

Copper-Catalyzed C—O Bond Formation: An Efficient One-Pot Highly Regioselective Synthesis of Furans from (2-Furyl)Carbene Complexes

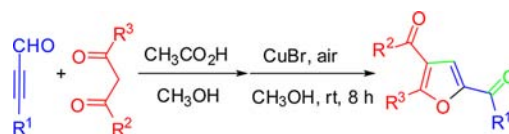
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ABSTRACT



A convenient one-pot Cu(I)-catalyzed strategy for regioselective synthesis of trisubstituted furan derivatives has been developed via (2-furyl) carbene complexes. This process has opened a new synthetic route to a variety of α -carbonyl furans using air as the oxidant affording furans in good yields.

Functionalized furans are extremely useful molecules which exhibit a wide range of biological activities¹ and appear as key structural units in many important pharmaceuticals, natural products,² and various materials. Furthermore, furans constitute important scaffolds and blocks in the construction of complicated organic compounds. Although many synthetic routes for their preparation have been developed, this field is still far from being solved. The development of efficient ways to construct furan molecules from readily available starting materials under mild

conditions continues to attract the interest of organic chemists due to their remarkable application value.

Transition-metal-catalyzed organic transformations have become one of the most powerful tools to prepare functionalized furan molecules in the past few years.³ Among the transition-metal-catalyzed reactions, Pd,⁴ Cu,⁵ Au,⁶ Ag,⁷ and Ru⁸ are the most versatile and widely used metals for the synthesis of furan derivatives. Despite the effort of several research groups to develop elegant transition-metal-catalyzed

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(1) (a) Bolognesi, M. L.; Budriesi, R.; Chiarini, A.; Poggesi, E.; Leonardi, A.; Melchiorre, C. *J. Med. Chem.* **1998**, *41*, 4484–4853. (b) Francesconi, I.; Wilson, W. D.; Tanious, F. A.; Hall, J. E.; Bender, B. C.; Tidwell, R. R.; McCurdy, D.; Boykin, D. W. *J. Med. Chem.* **1999**, *42*, 2260–2265. (c) Mortensen, D. S.; Rodriguez, A. L.; Carlson, K. E.; Sun, J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. J. *J. Med. Chem.* **2001**, *44*, 3838–3848. (d) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670–2673. (e) Dong, Y.; Shi, Q.; Liu, Y.; Wang, X.; Bastow, K. F.; Lee, K. *J. Med. Chem.* **2009**, *52*, 3586–3590. (f) Reichstein, A.; Vortherms, S.; Bannwitz, S.; Tentrop, J.; Prinz, H.; Müller, K. *J. Med. Chem.* **2012**, *55*, 7273–7284.

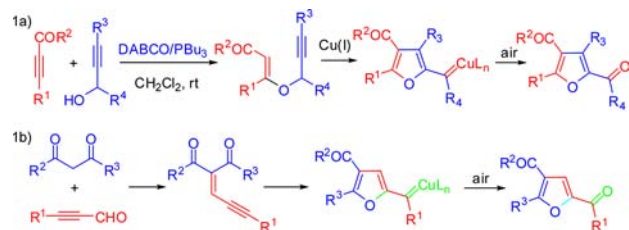
(2) (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955–2020. (b) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703–1708. (c) Marshall, J. A.; McNulty, L. M.; Zou, D. *J. Org. Chem.* **1999**, *64*, 5193–5200.

(3) (a) D'Souza, D. M.; Mueller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095–1108. (b) Xu, B.; Hammond, G. B. *J. Org. Chem.* **2006**, *71*, 3518–3521. (c) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2008**, *130*, 13528–13529. (d) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195–5197. (e) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452. (f) Bechem, B.; Patman, R. L.; Hashmi, A. S. K.; Krische, M. J. *J. Org. Chem.* **2010**, *75*, 1795–1798. (g) Wang, J. C.; Jung, C. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118–4119. (h) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386–12387. (i) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775–1778. (j) Godoi, B.; Schumacher, R. F.; Zeni, G. *J. Am. Chem. Soc.* **2011**, *133*, 2937–2980. (k) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009. (l) Jiang, H. F.; Yao, W. J.; Cao, H.; Huang, H. W. *J. Org. Chem.* **2010**, *75*, 5347–5350. (m) Cao, H.; Jiang, H.; Huang, H. *Synthesis-Stuttgart* **2011**, *7*, 1019–1036. (n) Wen, Y. M.; Zhu, S. F.; Jiang, H. F. *Synlett* **2011**, *7*, 1023–1027. (o) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165. (p) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662–2667. (q) Yin, B. L.; Zeng, G. H.; Cai, C. B.; Ji, F. H.; Huang, L.; Li, Z. G.; Jiang, H. F. *Org. Lett.* **2012**, *14*, 616–619.

