JOC Article

Synthesis of Conformationally Restricted 2,3-Diarylbenzo[*b*]furan by the Pd-Catalyzed Annulation of *o*-Alkynylphenols: Exploring a Combinatorial Approach

Youhong Hu,*,† Kenneth J. Nawoschik,† Yun Liao,† Jian Ma,† Reza Fathi,*,† and Zhen Yang*,†,‡

VivoQuest, Inc., 711 Executive Boulevard, Valley Cottage, New York 10989, and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing, P. R. China 100871

z.yang@vivoquest.com

Received October 14, 2003

The palladium/bpy-catalyzed annulation of *o*-alkynylphenol with various aryl halides to generate diversified 2,3-diarylbenzo[*b*]furan is herein described. This method provides an efficient synthetic pathway for the combinatorial synthesis of conformationally restricted 2,3-diarylbenzo[*b*]furan for drug discovery.

Introduction

Atropisomers, in which chirality is generated by the formation of two or more stable rotational isomers, are types of molecules that have a unique potential for asymmetric recognitions and have been used both in asymmetric catalysis (such as BINAP[1]) and in therapeutic medicine (such as vancomycin[2]). Realizing the importance of the diaryl-based atropisomers in biomedical research, we recently embarked on a new program to study the properties of an interesting candidate for atropisomerism consisting of a benzofuran scaffold with rotationally restricted diaryl frameworks (Figure 1).

Construction of a conformationally constrained diaryl system in association with a benzofuran pharmacophore acting independently as a template for further spatial representation of the molecule to the protein target exemplifies the medicinal chemistry approach that seeks to fix the position of the aryl groups in space. These structural features, along with a potential orthogonal site for diversification in benzofuran ring systems, serve therefore to define a distinctive class of compounds having valuable properties as potential candidates for lead identification.

While rotational restriction in the diaryl scaffold can be advantageous with respect to its potential ability for biological recognition, the restriction energy barrier inherent in the final molecule might be cumbersome for the chemical synthesis.

Recently, considerable attention has been directed toward the synthesis of 2,3-diarylbenzo[*b*]furan.[3] However, development of efficient and general methods to generate diversified 2,3-diarylbenzo[*b*]furans still presents a major challenge in organic synthesis. We report herein our finding that $Pd_2(dba)_3$/bipyridine is an effective catalyst for both the synthesis of discrete compounds and the construction of a molecular library of 2-substituted-3-arylbenzo[*b*]furan, the latter being a powerful paradigm in the development and design of potentially active compounds optimized for biological recognition.

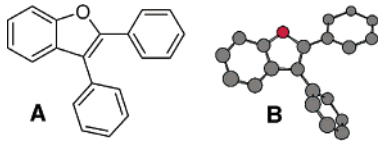


FIGURE 1. Structure of 2,3-diarylbenzo[*b*]furan **A** and its MM2-calculated minimum structure **B**.

The metal-catalyzed intramolecular cyclization of aryl-substituted alkynes possessing a nucleophile in proximity to the triple bond has been proven to be effective for the synthesis of five-membered heterocycles (Figure 2),[4] and the first report describing the synthetic efforts relevant to 2,3-diarylbenzo[*b*]furan with this approach was described by Arcadi in 1996.[5]

He accomplished the formation of the 2,3-disubstituted product **D** by the palladium-catalyzed annulation of *o*-alkynylphenol with various aryl halides (Scheme 1), alas in low yield. In his reaction, compound **E** was the major product, which was generated by direct cyclization of alkynylphenol.

† VivoQuest, Inc.
‡ Peking University.

(1) (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1−3. (b) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: New York, 2000. (c) Pu, L. *Chem. Rev.* **1998**, *98*, 2405. (d) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(2) (a) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172. (b) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096.

(3) (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (b) Hellwinkel, D.; Göke, K. *Synthesis* **1995**, 1135. (c) Katritzky, A. R.; Fali, C. N.; Li, J.-Q. *J. Org. Chem.* **1997**, *62*, 8205. Schmittel, M.; Langels, A. *J. Org. Chem.* **1998**, *63*, 7328. (d) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **2000**, 1432. (e) Dai, W.-M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377. (f) Morrison, B. J.; Musgrave, O. C. *Tetrahedron* **2002**, *58*, 4255. (g) Arcadi, A.; Cacchi, S.; Gluseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409.

