Sequential and One-Pot Reactions of Phenols with Bromoalkynes for the Synthesis of (*Z*)-2-Bromovinyl Phenyl Ethers and Benzo[*b*]furans
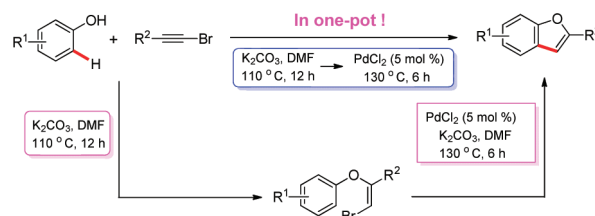
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ABSTRACT

Benzo[*b*]furans were prepared in one pot based on the addition/palladium-catalyzed C−H bond functionalization of phenols with bromoalkynes. The addition reactions of phenols to bromoalkynes generated (*Z*)-2-bromovinyl phenyl ethers in high yields with excellent regio- and stereoselectivity. The obtained (*Z*)-2-bromovinyl phenyl ethers subsequently proceeded by intramolecular cyclization to afford 2-substituted benzo[*b*]furans in good yields through palladium-catalyzed direct C−H bond functionalizations. It is important to note that the transformation of phenols with bromoalkynes into benzo[*b*]furans could be carried out in one pot with a simple and efficient tandem procedure.

Benzo[*b*]furans, which display a wide range of biological activities, are versatile synthetic blocks and important structural skeletons of natural products and potential drug molecules.[1] For their potential applications, the development of a convenient synthetic pathway is highly desirable. Among the traditional methods for the synthesis of benzo-[*b*]furans, palladium-catalyzed tandem Sonagashira coupling/5-*endo-dig* cyclization starting from alkynes and *o*-halophenols is the most efficient protocol.[2] And it offers increased functional group tolerance and improved yields of the desired compounds, but the scope of *o*-halophenols is limited. However, simple phenols without halogen and simple alkynes have rarely been used as starting material to

directly prepare them.[3] Recently, an iron-catalyzed oxidative Pechmann condensation reaction of simple phenols with *β*-ketoesters to benzo[*b*]furans was developed in the presence of an oxidant.[4]

Bromoalkynes, easily prepared from terminal alkynes with NBS in almost quantitative yields, are one kind of the most important intermediates and versatile building blocks in organic synthesis.[5] For example, they are widely used as one of the coupling partners in transition-metal-catalyzed carbon−carbon and carbon−heteroatom bond formations via cross-coupling reactions.[6] Meanwhile, transition-metal-catalyzed C(sp)−Br bonds of bromoalkynes were inserted into unsaturated compounds and C(sp3)−X bonds have been explored recently.[7] On the other hand, a silver-catalyzed nucleophilic addition of an acetic anion to bromoalkynes and a nucleophilic addition of an iodide anion to bromoalkynes were developed by Jiang in 2010.[8]

(1) For recent reviews, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (e) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) For representative examples, see: (a) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (e) Genin, E.; Amengual, R.; Michelet, V.; Savignac, M.; Jutand, A.; Neuville, L.; Genêt, J.-P. *Adv. Synth. Catal.* **2004**, *346*, 1733.

(3) For palladium-catalyzed synthesis of benzo[*b*]furans from phenols with propiolates, see: (a) Li, C.; Zhang, Y.; Li, P.; Wang, L. *J. Org. Chem.* **2011**, *76*, 4692. (b) For Zn(OTf)$_2$-catalyzed synthesis of benzo-[*b*]furans from phenols with proparyl alcohols, see: Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951.

(4) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387.

(5) Nie, X.; Wang, G. *J. Org. Chem.* **2006**, *71*, 4734.

The reported nucleophilic additions and transition-metal-catalyzed bond formation reactions encouraged us to explore the novel reactions on the basis of bromoalkynes. Herein, we report a base-promoted addition reaction of phenols to bromoalkynes under metal-free reaction conditions, which generated (*Z*)-2-bromovinyl phenyl ethers in high yields with excellent regio- and stereoselectivity. The obtained (*Z*)-2-bromovinyl phenyl ethers proceeded by intramolecular cyclization to afford the corresponding 2-substituted benzo[*b*]furans in good yields via palladium-catalyzed direct C−H bond functionalizations.[9] It is important to note that the transformation of phenols with bromoalkynes into benzo[*b*]furans could be carried out in one pot with a simple and efficient tandem procedure.

