Organic LETTERS

Letter

pubs.acs.org/OrgLett

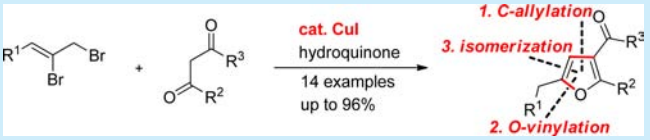
2,3-Dihalo-1-propenes as Building Blocks in Cu(I)-Catalyzed Domino Reactions: Efficient and Selective Synthesis of Furans

Dietmar Schmidt, Chandi C. Malakar, and Uwe Beifuss*

Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstraße 30, D-70599 Stuttgart, Germany

Supporting Information

ABSTRACT: The Cu(I)-catalyzed reaction of 2,3-dibromo-1-propenes with β-ketoesters and 1,3-diketones, respectively, in DMF at 120 °C using Cs_2CO_3 as a base and hydroquinone as an additive exclusively delivers 2,3,5-trisubstituted furans and related compounds with yields up to 96%. The highly regioselective domino process is based on an intermolecular *C*-allylation followed by an intramolecular Ullmann type *O*-vinylation and a double bond isomerization.



Significant progress has been made in the field of Cu(I)-catalyzed cross-couplings in recent years.[1] This holds especially true for the arylations of *C*-, *N*-, *O*-, and *S*-nucleophiles with aryl halides.[2] The corresponding vinylations are known but have been much less studied than the arylations.[3] The Cu(I)-catalyzed vinylation of heteronucleophiles has great potential in synthetic chemistry since it allows direct access to enamines and enamides,[3,4] enol ethers,[3,5] and vinyl sulfides.[3,6] The synthetic value of Cu(I)-catalyzed cross-couplings can be extended considerably by combining them with other reactions to new domino processes.[7] This approach has proven particularly valuable for the synthesis of heterocycles.[8] A prerequisite for the application of domino reactions is the use of bisfunctionalized substrates, such as biselectrophiles or bisnucleophiles.

So far, in most cases bishalides of types **A**–**D** (Figure 1) have been employed as biselectrophiles.[9] As part of our studies on

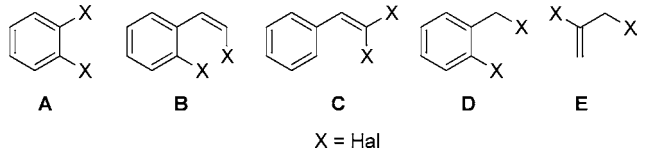


Figure 1. Biselectrophiles as substrates for transition-metal-catalyzed domino reactions.

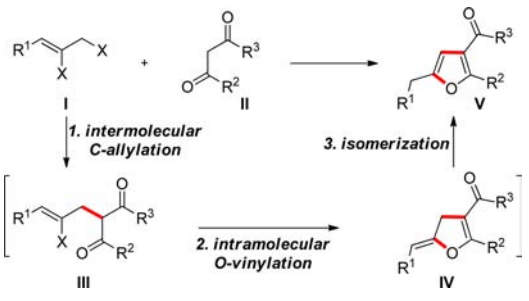
Cu(I)-catalyzed domino reactions for the synthesis of heterocycles,[10] we assumed that 2,3-dihalo-1-propenes **E** should be outstanding substrates for transition-metal-catalyzed domino reactions. 2,3-Dihalo-1-propenes **E** can easily be obtained from a number of substrates, such as α-haloacrylates, α-haloacroleins, and α-haloallylic alcohols, by convenient synthetic procedures.[11] 2,3-Dihalo-1-propenes have found use as substrates in a number of transformations,[12] but so far they have not been employed as reaction partners in transition-metal-catalyzed domino reactions.

The furan core is a frequently occurring structural motif in natural products and pharmaceuticals.[13] 2,3,5-Trisubstituted furans with an ester group at C-3, e.g., are found in furanocembranoids and pseudopteranes.[14] Substituted furans are also important building blocks and intermediates in organic synthesis.[15] This is why substantial effort has been devoted to the development of methods for the preparation of furans.[16] Apart from classical methods such as the Paal–Knorr and the Feist–Benary synthesis, several transition-metal-catalyzed methods have been developed. Many of them are based on cycloisomerizations and formal [4 + 1], [3 + 2], and [2 + 2 + 1] cycloadditions.[17] Despite considerable achievements, the selective and efficient synthesis of highly substituted furans from easily available substrates using reasonably priced reagents, catalysts, and ligands still remains a major challenge in furan synthesis.