10.1021/jo0303160 CCC: $27.50
Published on Web 03/09/2004

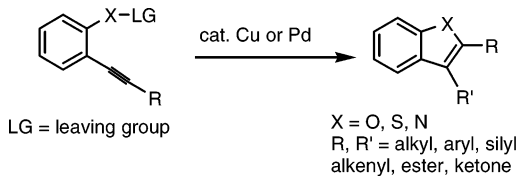
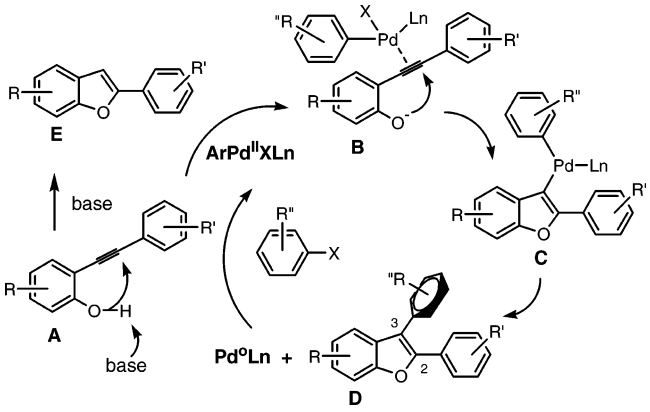


FIGURE 2. Transition-metal-catalyzed formation of five-membered heterocycles.

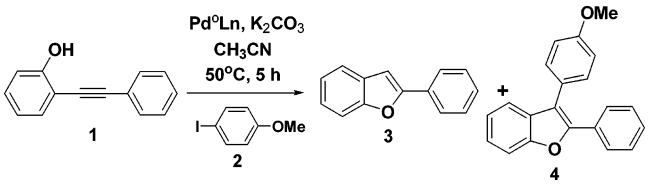
SCHEME 1. *O*-Alkynylphenol Cyclization



More recently, Flynn and colleagues[6] disclosed an efficient approach to synthesize 2-substituted-3-arylbenzo[*b*]furan by the palladium-catalyzed multicomponent sequential coupling strategy, starting from iodophenol and terminal phenyl acetylene. In this reaction, MeMgBr was used as an essential base to form the corresponding magnesium salts of phenolate and acetylene. Although the method was successfully applied to one substituted iodobenzene, utilization of MeMgBr to form the magnesium salts could hamper application of this method to other substrates having functional groups such as ketone, ester, or amide, thus limiting the universality required in diversity oriented synthesis. Short of a universal synthetic method that could be applied homogeneously across diverse building blocks to construct this type of motif, we decided to focus our efforts on the reevaluation of this reaction leading to the final desired products based on the earlier studies reported by Arcadi in 1996.

We have previously described syntheses of 2-substituted benzo[*b*]furan-3-carboxylate and 2-substituted 3-aroylbenzo[*b*]furan by the palladium-catalyzed carbonylative annulation of *o*-alkynylphenol, both in solution phase and solid phase.[7] As part of a combinatorial program at VivoQuest, we were interested in generating a library of 2-substituted 3-arylbenzo[*b*]furan-based heterocyclic atropisomers from the same starting material *o*-alkynylphenol to realize a strategy of diversity oriented synthesis and branching reaction pathways.[8]

TABLE 1. Palladium-Catalyzed Annulations of *o*-Alkynylphenol 1



entry	catalyst	yield of compd **4**[a]
1	$Pd(PPh_3)_4$	7
2	$Pd_2(dba)_3$	11
3	$Pd_2(dba)_2$/*Pt*-Bu_3	15
4	$Pd_2(dba)_3$/dppf	39
5	$Pd_2(dba)_2$/bpy	70

Results and Discussion

In our initial investigation, *o*-alkynylphenol **1** and *p*-methoxyiodobenzene **2** were used as substrates to form 2-substituted 3-arylbenzo[*b*]furan with $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd_2(dba)_3/PtBu_3$, and $Pd_2(dba)_3$/dppf) acting as catalysts. This proved unsuccessful, since the direct cyclized product **3** was predominant under a variety of tested conditions, and the desired compound **4** was always obtained as a minor product (see entries 1−4 in Table 1).