In the initial exploration of the addition reaction of simple phenols to bromoalkynes, 4-nitrophenol (**1a**) and phenylethynyl bromide (**2a**) were chosen as model substrates for our investigation. The effect of base on the model reaction was examined. To our delight, the model reaction proceeded smoothly and generated the corresponding addition product **3a** in 92 and 94% yields, when 2 equiv of K_2CO_3 and Cs_2CO_3 were used as bases in DMF at 110 °C for 12 h (Supporting Information, Table S1). It was found that other bases such as LiO^{t}Bu, K_3PO_4, KO^{t}Bu, KOH, Na_2CO_3, $KHCO_3$, and KF were inferior and generated the desired product **3a** in 18−73% yields. Only a trace amount of **3a** was detected when KOAc was used as a base. Unfortunately, organic bases such as Et_3N and DBU failed to promote the reaction. With respect to the base loading, 2 equiv of K_2CO_3 or Cs_2CO_3 were found to be optimal. When the model reaction was carried out in the presence of Cs_2CO_3, a significant solvent effect was observed. Among the solvents tested, DMF was found to be the best one. Good yields (71−80%) of **3a** were obtained when DMSO, DMA, and NMP were used as solvents respectively. However, when the reaction was carried out in CH_3CN, a 42% yield of **3a** was isolated. Only a trace amount of **3a** was detected when the reaction was carried

(6) (a) Besseliévre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (b) Shi, W.; Luo, Y.; Luo, X.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 14713. (c) Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 9447. (d) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630. (e) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980. (f) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (g) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (h) Xu, H.; Zhang, Y.; Huang, J.; Chen, W. *Org. Lett.* **2010**, *12*, 3704. (i) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (j) Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (k) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

(7) (a) Morishita, T.; Yoshida, H.; Ohshita, J. *Chem. Commun.* **2010**, *46*, 640. (b) Li, Y.; Liu, X.; Jiang, H.; Feng, Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 3338. (c) Chen, X.; Kong, W.; Cai, H.; Kong, L.; Zhu, G. *Chem. Commun.* **2011**, *47*, 2164.

(8) (a) Chen, Z.; Jiang, H.; Li, Y.; Qi, C. *Chem. Commun.* **2010**, *46*, 8049. (b) Chen, Z.; Li, J.; Jiang, H.; Zhu, S.; Li, Y.; Qi, C. *Org. Lett.* **2010**, *12*, 3262.

(9) Selected recent reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Bergman, R. G. *Nature* **2007**, *446*, 391. (e) Godula, K.; Sames, D. *Science* **2006**, *312*, 67.

Table 1. Addition Reaction of Phenols to Bromoalkynes, and Intramolecular Cyclization of (*Z*)-2-Bromovinyl Phenyl Ethers[a]

entry	R^1	R^2	**3**, yield [%][b]	**4**, yield [%][b]
1	*p*-NO$_2$	C_6H_5	**3a**, 94	**4a**, 92
2	*p*-CN	C_6H_5	**3b**, 92	**4b**, 91
3	*p*-CHO	C_6H_5	**3c**, 89	**4c**, 89
4	*p*-CO$_2$(*n*-C$_4$H$_9$)	C_6H_5	**3d**, 88	**4d**, 87
5	H	C_6H_5	**3e**, 78	**4e**, 86
6	*m*-CH$_3$	C_6H_5	**3f**, 73	**4f**, 85
7	*p*-CH$_3$	C_6H_5	**3g**, 75	**4g**, 81
8	*p*-CH$_3$O	C_6H_5	**3h**, 71	**4h**, 83
9	*o*-C$_6$H$_5$	C_6H_5	**3i**, 83	**4i**, 82
10	*p*-NO$_2$	*p*-FC$_6$H$_4$	**3j**, 81	**4j**, 82
11	*p*-NO$_2$	*p*-ClC$_6$H$_4$	**3k**, 78	**4k**, 85
12	*p*-NO$_2$	*p*-(*t*-C$_4$H$_9$)C$_6$H$_4$	**3l**, 94	**4l**, 90

[a] Reaction conditions: step 1: phenol (1.1 mmol), bromoalkyne (1.0 mmol), DMF (2.0 mL), Cs_2CO_3 (2.0 mmol) at 110 °C, 12 h; step 2: (*Z*)-2-bromovinyl phenyl ether (**3**, 1.0 mmol), PdCl$_2$ (0.05 mol), DMF (2.0 mL), K_2CO_3 (2.0 mmol) at 130 °C, 6 h. [b] Isolated yields.

out in THF, EtOH, DCE, dioxane, 1,2-dimethoxyethane, chlorobenzene, toluene, or benzene.