processes to form furan derivatives, the synthesis of α -carbonyl furans via (2-furyl)carbene complexes is still highly favorable. Fisher carbene complexes are one of the most versatile organometallic reagents⁹ and play a critical role in generating novel molecules in organic transformations.¹⁰ Transformation of the carbene complex attracts much attention, and a number of novel reactions involving this complex have been reported in modern organic synthesis. Therefore, in this context, we hope to describe a convenient method to synthesize α -carbonyl furans via direct oxidation of a (2-furyl)carbene intermediate by using air as the oxidant.

Recently, we have reported a novel Cu(I)-catalyzed¹¹ domino reaction for the synthesis of α -carbonyl furans via a rearrangement/dehydrogenation oxidation/carbene oxidation sequence of 1,5-enynes (Scheme 1a). Consequently, an insightful investigation has been employed to synthesize α -carbonyl furan derivatives through 5-exodig cyclization of an ene-yne-ketone,¹² which has been demonstrated in Scheme 1b.

Scheme 1. Synthesis of Furans via (2-Furyl)carbene Complexes



In our initial study, we examined the Cu(I)-catalyzed one-pot process with various oxidants and solvents to optimize the reaction conditions. 3-Phenylpropionaldehyde (**1a**) and pentane-2,4-dione (**2a**) were chosen as model substrates,

(4) (a) Ma, S.; Gu, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6182–6183. (b) Gu, Z.; Wang, X.; Shu, W.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 10948–10956.

(5) (a) Sromek, A.; Kel'in, A.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280–2282. (b) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98–101. (c) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95–98.

(6) (a) Dudnik, A.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645–7655. (b) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10501. (c) Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940–6941. (d) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925–3927.

(7) Cao, H.; Jiang, H. F.; Mai, R. H.; Zhu, S. F.; Qi, C. R. *Adv. Synth. Catal.* **2010**, *352*, 143–152.

(8) Zhang, M.; Jiang, H. F.; Neumann, H.; Beller, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2009**, *121*, 1709–1712.

(9) Dötz, K. H.; Stendel, J., Jr. *Chem. Rev.* **2009**, *109*, 3227–3274.

(10) (a) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270–9271. (b) Barluenga, J.; Vicente, R.; Barrio, P.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2004**, *126*, 5974–5975. (c) Barluenga, J.; Barrio, P.; Riesgo, L.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2007**, *129*, 14422–14426. (d) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970–5971. (e) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaria, J.; Brillet, C.; Garcia-Granda, S.; Piñera-Nicolás, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516–4517.

(11) (a) Cao, H.; Jiang, H. F.; Yao, W. J.; Liu, X. H. *Org. Lett.* **2009**, *11*, 1931–1933. (b) Cao, H.; Jiang, H. F.; Yuan, G. Q.; Chen, Z. W.; Qi, C. R.; Huang, H. W. *Chem.—Eur. J.* **2010**, *16*, 10553–10559. (c) Cao, H.; Jiang, H. F.; Huang, H. W.; Zhao, J. W. *Org. Biomol. Chem.* **2011**, *21*, 7257–7280.

Table 1. Optimization of Reaction Conditions^a

| entry | catalyst | temp (°C) | t (h) | solvent | yields (%) ^b |
|-------|-------------------|-----------|-------|---------------------------------|-------------------------|
| 1 | CuI | 50 | 12 | CH ₂ Cl ₂ | NP ^c |
| 2 | CuBr | 50 | 12 | CH ₂ Cl ₂ | NP |
| 3 | CuCl | 50 | 12 | CH ₂ Cl ₂ | NP |
| 4 | CuCN | 50 | 12 | CH ₂ Cl ₂ | NP |
| 5 | Cu ₂ O | 50 | 12 | CH ₂ Cl ₂ | NP |
| 6 | CuI | rt | 12 | CH ₂ Cl ₂ | 10 |
| 7 | CuBr | rt | 12 | CH ₂ Cl ₂ | 75 |
| 8 | CuCl | rt | 12 | CH ₂ Cl ₂ | 18 |
| 9 | CuCN | rt | 12 | CH ₂ Cl ₂ | trace |
| 10 | Cu ₂ O | rt | 12 | CH ₂ Cl ₂ | 73 |
| 11 | CuBr | rt | 10 | CH ₂ Cl ₂ | 78 |
| 12 | CuBr | rt | 8 | CH ₂ Cl ₂ | 78 |
| 13 | CuBr | rt | 4 | CH ₂ Cl ₂ | 61 |
| 14 | CuBr | rt | 20 | CH ₂ Cl ₂ | 78 |
| 15 | CuBr | rt | 8 | CH ₃ OH | 83 |
| 16 | CuBr | rt | 8 | CH ₃ CN | 75 |
| 17 | CuBr | rt | 8 | DMF | 77 |
| 18 | CuBr | rt | 8 | toluene | 39 |
| 19 | CuBr | rt | 8 | 1,4-dioxane | 73 |
| 20 | — | rt | 8 | CH ₃ OH | NP ^c |