We then tested bipyridine (bpy)[9] as a ligand in the following annulation reactions. In contrast to our earlier study, compound **4** was the major product.

Given the success of this new observation, we further studied the substrate's electronic effect on this bidented palladium complex. To this end, three additional *o*-alkynylphenols **1a**−**c** and six aryl iodides **2a**−**f** were chosen and were combined into 12 different groups. To our satisfaction, all the reactions proceeded successfully. Interestingly, the aryl iodides with electron-withdrawing groups (see entries 2, 4, 7, and 10) gave the best results, presumably due to their favorable effect on the oxidative addition to the Pd^0 complex. Table 2 lists the results of these favorable annulations (see the Supporting Information for details).

The positive result of this wider range of substrates which undergo cyclization to their corresponding 2,3-

(4) (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett*. **1992**, *333*, 3915. (b) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Orgnomet. Chem*. **1994**, *475*, 289. (c) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett*. **1998**, *63*, 5306. (d) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem*. **1998**, *63*, 7652. (e) Cacchi, S. *J. Organomet. Chem*. **1999**, *576*, 42. (f) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 297. (g) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (h) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett*. **2001**, *3*, 2973. (i) Roesch, K. R.; Larock, R. C. *J. Org. Chem*. **2001**, *66*, 412. (j) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G. Marinelli, F. *Synlett* **2002**, 453. (k) Yue, D.; Larock, R. C. *J. Org. Chem*. **2002**, *67*, 1905. (l) Hu, Y.-H.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem*. **2002**, *67*, 2365.

(5) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem*. **1996**, *61*, 9280.

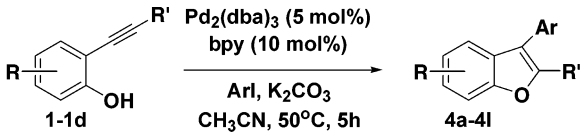
(6) (a) Chaplin, J. H.; Flynn, B. L. *Chem. Commun*. **2001**, 1594. (b) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem*. **2002**, *45*, 2670.

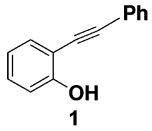
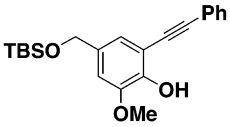
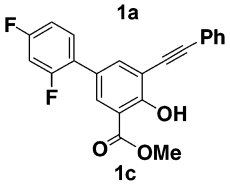
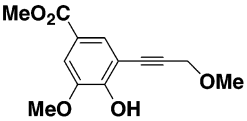
(7) (a) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 297. (b) Hu, Y.-H.; Yang, Z. *Org. Lett*. **2001**, *3*, 1387. (c) Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett*. **2001**, *42*, 1815. (d) Hu, Y.-H.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem*. **2002**, *67*, 2365. (e) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett*. **2002**, *4*, 2607. (e) Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett*. **2003**, *5*, 909. (f) Liao, Y.; Fathi, R.; Yang, Z. *J. Comb. Chem*. **2003**, *5*, 79.

(8) Liao, Y.; Hu, Y.-H.; Wu, J.; Zhu, Q.; Donovan, M.; Fathi, R.; Yang, Z. *Curr. Med. Chem*. **2003**, *10*, 2285.

(9) (a) Sinner, F.; Buchmeiser, M. R.; Tessadri, R.; Mupa, M.; Wurst, K.; Bonn, G. K. *J. Am. Chem. Soc*. **1998**, *120*, 2790. (b) Wu, G. G.; Wong, Y.-S.; Poirier, M. *Org. Lett*. **1999**, *1*, 745. (c) Buchmeiser, M. R.; Wurst, K. *J. Am. Chem. Soc*. **1999**, *121*, 11101. (d) Yagyu, T.; Osakada, K. *Organometallics* **2000**, *19*, 2125. (e) Silberg, J.; Schareina, T.; Kempe, R.; Wurst, K.; Buchmeiser, M. R. *J. Organomet. Chem*. **2001**, *622*, 6. (f) Buchmeiser, M. R.; Schareina, T.; Kempe, R.; Wurst, K. *J. Organomet. Chem*. **2001**, *634*, 39. (g) Mubofu, E. B.; Clark, J. H.; Macquarrie, D. J. *Green Chem*. **2001**, *3*, 1077.