Under the above metal-free reaction conditions, a variety of substituted phenols reacted smoothly with phenylethynyl bromide (**2a**) to generate the corresponding addition products in good yields (Table 1, **3a**−**i**) with excellent regio- and stereoselectivity. As can be seen from Table 1, the reactivity of the phenol with an electron-withdrawing group, such as NO_2, CN, CHO, or CO_2(*n*-C$_4$H$_9$) at the *para*-position, is more than that of the phenol without a substituted group and with an electron-donating group at the *para*- or *meta*-position (Table 1, **3a**−**d** vs **3e**−**h**). The *ortho*-position effect of phenol was not observed in the reaction of 2-phenylphenol with **2a**, which generated **3i** in 83% yield. The reactions of 4-nitrophenol with (4-fluorophenyl)-, (4-chlorophenyl)-, and (4-*tert*-butylphenyl)ethynyl bromides proceeded well and generated the corresponding products **3j**−**l** in good yields.

With prepared addition products (*Z*)-2-bromovinyl phenyl ethers **3a**−**l** in our hands, we then examined the second step: transforming **3a**−**l** into the corresponding 2-substituted benzo[*b*]furans using palladium-catalyzed direct C−H bond functionalization. First, the effect of a palladium source on the cyclization reaction of model substrate **3a** was examined in the presence of K_2CO_3 at 130 °C in DMF. The results indicated that the model reaction could be catalyzed by Pd^{II} salts or Pd^0 complexes and PdCl$_2$ displayed the highest reactivity in the model reaction and generated 5-nitro-2-phenylbenzofuran (**4a**) in 92% yield (Supporting Information, Table S2). When another palladium source, such as Pd(OAc)$_2$, Pd(CH$_3$CN)$_2$-Cl$_2$, Pd(PPh$_3$)$_2$Cl$_2$, or Pd(PPh$_3$)$_4$, was used instead of PdCl$_2$, 65−89% yields of **4a** were obtained. The base also

plays an important role in the cyclization reaction. K_2CO_3 was found to be the best one among the bases investigated. Other bases such as K_3PO_4, KO^tBu, Cs_2CO_3, and Na_2CO_3 were inferior and generated **4a** in 16−76% yields. Only a trace amount of **4a** was detected when KOAc or DBU was used as a base. The effect of solvent on the model reaction was also examined, and a significant solvent effect was observed. When the model reaction was carried out in the presence of $PdCl_2$ (5.0 mol %) and K_2CO_3, DMF was the most suitable reaction medium. A 51% yield of **4a** was isolated when the reaction was carried out in DMA. However, only a trace amount of **4a** was detected when the reaction was performed in DMSO, NMP, THF, CH_3CN, toluene, benzene, or 1,2-dichloroethane.

Under the optimization reaction conditions, the above prepared addition products (Z)-2-bromovinyl phenyl ethers **3a−l** proceeded through a palladium-catalyzed intramolecular cyclization smoothly via the direct C−H bond functionalization to generate the corresponding 2-substituted benzo[b]furans, **4a−l**. As can be seen from Table 1, substrates derived from phenylethynyl bromide and substituted phenols with either electron-donating or-withdrawing groups attached to the benzene rings were able to undergo an intramolecular cyclization reaction and generate the corresponding products **4a−i** in 81−92% yields. It should be noted that the palladium-catalyzed intramolecular cyclization reaction of (Z)-2-bromovinyl phenyl ether could tolerate an *ortho*-substituted group (**4i**). When substrates derived from 4-nitrophenol and substituted phenylethynyl bromide were also surveyed, 82−90% yields of **4j−l** were obtained. The results also showed that the electronic effect of phenylethynyl bromide substituents on the benzene rings had little impact on the yields of the products.