It was envisioned that the synthesis of 2,3,5-trisubstituted furans **V** could be achieved by reaction between a 2,3-dihalo-1-propene **I** acting as a biselectrophile and a 1,3-dicarbonyl **II** as a bisnucleophile by means of a Cu(I)-catalyzed domino intermolecular *C*-allylation (**I** + **II** → **III**)/intramolecular *O*-vinylation (**III** → **IV**)/isomerization (**IV** → **V**) (Scheme 1).

Here, we introduce 2,3-dihalo-1-propenes as a new class of biselectrophilic substrates in transition-metal-catalyzed domino processes. The novel and efficient Cu(I)-catalyzed domino reaction between readily available 2,3-dibromo-1-propenes and

Scheme 1. Proposed Route for the Cu(I)-Catalyzed Synthesis of Furans



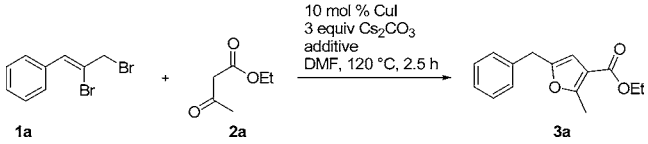
Received: August 10, 2014
Published: September 5, 2014

   dx.doi.org/10.1021/ol502371j | *Org. Lett.* 2014, 16, 4862–4865

1,3-dicarbonyls, such as β-ketoesters and 1,3-diketones, allows for the straightforward and selective synthesis of 2,3,5-trisubstituted furans and related skeletons.

The reaction between 2,3-dibromo-1-phenyl-1-propene (**1a**) and ethyl acetoacetate (**2a**) to **3a** was chosen as a model reaction. The required 2,3-dibromo-1-propene **1a** could be obtained in gram quantities by reduction of α-bromo cinnamic aldehyde (**4a**) (1 equiv of $NaBH_4$, $MeOH/CH_2Cl_2$ rt, 30 min)[18] followed by bromination of the resulting alcohol **5a** (1.1 equiv of Br_2, 1.2 equiv of PPh_3, 0 °C → rt, 2 h).[19] In a first attempt, 1 equiv of **1a** and 2 equiv of **2a** were reacted with 10 mol % CuI and 3 equiv of Cs_2CO_3 in DMF at 120 °C for 2.5 h in the presence of an additive (Table 1). With 20 mol % of an additive such as 3,4,7,8-

Table 1. Initial Experiments[a]



entry	additive	yield (%)
1	3,4,7,8-tetramethyl-1,10-phenanthroline	26
2	pivalic acid[b]	25
3	*N*,*N*-dimethylethylenediamine	28
4	picolinic acid	31
5	ethyl nicotinate	37
6	catechol	27
7	hydroquinone	50

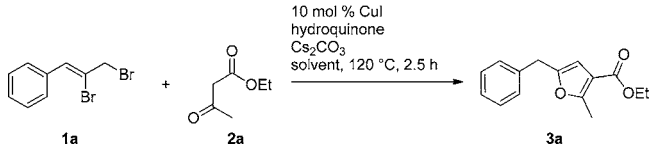
[a]1 equiv of **1a** was reacted with 2 equiv of **2a** in the presence of 20 mol % of an additive. [b]The reaction was performed with 2.4 equiv of the additive.

tetramethyl-1,10-phenanthroline, pivalic acid, *N*,*N*-dimethylethylenediamine, picolinic acid, ethyl nicotinate, or catechol, the 2-methyl-5-(phenylmethyl)-3-furancarboxylic acid ethyl ester (**3a**) was isolated as the main product in all cases (Table 1, entries 1−6). The yields were in the range between 25% and 37%. The yield could be substantially improved to 50% by running the reaction in the presence of 0.2 equiv of hydroquinone (Table 1, entry 7). Therefore, all further experiments were performed using hydroquinone as the additive.

In addition to DMF, the reaction could be carried out in a number of other solvents, including DMSO, dioxane, NMP, and acetonitrile. However, in all cases the yields were inferior compared to DMF (Table 2, entries 1−5).