TABLE 2. Palladium-Catalyzed Annulations of Diversified Aryl Iodides and *o*-Alkynylphenols



entry	*o*-arkynylphenol	aryl iodide	product (yield)[a]
1	 1	*p*-MePhI 2a	4a (64%)
2	1	*p*-NO_2PhI 2b	4b (87%)
3	1	*m*-MeOPhI 2c	4c (74%)
4	1	*p*-MeCOPhI 2d	4d (85%)
5	1	PhI 2e	4e (52%)
6	1	2-iodothiophene 2f	4f (66%)
7	 1a	2d	4g (82%)
8	1a	2a	4h (70%)
9	1a	2c	4i (70%)
10	 1c	2d	4j (72%)
11	1c	2a	4k (55%)
12	 1d	2d	4l (64%)

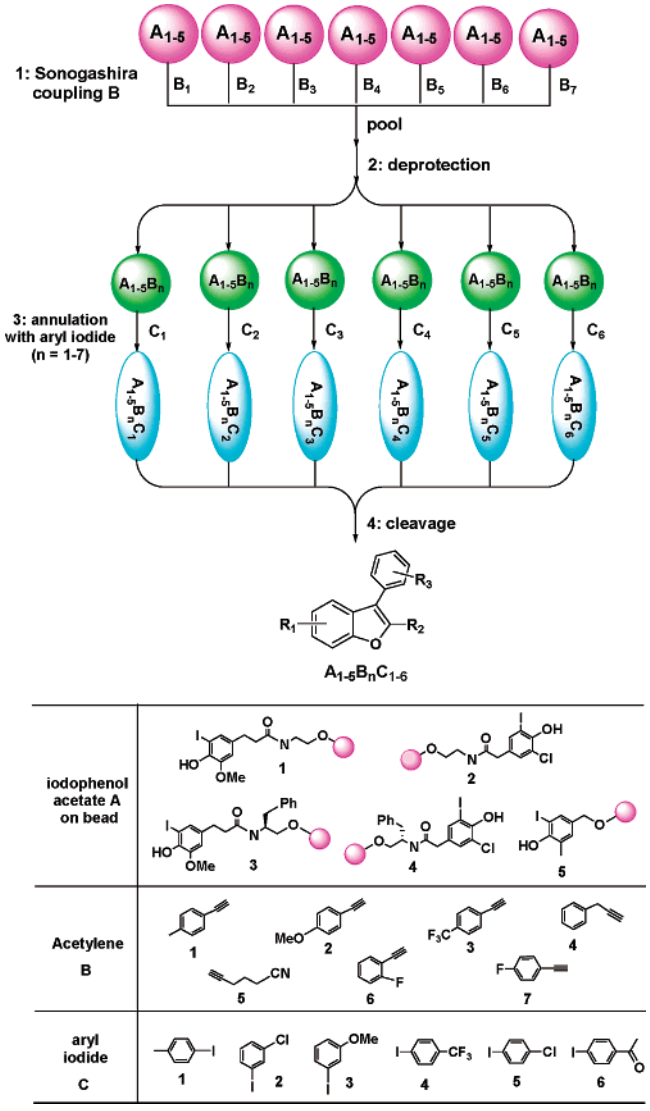
[a] Pure compound after flash chromatography.

diarylbenzo[*b*]furans was to offer an ideal route for the preparation of a wide variety of analogues. We therefore initiated a program for the solid-phase synthesis of a molecular library based on this scaffold, using silyl linker based high-capacity polystyrene macrobeads.[7c,e,10]

After extensive efforts on the solid-phase synthesis, we found that catalytic amounts of the catalyst $Pd_2(dba)_3$/bpy were not able to generate satisfactory results at 50 °C due to either direct cyclization or substrate decomposition under a variety of tested conditions. Eventually, we decided in favor of using 2 equiv of $Pd_2(dba)_3$ and 4 equiv of bpy and allowing the reaction to proceed at room temperature for 2 days. Using this methodology, a 210-compound library was made by means of radio frequency-tags-based IRORI Micro-Kans[11] as illustrated in Scheme 2.