With the above addition reaction of simple phenols with bromoalkynes in the presence of K_2CO_3 generating (Z)-2-bromovinyl phenyl ethers in high yields, and the obtained (Z)-2-bromovinyl phenyl ethers undergoing palladium-catalyzed intramolecular cyclization to the corresponding 2-substituted benzo[b]furans in good yields in our hand, we next tried the reaction of simple phenols with bromoalkynes in the presence of a base and palladium catalyst in one pot because the transformation in one pot can simplify the sequence procedures and enhance the reaction efficiency. When the model reaction of **1a** with **2a** was carried out in the presence of K_2CO_3 (2.0 equiv) in DMF at 110 °C for 12 h, then $PdCl_2$ (5.0 mol %) was added, and the reaction was performed at 130 °C for 6 h. To our pleasure, the final product **4a** was isolated in 91% yield (Scheme 1, **4a**). Compared with the above two-step procedure synthesis, this tandem reaction in one pot could enhance the efficiency of preparing the target products from simple starting materials, avoid the separation of intermediates, save the use of solvents, and reduce the amount of pollutant waste emission. To examine the generality of this one-pot reaction, a variety of simple phenols and bromoalkynes were used as starting materials for the investigation. As can be seen from Scheme 1, the reactivity of the phenols with

Scheme 1. Palladium-Catalyzed One-Pot Synthesis of Benzo-[b]furans[a]
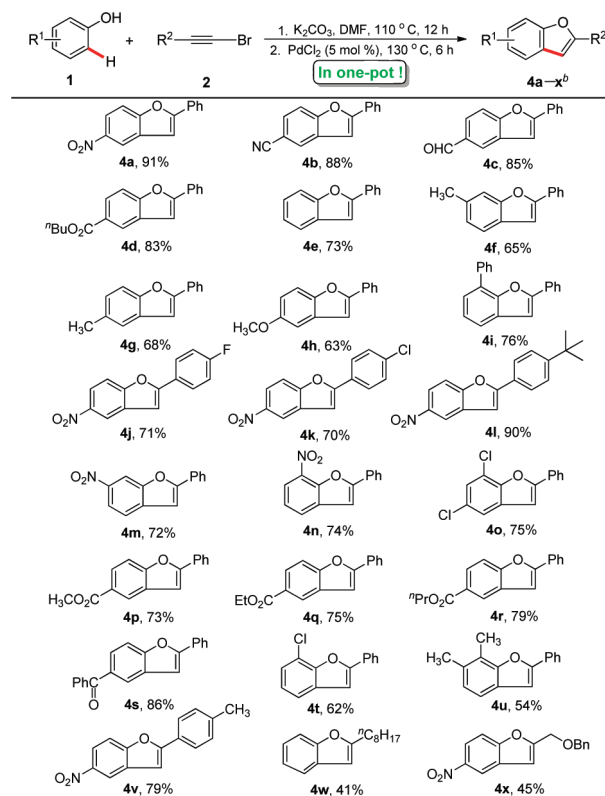
[a] Reaction conditions: phenol (1.1 mmol), bromoalkyne (1.0 mmol), DMF (2.0 mL), K_2CO_3 (2.0 mmol) at 110 °C for 12 h; then $PdCl_2$ (0.05 mmol) was added, at 130 °C for 6 h. [b] Isolated yields.

the electron-withdrawing groups at *para*-positions, such as NO_2, CN, CHO, COPh, and CO_2R groups, is more than that of the phenols with the electron-donating groups at *para*- or *meta*-positions (Scheme 1, **4a−d** and **4p−s** vs **4f−h**). The one-pot reaction also tolerated the *ortho*-substituted phenols with phenylethynyl bromide and generated the corresponding **4i**, **4n**, **4o**, **4t**, and **4u** in moderate to good yields under the present reaction conditions. When both *ortho*- and *meta*-positions of phenol were occupied by a methyl group, a 54% yield of the product **4u** was obtained. It should be noted that the cyclization products of 3-substituted phenols with phenylethynyl bromide were 6-substituted-2-phenylbenzofurans (**4f** and **4m**). When the reactions of 4-nitrophenol (**1a**) with substituted phenylethynyl bromides, such as (4-fluorophenyl)-, (4-chlorophenyl)-, (4-methylphenyl)-, and (4-*tert*-butylphenyl)ethynyl bromides, were carried out in one pot, the corresponding products were obtained in 70−90% yields (Scheme 1, **4j−l** and **4v**). It is important to note that about 40% yields of the desired products (**4w** and **4x**) were obtained when aliphatic alkyne bromides were used as one of the substrates.

The reaction was also extended to iodoalkyne with phenol. The addition of 4-nitrophenol to phenylethynyl iodide was clean, and an 88% yield of (Z)-2-iodovinyl phenyl ether was isolated (Supporting Information, Scheme S1). The one-pot reaction of 4-nitrophenol and phenylethynyl

iodide also proceeded efficiently to generate **4a** in 80% yield.