^a Reaction conditions: 3-Phenylpropionaldehyde (**1a** 0.5 mmol), pentane-2,4-dione (**2a** 0.6 mmol), AcOH (5 mmol %), copper(I) catalyst (3%), solvent (3 mL), rt–50 °C. ^b GC yields. ^c No product.

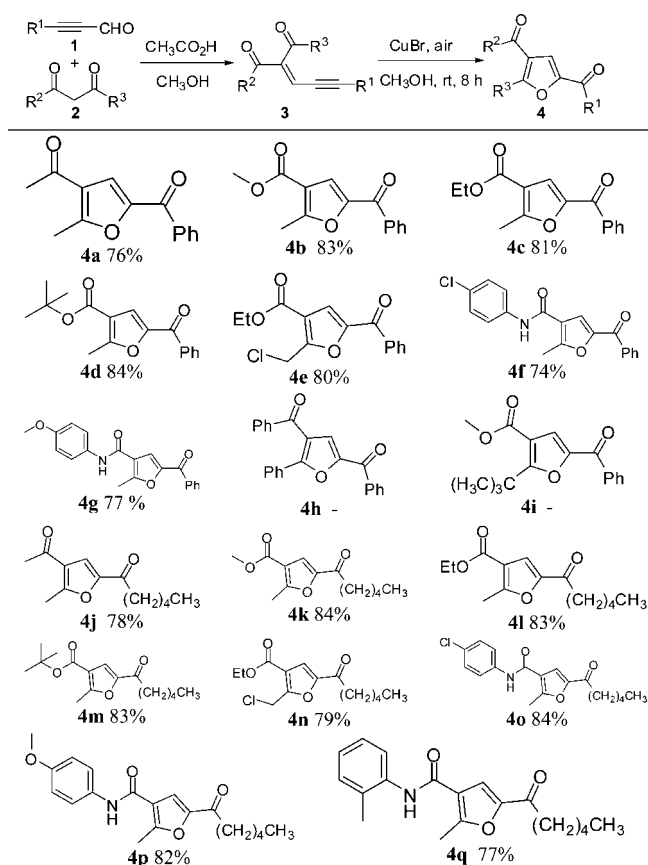
and the results are described in Table 1. The intermediate product **3a** was easy to prepare. In a typical procedure, **1a** (0.5 mmol), **2a** (0.6 mmol), and AcOH (5 mmol %) were stirred for 30 min in CH₂Cl₂ (3 mL) at room temperature. Subsequently, various copper(I) catalysts, such as CuI, CuBr, CuCl, CuCN, and Cu₂O, were tested at 50 °C for 12 h (Table 1, entries 1–5). However, no product was observed and the entire intermediate product **3a** disappeared by GCMS, because the reaction may be too severe at 50 °C. In the next step, the effects of temperature were tested next. Interestingly, the desired product **4a** was obtained in 75% GC yields, as the reaction was carried out at rt in the presence of CuBr (Table 1, entry 7). The results showed that this reaction was highly sensitive to temperature variations. Other Cu(I)-catalysts, such as CuI, CuCl, CuCN, and Cu₂O, were also effected to generate the corresponding product in moderate to good yields (Table 1, entries 6, 8–10). The reaction time was also examined, and the results showed that 8 h was the best choice. Subsequently, we tried to improve the yields

(12) (a) Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 5260–5261. (b) Miki, K.; Yokoi, T.; Nishino, F.; Kato, Y.; Washitake, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 1557–1564. (c) Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564–4565. (d) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267–1269. (e) Patti, R. K.; Waynant, K. V.; Herndon, J. W. *Org. Lett.* **2011**, *13*, 2848–2851. (f) Duan, S.; Sinha-Mahapatra, D. K.; Herndon, J. W. *Org. Lett.* **2008**, *10*, 1541–1544. (g) Vicente, R.; González, J.; Riesgo, L.; González, J.; López, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 1–6.

by examining different solvents. Among the solvents, we were delighted to find that the product **4a** was readily formed in 83% yields in CH₃OH (Table 1, entry 15). Other solvents, such as CH₃CN, DMF, toluene, and 1,4-dioxane, were also afforded in moderate to good yields (Table 1, entries 16–19). Finally, control experiments revealed that no product was formed in the absence of CuBr (Table 1, entry 20).