Accordingly, the on-bead iodophenol acetates A_{1-5}[7e] (see Scheme 2) were split into seven pools and coupled with seven terminal acetylenes B_{1-7}, respectively, to give 35 coupling products. The compounds on the beads were pooled, and then underwent deacetylation with NH_2NH_2 in THF. The generated *o*-alkynylphenols ($A_{1-5} \times B_n$ in Scheme 2) were subjected to a second splitting into six

SCHEME 2. Solid-pHase Synthesis of 210-Membered 2-Substituted 3-Arylbenzo[*b*]furan Library[a]



[a] Conditions: (1) $PdCl_2(PPh_3)_2$ (0.3 equiv), CuI (0.2 equiv), DIEPA, acetylene, CH_3CN, 25 °C, 24 h; (2) NH_2NH_2/THF (0.1 M), 25 °C, 4 h; (3) $Pd_2(dba)_2$ (2.2 equiv), bpy (4.4 equiv), ArI, CsOAc, DMF, 25 °C, 48 h; (4) HF/Py (5% in THF), 25 °C, 1 h; then TMSOMe for 0.5 h.

(10) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Chem. Chem.* **2001**, *3*, 312.

(11) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed.* **1995**, *34*, 2289−2291.

pools for the palladium-catalyzed cyclization with aryl iodide to give 2,3-disubstituted benzo[*b*]furans, which after cleavage from the solid support by HF/Py and TMSOMe afforded a 210-membered library $A_{1-5}B_nC_{1-6}$ (see the Supporting Information for details).

To confirm the results, all the final products were subjected to LC−MS analysis, and 35 of them were selectively identified by ^{1}H NMR. Based on the LC−MS analysis results, among the 210 compounds that were synthesized, 104 gave the desired products with over 80% purity; 51 were between 70 and 80% purity; 29 were around 60% purity, and the rest of the 26 compounds were under 50% purity. As observed in the solution-phase synthesis, the aryl iodides with electron-withdrawing groups gave better annulations results than other types of aryl iodides.

In summary, we have described herein a practical method for the combinatorial synthesis of conformationally restrained molecules. In parallel with established methods in medicinal chemistry which seek to restrict the free bond rotation as a powerful tool for lead optimization, we have constructed a priori a large number of complex and diverse 2-substituted 3-arylbenzo[*b*]furans,[12] which encompass all the properties that are important in finding the lead molecule in advance. In addition, the synthesized compounds have been utilized directly in various biological assays without further purifications and some interesting compounds have been identified from our in-house target-based assays. This demonstrates the effectiveness of our approach in the exploration of molecular diversity in combination with rational and classical approaches for drug discovery.

Experimental Section

Synthesis of α-Alkynylphenol 1C. A mixture of phenyl iodide A (0.2 mmol), acetylene B (0.3 mmol), copper(I) iodide (3.8 mg, 0.02 mmol), and dichlorobis(triphenylphosphine)-palladium (70.1 mg, 0.01 mmol) in dry acetonitrile (40 mL) was degassed with argon for 10 min. The reaction mixture was treated with triethylamine (280 μL, 2.0 mmol) and stirred at 25 °C for 24 h. The reaction mixture was concentrated, and the residue was purified by a flash column chromatography to afford the coupling product. The coupling product was treated with $NH_3{\cdot}H_2O$ (0.5 mL) in a solvent of THF and MeOH (1:1, 10 mL) at 25 °C for 30 min, followed by concentration; the residue was purified by a flash column chromatography to give the pure product in 72% yield: ^{1}H NMR δ 11.35 (s, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.72 (d, J = 1.5 Hz, 1H), 7.35 (m, 1H), 6.87 (m, 2H), 4.37 (s, 2H), 3.95 (s, 3H), 3.45 (s, 3H); ^{13}C NMR δ 170.2, 161.8, 139.4, 131.1, 130.9, 130.5, 130.4, 125.9, 112.7, 111.8, 111.7, 104.7, 104.5, 104.3, 90.6, 81.0, 60.5, 57.8, 52.7; MS [$C_{18}H_{14}F_2O_4$], m/z (M^+) calcd 332, found 332.