To facilitate the first step of the transformation, i.e. the *C*-allylation, it was considered to increase the amount of the β-ketoester. In order to avoid partial decomposition of the dibromide **1a** observed with the initial experiments (Table 1, entries 1−6), it was decided to increase the amount of hydroquinone. In a control experiment that was carried out in the absence of any hydroquinone the yield of **3a** amounted to only 34% (Table 2, entry 6). This outcome highlights the role of this additive for the transformation. It is assumed that hydroquinone inhibits the polymerization/decomposition of the 2,3-dihalo-1-propene **1a** and/or the furan **3a**.[20] As expected, the yield of **3a** could be substantially improved by simultaneously increasing the amount of β-ketoester **2a** and that of hydroquinone. With 4 equiv of **2a** and 1 equiv of the additive, the furan **3a** could be isolated in 75% yield (Table 2, entry 7). With 6 equiv of **2a** and 4 equiv of Cs_2CO_3 a similar result was observed (Table 2, entry 8).

Table 2. Influence of Solvents and Reagent Concentrations[a]

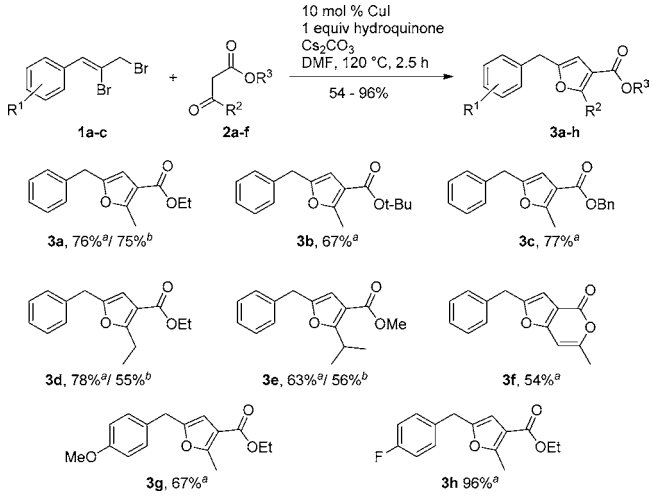


entry	**2a** (equiv)	solvent	Cs_2CO_3 (equiv)	hydroquinone (equiv)	yield (%)
1	2	DMSO	3	0.2	37
2	2	dioxane	3	0.2	36
3	2	NMP	3	0.2	39
4	2	DMF	3	0.2	50
5	2	CH_3CN	3	0.2	15
6	2	DMF	3	none	34
7	4	DMF	3	1	75
8	6	DMF	4	1	76

[a]1 equiv of **1a** was reacted.

Then, the 1,3-dicarbonyl scope of the transformation was studied. In a first set of experiments, **1a** was reacted with a number of β-ketoesters **2** (Scheme 2). The method is not

Scheme 2. Reaction of 1a−c with β-Ketoesters and Related Compounds 2a−f



[a]Yield refers to reaction of 1 mmol of **1** with 6 mmol of **2** and 4 mmol of Cs_2CO_3. [b] Yield refers to reaction of 1 mmol of **1** with 4 mmol of **2** and 3 mmol of Cs_2CO_3.

restricted to acetoacetates, such as *tert*-butyl acetoacetate (**2b**) and benzyl acetoacetate (**2c**), but can also be performed with other β-ketoesters, such as ethyl-3-oxo-pentanoate (**2d**) and methyl-4-methyl-3-oxo-pentanoate (**2e**), to deliver the corresponding furans **3d,e**. Yields were in the range between 63% and 78%. Remarkably, the reaction was also feasible with 6-methyl-4-hydroxy-2*H*-pyran-2-one (**2f**). Using this substrate, the bicyclic heterocycle **3f** was isolated in 54% yield. The reactions were performed under the conditions of Table 2, entry 8, i.e. with 6 equiv of the respective β-ketoester **2** and 4 equiv of Cs_2CO_3. Running the reactions under the conditions of Table 2, entry 7, caused yield losses in some cases; see, for example, the formation of **3d** and **3e** (Scheme 2).