Under the optimized conditions, the substrate scopes were explored, and the results are described in Scheme 2. First, **1a** was fixed as the substrate to examine a variety of open chain 1,3-dicarbonyl compounds. As shown by the results in Scheme 2, various open chain 1,3-dicarbonyl compounds reacted with **1a** smoothly. This novel transformation showed high functional group tolerance (such as R² = CH₃, CH₃O, EtO, (CH₃)₃CO, *p*-Cl-PhNH, *p*-CH₃O-PhNH), and in most cases the corresponding products (**4a–4f**) were obtained in good yields. When the reaction was carried out using 1,3-diphenylpropane-1,3-dione as the substrate, only a trace amount of desired product **4h** was detected by GCMS, possibly due to the phenyl decreasing nucleophilic nature of carbonyl during the cyclization process. It is also worth noting that the reaction was insensitive to the sterically hindered group (R² = (CH₃)₃CO) but sensitive to the sterically hindered substrate (R³ = (CH₃)₃C; R² = CH₃O).

Scheme 2. CuBr-Catalyzed Synthesis of Furans via **1a** with Open Chain 1,3-Dicarbonyl Compounds^a

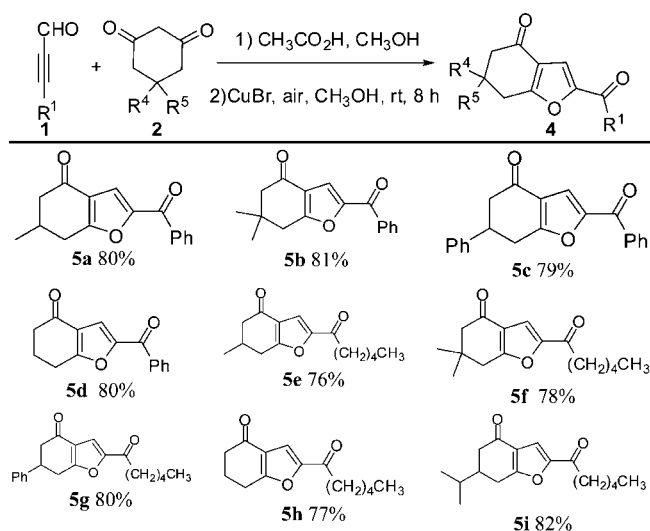


^a Isolated yields.

Subsequently, **1b** as the substrate was also tested with various open chain 1,3-dicarbonyl compounds, and the results indicated that all of the substrates provided similar isolated yields for the formation of furans. Notably, no other regioisomers were detected in the reaction, which indicated that this one-pot transformation was regio- and chemoselective.

For further investigation, commercially available cyclic 1,3-dicarbonyl compounds were employed to explore the scope of this transformation, and the results are summarized in Scheme 3. Interestingly, it was found that the reaction would be successfully extended to cyclic 1,3-dicarbonyl compounds under the optimum conditions and afforded the corresponding products in good yields, such as 5-methylcyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione, 5-phenylcyclohexane-1,3-dione, cyclohexane-1,3-dione, and 5-isopropylcyclohexane-1,3-dione. These results indicated that the catalytic system is applicable to both open and cyclic 1,3-dicarbonyl compounds.

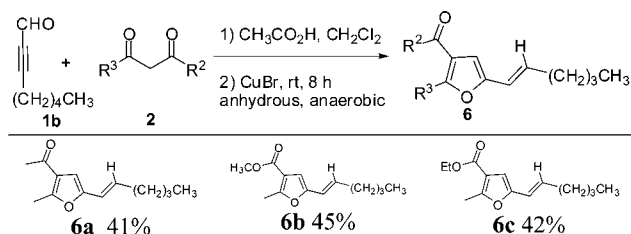
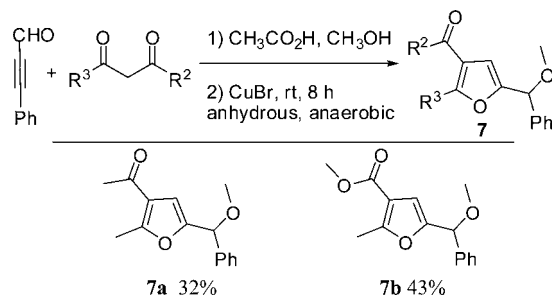
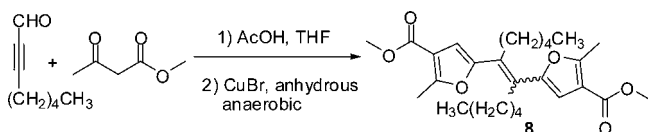
Scheme 3. CuBr-Catalyzed Synthesis of Furans from **1** with Cyclic 1,3-Dicarbonyl Compounds^a



^a Isolated yields.