The prepared (*Z*)-2-bromovinyl phenyl ether (**3a**), with the bromine functional group on the terminal carbon−carbon double bond, as a very useful intermediate in organic synthesis,[7b,10] then reacted with *p*-tolylboronic acid, *p*-(*tert*-butyl)phenylacetylene, and *p*-(*tert*-butyl)phenol under Suzuki, Sonogashira, and Ullmann reaction conditions,[11] and the corresponding cross-coupling products were isolated in 82−96% yields (Supporting Information, Scheme S2). The obtained products are the key frameworks for the preparation of a variety of target compounds with applications ranging from natural products and pharmaceuticals to organic materials.[12]

Scheme 2. Proposed Reaction Mechanism
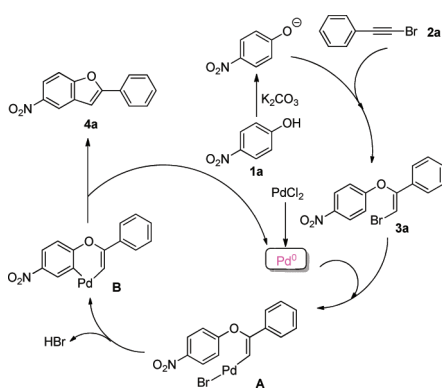
The reaction occurs probably involving an intermolecular addition reaction of phenol to bromoalkyne, affording (*Z*)-2-bromovinyl phenyl ether, and an intramolecular cyclization of (*Z*)-2-bromovinyl phenyl ether through C−H activation, affording 2-substituted benzo[*b*]furans (Scheme 2). First, the intermolecular nucleophilic addition of 4-nitrophenol (**1a**) to phenylethynyl bromide (**2a**) in the presence of K_2CO_3 generated (*Z*)-2-bromovinyl phenyl ether (**3a**) with excellent regio- and stereoselectivity.[11b] The obtained

3a reacted with Pd^0 from its precursor $PdCl_2$ to form an intermediate **A** via oxidative addition. Subsequently, **A** underwent an intramolecular electrophilic aromatic palladation of **A**, through C−H activation of the aromatic hydrogen, and subsequent proton abstraction,[13] forming an intermediate **B**, which followed by a reductive elimination to afford benzo[*b*]furan (**4a**) via the carbon−carbon bond formation and regenerate Pd^0 for its catalytic cycle. It should be noted that the conversion yields of **3a−i** to **4a−i** in Table 1 are in agreement with the electronic effect of substituted groups on the benzene rings in the insertion of Pd(II) to Ar−H.

In conclusion, we have developed a novel and efficient protocol for the synthesis of benzo[*b*]furans from simple phenols and alkynyl bromides. The reactions could be carried out in sequential and one-pot reactions of phenols with bromoalkynes on the basis of addition/palladium-catalyzed C−H bond functionalization. The addition reactions of phenols to bromoalkynes generated (*Z*)-2-bromovinyl phenyl ethers in high yields with excellent regio- and stereoselectivity. The obtained (*Z*)-2-bromovinyl phenyl ethers proceeded by intramolecular cyclization to afford benzo[*b*]furans in good yields through palladium-catalyzed direct C−H bond functionalizations. It is important to note that the transformation of phenols with bromoalkynes into benzo[*b*]furans could be carried out in one pot with a simple and efficient tandem procedure. The method provides an efficient, wide scope and attractive alternative to Sonagashira coupling/5-*endo-dig* cyclization, which requires the use of *ortho*-halogen-substituted phenols.

Supporting Information Available. Analytical data and spectra (¹H and ¹³C NMR) for all the products; typical procedure, Table S1, Table S2, Scheme S1, and Scheme S2. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) (a) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (b) Liu, Y.; Zhong, Z.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2002**, *67*, 7451.

(11) (a) Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109. (b) Xu, H.; Gu, S.; Chen, W.; Li, D.; Dou, J. *J. Org. Chem.* **2011**, *76*, 2448.

(12) (a) Inoue, M.; Ohashi, I.; Kawaguchi, T.; Hirama, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1777. (b) Belecki, K.; Crawford, J. M.; Townsend, C. A. *J. Am. Chem. Soc.* **2009**, *131*, 12564. (c) Lin, S.; Horsman, G. P.; Chen, Y.; Li, W.; Shen, B. *J. Am. Chem. Soc.* **2009**, *131*, 16410. (d) Pandithavidana, D. R.; Poloukhtine, A.; Popik, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 351. (e) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652.

(13) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.