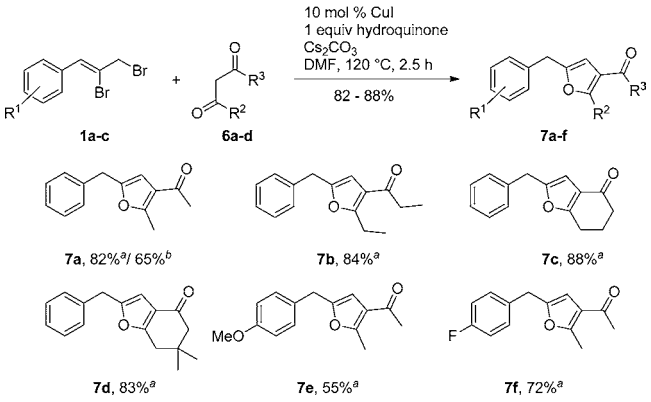
To establish that the new domino process is not restricted to 2,3-dibromo-1-phenyl-1-propene (**1a**), (*Z*)-2,3-dibromo-1-(4-methoxyphenyl)-1-propene (**1b**) and (*Z*)-2,3-dibromo-1-(4-

dx.doi.org/10.1021/ol502371j | Org. Lett. 2014, 16, 4862−4865

fluorophenyl)-1-propene (**1c**) were selected as substrates. The two 1-aryl-2,3-dibromo-1-propenes **1b,c** were prepared from the corresponding cinnamic aldehydes in three steps using standard procedures: First, the respective cinnamic aldehydes were transformed into the corresponding α-bromo cinnamic aldehydes **4b,c** by bromination/dehydrobromination (1.1 equiv of Br_2, pyridine, 0 °C → rt, 2 h).[21] This was followed by reduction to the allylic alcohols **5b,c** with $NaBH_4$ (1 equiv of $NaBH_4$, MeOH/CH_2Cl_2, rt, 30 min).[18] The resulting alcohols **5b,c** were treated with Br_2/PPh_3 to deliver the 2,3-dibromo-1-propenes **1b,c** (1.1 equiv of Br_2/1.2 equiv of PPh_3, CH_2Cl_2, 0 °C → rt, 2 h).[19] Subsequently, **1b** and **1c** were reacted with ethyl acetoacetate (**2a**) under standard conditions to deliver the corresponding furans **3g,h** with yields up to 96% (Scheme 2). This clearly demonstrates that the domino reaction can be achieved with different 1-aryl substituted 2,3-dibromo-1-propenes as starting materials.

In a second set of experiments it was shown that 2,3-dibromo-1-phenyl-1-propene (**1a**) can also be reacted with 1,3-diketones to deliver the corresponding furans (Scheme 3). With

Scheme 3. Reaction of 1a−c with 1,3-Diketones 6a−d

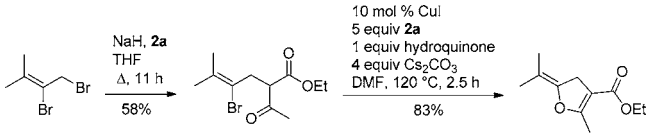


[a]Yield refers to reaction of 1 mmol of **1** with 6 mmol of **6** and 4 mmol of Cs_2CO_3. [b] Yield refers to reaction of 1 mmol of **1** with 4 mmol of **6** and 3 mmol of Cs_2CO_3.

acetylacetone (**6a**) and 3,5-heptanedione (**6b**) the 2,3,5-trisubstituted furans **7a** and **7b** were formed exclusively in 82% and 84% yield, respectively. Cyclic 1,3-diketones could also serve as substrates for the domino reaction. Reaction of **1a** with 1,3-cyclohexanedione (**6c**) and 5,5-dimethyl-1,3-cyclohexanedione (**6d**) delivered the benzofurans **7c** and **7d** as single products with 88% and 83% yield, respectively. Again, it was advantageous to carry out the reactions under the conditions of Table 2, entry 8. Attempts to reduce the amount of the 1,3-diketone did not pay off (see the formation of **7a**). Acetylacetone (**6a**) could also be reacted with the 1-aryl substituted 2,3-dibromo-1-propenes **1b** and **1c** as starting materials. The corresponding furans **7e,f** were isolated as single products in 55% and 72% yield, respectively.