For information regarding the synthesis of intermediates **1**, **1a** and **1d**, see ref 4l.

General Procedure for the Palladium-Catalyzed Formation of 2,3-Biarylbenzo[*b*]furans. To a solution of acetonitrile (3.0 mL), ArI (2.0 mmol, 200mol %), bpy (16 mg, 0.1 mmol, 10 mol %), and K_2CO_3 (552 mg, 4.0 mmol) was added $Pd_2(dba)_3$ (46 mg, 0.05 mmol, 5 mol %), and the mixture was stirred at 50 °C for 1 h. To this solution was added a solution of *o*-alkylnylphenol (1.0 mmol, 100 mol %) in acetonitrile (2 mL), and the reaction mixture was stirred at 50 °C for 5 h under Ar_2 atmosphere. The reaction mixture was then concentrated, and the residue was filtered through a silica gel pad and eluted with EtOAc. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel to give the corresponding cyclization product.

Compound 4. Purification by flash chromatography (hexane/EtOAc = 20/1) gave **4** in 70% yield: ^{1}H NMR δ 7.71 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.34 (m, 4H), 7.26 (m, 1H), 7.03 (d, J = 8.0 Hz), 3.90 (s, 3H); ^{13}C NMR δ 159.1, 153.9, 150.3, 130.9, 130.8, 130.5, 128.4, 128.2, 126.9, 124.9, 124.6, 122.8, 120.0, 117.1, 114.4, 111.1, 55.3; MS (APCI) [$C_{21}H_{16}O_2$] m/z (M^+ + 1) calcd 301, found 301.

Compound 4a. Purification by flash chromatography (hexane/EtOAc = 20/1) gave **4a** in 64% yield: ^{1}H NMR δ 7.70 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 7.5 Hz, 2H), 7.37−7.24 (m, 9H), 2.47 (s, 3H); ^{13}C NMR δ 153.9, 150.3, 137.3, 130.8, 130.3, 129.7, 129.6, 129.5, 128.3, 128.2, 126.9, 124.5, 122.8, 120.0, 117.4, 111.0, 21.3; MS (APCI) [$C_{21}H_{16}O$] m/z (M^+) calcd 284, found 284.

Compound 4b. Purification by flash chromatography (hexane/EtOAc = 15/1) gives **4b** in 84% yield: ^{1}H NMR δ 8.32 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.60 (m, 3H), 7.52 (d, J = 8.0 Hz, 1H), 7.37 (m, 4H), 7.30 (dd, J = 8.0 Hz, 1H); ^{13}C NMR δ 154.2, 151.9, 147.1, 140.2, 130.5, 129.8, 129.2, 128.9, 128.8, 127.5, 125.3, 124.3, 123.5, 119.5, 115.4, 111.5; MS (APCI) [$C_{20}H_{13}NO_3$] m/z (M^+) calcd 315, found 315.

Compound 4c. Purification by flash chromatography (hexane/EtOAc = 20/1) gave **4c** in 74% yield: ^{1}H NMR δ 7.71 (dd, J = 6.5, 1.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.40 (m, 1H), 7.34 (m, 5H), 7.26 (m, 1H), 7.11 (d, J = 7.0 Hz), 7.07 (m, 1H), 6.98 (dd, J = 8.0, 1.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR δ 160.0, 153.9, 150.6, 134.2, 130.6, 130.2, 130.0, 128.4, 128.4, 127.1, 124.7, 122.9, 122.2, 120.1, 117.4, 115.02, 113.5, 111.1, 55.3; MS (APCI) [$C_{21}H_{16}O_2$] m/z (M^+ + 1) calcd 301, found 301.

