **6c**	94
3	 **3d**	4	 **6d**	85
4	 **3e**	6	 **6e**	72
5	 **3f**	5	 **6f**	57
6	 **3g**	20	 **6g**	67
7	 **3h**	32	 **6h**	80

[a] Isolated yield based on **3**.

α-(2-bromobenzyl)-*β*-keto esters structurally similar to **2a** and examined their intramolecular coupling reactions under the optimized conditions. The results are listed in Table 2. The ethyl ester **2b** worked equally well as the methyl ester **2a** (entry 1, Table 2). Substrates **2c**,**d** having a *γ*-substituent (Me or allyl) also afforded the desired products **5c**,**d** in excellent yields (entries 2 and 3, Table 2). For substrate **2f** with a substituent at the benzyl carbon, the expected 2,3,4-trisubstituted 4*H*-1-benzopyran **5f** was obtained in high yield (entry 5, Table 2). In the case of substituted acetophenone **2e**, a higher reaction temperature was required (entry 4, Table 2). This could presumably be attributed to the steric hindrance of the bulky phenyl group in **2e**. Besides *β*-keto esters, 1,3-diketones could also serve as the precursors for this Ullmann-type coupling. This was exemplified by the reaction of **2g** in which the corresponding tricyclic compound **5g** was achieved in 89% yield within a short period of time (entry 6, Table 2). Moreover, substrates bearing an electron-donating or electron-withdrawing substituent at the aryl ring also underwent smooth cyclization (entries 7 and 8, Table 2), indicating the generality of the above O-arylation.

We attempted to utilize aryl chlorides rather than aryl bromides in the coupling reactions. However, under the above optimized conditions, the chloro analogue of aryl bromide **2a** remained unchanged even at a higher temperature (dioxane, reflux).

In light of the above results, we were motivated to extend the methodology to the intramolecular coupling of *δ*-(2-bromophenyl)-*β*-keto esters, such as **3a**, in an attempt to get the cyclization product as the corresponding 3,4-dihydro-2*H*-1-benzopyran derivative with an exocyclic double bond. The reaction of **3a** was very slow under the optimized conditions. When the reaction was carried out at a higher temperature (dioxane, reflux) for 20 h, to our surprise, 3,4-dihydronaphthalen-2(1*H*)-one **6a** was obtained exclusively in 90% yield (eq 2).



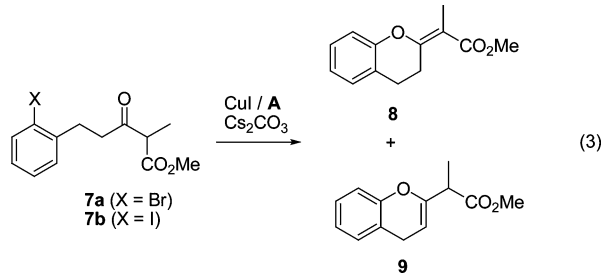
3a **6a** (90%) (2)

Apparently intramolecular C-arylation rather than O-arylation occurred for **3a**. This prompted us to examine other *β*-keto esters of typical structures, and the results are illustrated in Table 3. The reactions were carried out under the conditions shown in eq 2 without further optimization. With the introduction of a substituent at *γ*- or *δ*-position of the *β*-keto esters, the

C-arylation proceeded smoothly and was complete within a shorter time as compared to that of **3a** or **3b** (entries 2−5, Table 3). This trend might be attributed to the helpful steric impact of the substituents on the cyclization. Both *m*-methoxy-substituted substrate **3g** and *p*-acetyl-substituted substrate **3h** afforded the corresponding products **6g** and **6h**, respectively, demonstrating the generality of the above methodology (entries 6 and 7, Table 3). To the best of our knowledge, there is no report on the copper-catalyzed intramolecular C-arylation, although progress has been made on the intermolecular C-arylation in recent years.[14,15]

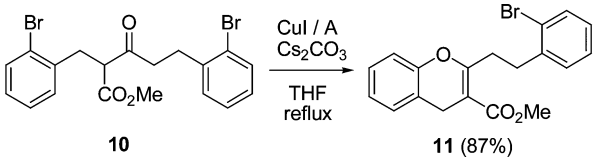
We further prepared α-methyl-substituted *δ*-(2-bromophenyl)-*β*-keto ester **7a** and subjected it to the same treatment described above in an attempt to create an all-carbon quaternary center in the corresponding C-arylation product. However, no C-arylation product could be detected. Instead, the O-arylation products **8** and **9** were now isolated in an overall 75% yield with a ratio of ∼1:1 (eq 3). Obviously, the inhibition of C-arylation should be attributed to the steric hindrance caused by the methyl group at the α-position. A similar situation was also reported in the intermolecular arylation of 1,3-dicarbonyls[14f] as well as in O-vinylation cases.[3f] Compound **8** was obtained as a single stereoisomer whose configuration was determined by its NOESY experiments. The formation of 4*H*-1-benzopyran **9** should be attributed to the isomerization of **8** under the experimental conditions. This was evidenced by the treatment of a pure sample of **8** under the above reaction conditions in which about 50% of **8** underwent isomerization to **9**. Moreover, when we carried out the reaction of **7a** with an excess of CuI (1.5 equiv) and DMEDA (3 equiv) at a lower temperature (90 °C) for 20 h, only **8** was obtained in 45% yield, while no **9** could be detected. However, the reaction was contaminated by the generation of 1-(2-bromophenyl)-3-pentanone in 25% yield as the direct decarboxylative product. Apparently, the presence of excess CuI/DMEDA encouraged the decarboxylation of the substrate **7a**. As a comparison, we prepared aryl iodide **7b** as the analogue of **7a**. Treatment of **7b** with CuI (10 mol %), DMEDA (20 mol %), and Cs_2CO_3 (2 equiv) in THF at reflux for 11 h led to the formation of 3,4-dihydro-2*H*-1-benzopyran **8** in 70% yield, while no decarboxylation byproduct could be isolated. The reason for the excellent stereoselectivity in **8** remains unclear.