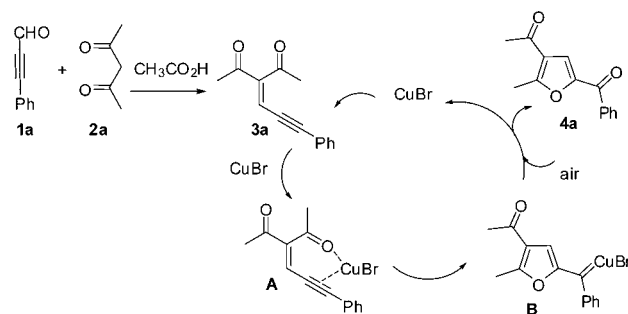
Notably, the 2-vinylfuran derivatives were formed in the presence of CuCl₂ (5 mol %) in CH₂Cl₂ at rt, when the reaction was conducted and carried out using **1b** and **2** as substrates (Scheme 4). This is a novel and efficient transformation to create a C–C double bond for the construction of 2-vinylfuran derivatives via Cu-catalyzed 1,2 H-migration. The new Cu-catalyzed process for the synthesis of trisubstituted furans was obtained in 41–45% yields.

To our delight, the new furan products were obtained in moderate yields, when the reaction was carried out in methanol under anhydrous and anaerobic conditions with CuBr for 8 h (Scheme 5). Our findings open a novel Cu(I)-catalyzed synthetic route to prepare methyl ether furans, initiating further studies and applications on the transformation which are ongoing in our laboratory.

Scheme 4. Cu-Catalyzed Synthesis of 2-Vinyl Furans^a^a Isolated yields.**Scheme 5.** Cu(I)-Catalyzed Synthesis of Methyl Ether Furans^a^a Isolated yield.**Scheme 6.** Formation of the Furyl Dimer

To gain further insight into the mechanism of this Cu(I)-catalyzed transformation, we envision the possibility of trapping the reaction intermediates. Recently, Barluenga¹³ reported the Cu(I)-catalyzed process yields the furyl dimer via a copper(I) carbene complex. Inspired by the result, we attempted to trap copper carbene (Scheme 6). The reaction was carried out with CuBr at rt in THF under anhydrous and anaerobic conditions for 6 h. To our delight, the furyl dimer (**5**) was observed by GCMS. The results clearly indicated that the copper carbene complex possibly formed during the process.

On the basis of the above experimental results, a proposed CuBr -catalyzed mechanism has been depicted in Scheme 7. AcOH -promoted intermolecular dehydration of

Scheme 7. Proposed Reaction Mechanism

1a and **2a** has occurred to generate intermediate **3a** which is followed by coordination of the Cu(I) species to form complex **A**, where Cu(I) is coordinated to a carbonyl group and the alkyne. And then an intramolecular 5-exodig cyclization by nucleophilic attack of the carbonyl O-atom onto C4 has taken place to give the (2-furyl)carbene complex **B** which has undergone carbene oxidation with an oxygen metathesis to generate the desired product **4a**.

In conclusion, we have successfully developed a novel and convenient one-pot Cu(I) -catalyzed approach for the preparation of 2-carbonyl furans via (2-furyl)carbene complexes. It provides a versatile synthetic route to form C–O bonds via the oxidation of (2-furyl)carbene complexes. Although furan derivatives have been described from enyne-carbonyl compounds, this method is unique in that the present process is the first example of the regioselective synthesis of 2-carbonyl furans from an enyne-carbonyl compound via copper carbene oxidation. Moreover, this unprecedented process is applicable to a variety of open and cyclic 1,3-dicarbonyl compounds and affords highly functionalized furans in good yields. Further investigation into the scope and synthetic applications of (2-furyl)carbene complexes is being carried out in the future.

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Supporting Information Available. Experimental procedure and characterization of compounds **4a–4q**, **5a–5i**, **6a–6c**, **7a–7b**. This material is available free of charge via the Internet at <http://pubs.acs.org>

(13) Hofmann, P.; Shishkov, I. V.; Rominger, F. *Inorg. Chem.* **2008**, *47*, 11755–11762.

The authors declare no competing financial interest.