Compound 4d. Purification by flash chromatography (hexane/EtOAc = 10/1) gave **4d** in 85% yield: ^{1}H NMR δ 8.06 (dm, J = 8.5 Hz, 2H), 7.63 (m, 4H), 7.58 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 7.5, 1.0 Hz, 1H), 7.37 (dd, J = 7.5, 1.0 Hz, 1H), 7.33 (m, 3H), 7.27 (dd, J = 8.0, 1.0 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR δ 197.7, 154.1, 151.3, 138.2, 136.2, 130.2, 129.9, 129.7, 129.5, 129.0, 128.8, 128.6, 127.3, 124.9, 123.2, 119.8, 116.5, 111.3, 26.7; MS (APCI) [C22H16O2] m/z (M^+ + 1) calcd 313, found 313.

Compound 4e. Purification by flash chromatography (hexane/EtOAc = 20/1) gives **4e** in 52% yield: ^{1}H NMR δ 7.65 (dm, J = 8.5 Hz, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (m, 3H), 7.47 (m, 2H), 7.41 (d, J = 7.5 Hz, 1H), 7.34−2.28 (m, 4H), 7.24 (m, 1H); ^{13}C NMR δ 154.0, 150.5, 132.9, 130.7, 130.2, 129.8, 128.9, 128.4, 128.4, 127.6, 127.0, 124.7, 122.9, 120.0, 117.5, 111.1; MS (APCI) [$C_{20}H_{14}O$] m/z (M^+ + 1) calcd 271, found 271.

Compound 4f. Purification by flash chromatography (hexane/EtOAc = 10/1) gave **4f** in 66% yield: ^{1}H NMR δ 7.76 (d, J = 6.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.45 (d, J = 5.0 Hz, 1H), 7.35 (m, 4H), 7.28 (m, 1H), 7.20 (d, J = 3,5 Hz, 1H), 7.17 (m, 1H); ^{13}C NMR δ 153.8, 151.7, 133.3, 130.3, 130.2, 128.7, 128.5, 127.6, 127.4, 127.3, 126.2, 124.9, 123.1, 120.2, 110.7; MS (APCI) [$C_{18}H_{12}OS$], m/z (M^+ + 1) calcd. 277, found 277; MS (APCI) [$C_{18}H_{12}OS$] m/z (M^+ + 1) calcd 227, found 227.

Compound 4g. Purification by flash chromatography (hexane/EtOAc = 3/1) gave **4g** in 82% yield: ^{1}H NMR δ 8.05 (d, J = 8.0 Hz, 2H), 7.65 (m, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.32 (m, 3H), 7.05 (s, 1H), 6.91 (s, 1H), 4.80 (s, 2H), 4.08 (s, 3H), 2.67 (s, 3H), 0.95 (s, 6H), 0.01 (s, 9H); ^{13}C NMR δ 197.9, 151.9, 145.4, 142.9, 138.5, 138.0, 136.4, 131.1, 130.4, 130.1, 129.2,

(12) During preparation of our manuscript, a related paper was published: Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett*. **2003**, *5*, 2441. The paper reported a similar approach to synthesize furo[2,3-*b*]pyridones by one-pot coupling of 3-iodopyridones, alkynes, and organic halides. The authors proposed that the complexation of palladium catalyst to the *o*-alkoxy group on the phenyl ring might contribute to generation of the desired compounds, which might limit the scope of substrate for the reaction.

129.0, 128.7, 127.6, 117.0, 109.4, 106.0, 65.5, 56.4, 26.9, 26.2, 18.7, −4.9; MS (APCI) [$C_{30}H_{34}O_4Si$] *m*/*z* ($M^+ + 1$) calcd 487, found 487.

Compound 4h. Purification by flash chromatography (hexane/EtOAc = 5/1) gave **4h** in 70% yield: ^{1}H NMR δ 7.72 (dm, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (m, 5H), 7.04 (s, 1H), 6.92 (s, 1H), 4.80 (s, 2H), 4.08 (s, 3H), 2.45 (s, 3H), 0.97 (s, 6H), 0.01 (s, 9H); ^{13}C NMR δ 150.7, 144.9, 142.4, 137.2, 131.7, 130.6, 129.7, 129.5, 129.5, 128.6, 128.2, 128.1, 126.9, 124.9, 117.7, 109.6, 105.6, 65.3, 56.1, 25.9, 21.3, 18.4, −5.2; MS (APCI) [$C_{29}H_{34}O_3Si$] *m*/*z* ($M^+ + 1$) calcd 459, found 459.