The above results clearly demonstrate that the competition between O-arylation and C-arylation depends heavily on the structural pattern of the substrates, which in turn implies that the relative stability of the possible seven-membered (including Cu) transition state[3d,9b,14f] conformations for O- and C-cyclization is sensitive to the substituent effect. The transition structures for the O-arylation of **2a**−**i** have an endocyclic double bond, while the transition structures for the O-arylation of **7a** require an exocyclic double bond. Apparently, the transition states of O-arylation are more favorable with an endocyclic double bond



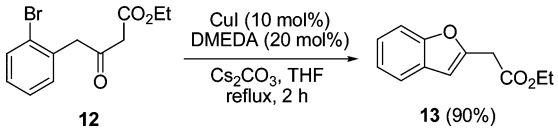
(3)

than with an exocyclic double bond. This was evidenced by the fact that the O-arylation of **2a** proceeded smoothly in refluxing THF, while the reaction of **7a** had to be conducted at a higher temperature. In a similar fashion, the transition structures for the C-arylation of **3a**−**h** also possess an endocyclic enol double bond, while those for the O-arylation of **3a**−**h** would have an exocyclic double bond. As a result, C-arylation predominated in the cyclization of **3a**−**h**. To provide further evidence on this assumption, we synthesized compound **10** having two aryl bromide moieties. The cyclization of **10** would have two possibilities: to generate 4*H*-1-benzopyran (similar to **5**) or to generate 3,4-dihydro-2*H*-1-benzopyran (similar to **8**). It turned out that only 4*H*-1-benzopyran **11** was achieved in high yield (eq 4), in good agreement with our hypothesis.



(4)

On the basis of the above six-membered ring closure, we were curious of the possibility of C-arylation in five-membered ring closure. However, the reaction of *γ*-(2-bromophenyl)-*β*-keto ester **12** gave only the corresponding benzo[*b*]furan **13** as the O-arylation product, while no C-arylation could be observed (eq 5).



(5)

In summary, we have successfully developed an efficient protocol for the copper-catalyzed intramolecular O- and C-arylation of *β*-keto esters via a six-membered ring closure. While the reactions of α-(2-bromobenzyl)-*β*-keto esters afforded the corresponding substituted 4*H*-1-benzopyrans in high yields via O-arylation, those of *δ*-(2-bromophenyl)-*β*-keto esters led to the exclusive formation of 3,4-dihydronaphthalen-2(1*H*)-one derivatives via C-arylation. Thus, with the appropriate choice of substrates, chemoselective O-arylation or C-arylation could be well implemented. This finding should be of important implication in the further development of copper-catalyzed Ullmann coupling reactions.

Experimental Section

Typical Procedure for Copper-Catalyzed O-Arylation: *N*,*N*′-Dimethylethylenediamine (4.3 *μ*L, 0.04 mmol) in THF (2 mL) was added to the mixture of CuI (3.8 mg, 0.02 mmol), aryl bromide **2a** (57 mg, 0.2 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) in a round flask under nitrogen. The mixture was stirred at refluxing temper-

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(15) For a comprehensive review on palladium-catalyzed α-arylation of carbonyl compounds, see: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

ature for 1 h. TLC monitoring indicated that all the starting material **2a** was consumed. The resulting mixture was then cooled to room temperature, and ethyl acetate (20 mL) was added. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel with hexane/ethyl acetate (15:1, v/v) as the eluent to give the cyclized product **5a** as a colorless oil.[16] Yield: 40.5 mg (99%).

Typical Procedure for Copper-Catalyzed C-Arylation: *N*,*N*′-Dimethylethylenediamine (4.3 μL, 0.04 mmol) in dioxane (2 mL) was added to the mixture of CuI (3.8 mg, 0.02 mmol), aryl bromide **3a** (57 mg, 0.2 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) in a round flask under nitrogen. The mixture was stirred at refluxing temperature for 20 h. TLC monitoring indicated that all the starting material **3a** was consumed. The resulting mixture was then cooled to room temperature, and ethyl acetate (20 mL) was added. The same workup procedure described in the above O-arylation process was followed to give product **6a** as a colorless liquid.[17] Yield: 37 mg (90%).

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Supporting Information Available: Characterization of **2**, **3**, and **5**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060747T

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