It was expected that 1-alkyl-substituted 2,3-dihalo-1-propenes could also serve as substrates for the synthesis of furans. This view was supported by the fact that the Cu(I)-catalyzed reaction of 2-acetyl-4-bromo-5-methylhex-4-enoic acid ethyl ester (**9**), which was obtained by allylation of ethyl acetoacetate (**2a**) with 1,2-dibromo-3-methyl 2-butene (**8**), exclusively yields 4,5-dihydro-2-methyl-5-(1-methylethylidene)-3-furancarboxylic acid ethyl ester (**10**) as the product of an intramolecular *O*-vinylation in 83% yield (Scheme 4). However, so far all attempts

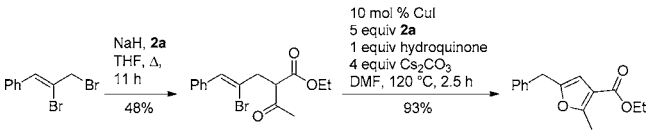
Scheme 4. Synthesis and Cyclization of 2-Acetyl-4-bromo-5-methyl-4-hexenoic Acid Ethyl Ester (9)



to achieve the synthesis of **10** in one step from 1,2-dibromo-3-methyl 2-butene (**8**) and ethyl acetoacetate (**2a**) under the conditions of the Cu(I)-catalyzed domino reaction were not met with success.

To prove that the reaction proceeds as a domino *C*-allylation/*O*-vinylation/isomerization, the presumed intermediate **11** was prepared by a reaction between 2,3-dibromo-1-phenyl-1-propene (**1a**) and ethyl acetoacetate (**2a**) and subjected to the conditions of the Cu(I)-catalyzed reaction (Scheme 5). The

Scheme 5. Synthesis and Cyclization of 2-Acetyl-4-bromo-5-phenyl-4-pentenoic Acid Ethyl Ester (11)



reaction of 1 equiv of **11** in the presence of 5 equiv of **2a**, 10 mol % CuI, 4 equiv of Cs_2CO_3, and 1 equiv of hydroquinone delivered 93% of the furan **3a** as the product of an intramolecular *O*-vinylation/isomerization.[6,22] The finding that despite a 5-fold excess of **2a** the furan **3a** was formed exclusively and not a trace of the product of an intermolecular *C*-vinylation could be observed provides strong support for the reaction mechanism assumed.

In summary, it has been shown that 2,3,5-trisubstituted furans and related skeletons can be synthesized in an efficient and selective one-pot process by reacting 1-substituted 2,3-dibromo-1-propenes with 1,3-dicarbonyls, such as β-ketoesters and 1,3-diketones. Future studies will address the potential of 2,3-dihalo-1-propenes in other transition-metal-catalyzed reactions for the preparation of carbo- and heterocyclic systems.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and $^1H-^{13}C$ NMR spectra for **3a−h**, **7a−f**, **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ubeifuss@uni-hohenheim.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. J. Conrad and Mr. M. Wolf for NMR spectra and Dr. A. Baskakova and Dipl.-Chem. H.-G. Imrich (all affiliated with the University of Hohenheim) for mass spectra.

REFERENCES

(1) Evano, G.; Blanchard, N. *Copper-Mediated Cross-Coupling Reactions*; Wiley: Hoboken, NJ: 2014.

(2) For reviews, see: (a) Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525. (b) Liu, Y.; Wan, J.-P. *Chem.—Asian J.* **2012**, *7*, 1488. (c) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (e) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.

(3) For a review, see: Jouvin, K.; Evano, G. Beyond Ullmann-Goldberg Chemistry: Vinylation, Alkynylation, and Allenylation of Heteronucleophiles. In *Copper-Mediated Cross-Coupling Reactions*; Evano, G., Blanchard, N., Eds.; Wiley: Hoboken, NJ, 2014; pp 187−238 and references cited therein.

(4) For some recent reports, see: (a) Zhou, C.; Ma, D. *Chem. Commun.* **2014**, *50*, 3085. (b) Kuranaga, T.; Sesoko, Y.; Inoue, M. *Nat. Prod. Rep.* **2014**, *31*, 514. (c) Kiruthika, S. E.; Perumal, P. T. *Org. Lett.* **2014**, *16*, 484.

(5) For some recent reports, see: (a) Kundu, D.; Maity, P.; Ranu, B. C. *Org. Lett.* **2014**, *16*, 1040. (b) Jouvin, K.; Bayle, A.; Legrand, F.; Evano, G. *Org. Lett.* **2012**, *14*, 1652. (c) Kabir, M. S.; Lorenz, M.; Namjoshi, O. A.; Cook, J. M. *Org. Lett.* **2010**, *12*, 464.

(6) For a recent report, see: Ji, Y.; Li, P.; Zhang, X.; Wang, L. *Org. Biomol. Chem.* **2013**, *11*, 4095.