Compound 4i. Purification by flash chromatography (hexane/EtOAc = 4/1) gave **4i** in 70% yield: ^{1}H NMR δ 7.71 (dm, J = 8.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.34−7.27 (m, 3H), 7.10 (dm, J = 7.5 Hz, 1H), 7.05 (m, 2H), 6.97 (dm, J = 8.5 Hz, 1H), 6.92 (s, 1H), 4.80 (s, 2H), 4.08 (s, 3H), 3.81 (s, 3H), 0.96 (s, 6H), 0.00 (s, 9H); ^{13}C NMR δ 159.9, 150.9, 144.9, 142.4, 137.3, 134.1, 131.5, 130.4, 129.9, 128.3, 128.2, 127.1, 122.1, 117.6, 114.8, 113.4, 109.5, 105.6, 65.3, 56.1, 55.2, 25.9, 18.3, −5.2; MS (APCI) [$C_{29}H_{34}O_4Si$] *m*/*z* ($M^+ + 1$) calcd 475, found 475.

Compound 4j. Purification by flash chromatography (hexane/EtOAc = 5/1) gave **4j** in 72% yield: ^{1}H NMR δ 8.15 (m, 1H), 8.10 (dm, J = 8.5 Hz, 2H), 7.93 (t, J = 1.5 Hz, 1H), 7.70 (dm, J = 8.5 Hz, 2H), 7.43 (m, 1H), 6.95 (m, 2H), 4.64 (s, 2H), 4.05 (s, 3H), 3.51 (s, 3H), 2.66 (s, 3H); ^{13}C NMR δ 197.6, 164.9, 152.9, 152.5, 136.5, 136.0, 131.8, 131.7, 131.7, 131.6, 130.3, 129.6, 129.4, 129.0, 128.7, 128.7, 125.4, 125.4, 120.1, 115.5, 111.8, 104.5, 65.1, 58.7, 52.5, 26.7; MS (APCI) [$C_{26}H_{20}F_2O_5$] *m*/*z* ($M^+ + 1$) calcd 451, found 451.

Compound 4k. Purification by flash chromatography (hexane/EtOAc = 5/1) gave **4k** in 55% yield: ^{1}H NMR δ 8.12 (m, 1H), 7.92 (m, 1H), 7.46 (d, J = 7.5 Hz, 2H), 7.42 (m, 1H), 7.32 (d, J = 8.5 Hz), 6.95 (m, 2H), 4.64 (s, 2H), 4.04 (s, 3H), 3.49 (s, 3H), 2.43 (s, 3H); ^{13}C NMR δ 165.2, 152.5, 151.9, 137.9, 131.8, 131.8, 131.7, 131.7, 130.3, 129.9, 129.7, 129.1, 128.3, 128.3, 127.9, 125.7, 125.7, 120.9, 115.2, 111.7, 104.4, 65.1, 58.6, 52.4, 21.3; MS (APCI) [$C_{26}H_{20}F_2O_4$] *m*/*z* ($M^+ + 1$) calcd 423, found 423.

Compound 4l. Purification by flash chromatography (hexane/EtOAc = 2/1) gives **4l** in 64% yield: ^{1}H NMR δ 8.12 (dm, J = 8.5 Hz, 2H), 7.99 (d, J = 1.5 Hz, 1H), 7.69 (dm, J = 9.0 Hz, 2H), 7.58 (d, J = 1.5 Hz, 1H), 4.58 (s, 2H), 4.08 (s, 3H), 3.93 (s, 3H), 3.47 (s, 3H), 2.67 (s, 3H); ^{13}C NMR δ 197.6, 167.1, 152.3, 146.6, 145.3, 136.4, 136.1, 129.3, 128.9, 128.8, 126.5, 121.1, 115.3, 108.1, 65.1, 58.6, 56.3, 52.3, 26.7; MS (APCI) [$C_{21}H_{20}O_6$] *m*/*z* ($M^+ + 1$) calcd 369, found 369.

Supporting Information Available: Experimental procedures and NMR and LC−MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0303160