(7) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(8) (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084. (b) Liu, T.; Fu, H. *Synthesis* **2012**, *44*, 2805. (c) Liu, Y.; Wan, J.-P. *Org. Biomol. Chem.* **2011**, *9*, 6873.

(9) Ball, C. J.; Willis, M. C. *Eur. J. Org. Chem.* **2013**, 425.

(10) For some recent examples, see: (a) Sudheendran, K.; Malakar, C. C.; Conrad, J.; Beifuss, U. *Adv. Synth. Catal.* **2013**, *355*, 2400. (b) Malakar, C. C.; Baskakova, A.; Conrad, J.; Beifuss, U. *Chem.—Eur. J.* **2012**, *18*, 8882. (c) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1972.

(11) (a) Augustine, J. K.; Bombrun, A.; Venkatachaliah, S.; Jothi, A. *Org. Biomol. Chem.* **2013**, *11*, 8065. (b) Arthuis, M.; Lecup, A.; Roulland, E. *Chem. Commun.* **2010**, *46*, 7810. (c) Li, W.; Li, J.; Wan, Z.-K.; Wu, J.; Massefski, W. *Org. Lett.* **2007**, *9*, 4607. (d) Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218. (e) Allen, C. F. H.; Edens, C. O., Jr. *Org. Synth.* **1945**, *25*, 92.

(12) (a) Grassi, D.; Alexakis, A. *Org. Lett.* **2012**, *14*, 1568. (b) Ohno, H.; Iuchi, M.; Kojima, N.; Yoshimitsu, T.; Fujii, N.; Tanaka, T. *Chem.—Eur. J.* **2012**, *18*, 5352. (c) Gatti, M.; Drinkel, E.; Wu, L.; Pusterla, I.; Gaggia, F.; Dorta, R. *J. Am. Chem. Soc.* **2010**, *132*, 15179. (d) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413. (e) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58. (f) Demir, A. S.; Akhmedov, I. M.; Sesenoglu, Ö. *Tetrahedron* **2002**, *58*, 9793. (g) Mori, M.; Chiba, K.; Okita, M.; Kayo, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 375.

(13) For a review, see: Keay, B. A.; Dibble, P. W. Furans and their Benzo Derivatives: Applications. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. *2*, p 395.

(14) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298.

(15) For a review, see: Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795.

(16) For reviews, see: (a) Moran, W. J.; Rodríguez, A. *Org. Prep. Proced. Int.* **2012**, *44*, 103. (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (c) Friedrichsen, W. Furans and their Benzo Derivatives: Synthesis. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. *2*, p 351.

(17) For some recent transition-metal-catalyzed approaches to furans, see: (a) Ma, Y.; Zhang, S.; Yang, S.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 7870. (b) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743. (c) Butkevich, A. N.; Meerpoel, L.; Stansfield, I.; Angibaud, P.; Corbu, A.; Cossy, J. *Org. Lett.* **2013**, *15*, 3840. (d) Yang, Y.; Yao, J.; Zhang, Y. *Org. Lett.* **2013**, *15*, 3206. (e) Cao, H.; Zhan, H.; Cen, J.; Lin, J.; Lin, Y.; Zhu, Q.; Fu, M.; Jiang, H. *Org. Lett.* **2013**, *15*, 1080. (f) Jiang, H.; Zeng, W.; Li, Y.; Wu, W.; Huang, L.; Fu, W. *J. Org. Chem.* **2012**, *77*, 5179.

(18) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1206.

(19) (a) Schaefer, J. P.; Higgins, J. G.; Shenoy, P. K. *Org. Synth.* **1968**, *48*, 51. (b) Schaefer, J. P.; Higgins, J.; Shenoy, P. K. *Org. Synth.* **1969**, *49*, 6.

(20) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700.

(21) Sakakura, A.; Yamada, H.; Ishihara, K. *Org. Lett.* **2012**, *14*, 2972.

(22) For intramolecular Cu(I)-catalyzed *O*-vinylations, see: (a) Zhou, W.; Chen, W.; Wang, L. *Org. Biomol. Chem.* **2012**, *10*, 4172. (b) Chen, L.; Fang, Y.; Zhao, Q.; Shi, M.; Li, C. *Tetrahedron Lett.* **2010**, *51*, 3678. (c) Fang, Y.; Li, C. *J. Am. Chem. Soc.* **2007**, *129*, 8092. (d) Fang, Y.; Li, C. *Chem. Commun.* **2005**, 3574.