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Nano-Cu_2O-Catalyzed Formation of C−C and C−O Bonds: One-Pot Domino Process for Regioselective Synthesis of α-Carbonyl Furans from Electron-Deficient Alkynes and 2-Yn-1-ols

Hua Cao, Huanfeng Jiang,* Gaoqing Yuan, Zhengwang Chen, Chaorong Qi, and Huawen Huang[a]

Abstract: The formation of carbon–carbon and carbon–oxygen bonds continues to be an active and challenging field of chemical research. Nanoparticle catalysis has attracted considerable attention owing to its environmentally benign and high activity toward the reactions. Herein, we described a novel and effective nano-Cu_2O-catalyzed one-pot domino process for the regioselective synthesis of α-carbonyl furans. Various electron-deficient alkynes with 2-yn-1-ols underwent this process smoothly in moderate to good yields in the presence of air at atmospheric pressure. It is especially noteworthy that a novel 2,4,5-trisubstituted 3-ynylfuran was formed in an extremely direct manner without tedious stepwise synthesis. Additionally, as all of the starting materials are readily available, this method may allow the synthesis of more complex α-carbonyl furans. An experiment to elucidate the mechanism suggested that the process involved a carbene intermediate.

Keywords: copper · domino reactions · furans · nanoparticles · regioselective synthesis

Introduction

Transition-metal-catalyzed domino reactions are versatile tools for the preparation of complex and diverse heterocyclic compounds from readily accessible starting materials in a single operation under mild conditions.[1] The protocol to achieve this goal is a critical part of much organic synthesis and remains a continuing challenge that reflects the growing needs for the pharmaceutical, food, and agricultural industries. In the past few years, organic chemists have been expected not only to design new chemical reactions for the formation of carbon–carbon and carbon–oxygen bonds but also to improve the catalyst systems to maximize resource utilization and to decrease waste, especially for environmental health and safety. Hence, the search for an inexpensive, environmentally friendly, and nontoxic catalyst system for the formation of carbon–carbon and carbon–oxygen bonds is a major objective.[2]

In this context, nanoparticle catalysts have been widely investigated[3] and have shown good catalytic activities due to their high surface areas and reactive morphologies.[4] In comparison with homogeneous catalysts, heterogeneous catalysts have advantages with respect to product and catalyst isolation, catalyst reuse, operational handling, and environmental considerations.[5] Also, there has been increasing emphasis on the use and development of environmentally friendly solid-catalyst systems to reduce the amount of toxic waste.[6] Therefore, more and more organic-synthesis chemists have focused much of their attention on the application of nanoscience and technology, such as organic transformations and nanocatalysts.[7]

Furans are important fine chemicals that exhibit a wide range of biological activities,[8] and many naturally occurring compounds[9] contain the furan skeleton as a key structural unit, such as pseudopterolide A[10] and kallolide A[11]. It should be noted that α-carbonyl furans have been extensively used as building blocks for the synthesis of more elaborate heterocyclic compounds (Scheme 1).[12] Although several transition-metal-catalyzed reactions have been reported for the synthesis of furan derivatives during the last few years,[13] there has only been a rare example for the synthe-

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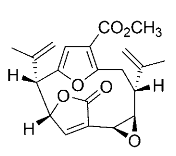
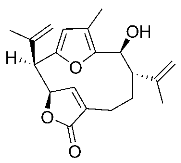
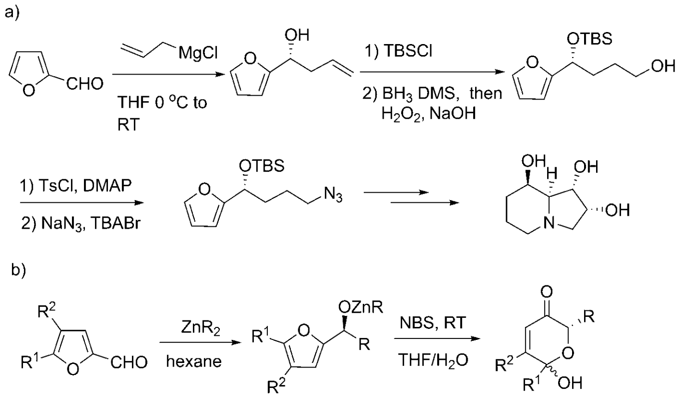


Pseudopterolide A



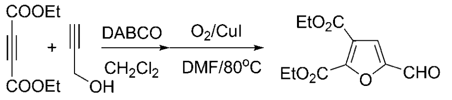
Kallolide A



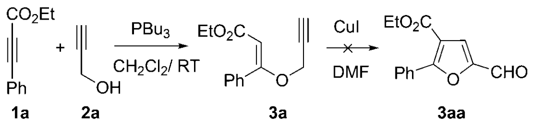
Scheme 1. a) General method for the synthesis of the natural product (−)-epi-swainsonine from furan-2-carbaldehyde. b) Synthesis of useful intermediate pyranones from furan-2-carbaldehydes. BH_3–DMS: borane–dimethylsulfide; DMAP: 4-dimethylaminopyridine; NBS: *N*-bromosuccinimide; RT: room temperature; TBABr: tetrabutylammonium bromide; TBS: *tert*-butyldimethylsilyl; THF: tetrahydrofuran; TsCl: toluene-4-sulfonyl chloride.

sis of α-carbonyl furans.[14] Therefore, the design and development of a new method to synthesize α-carbonyl furans is essential.

Very recently, we reported a novel one-pot CuI-catalyzed domino process for the regiospecific synthesis of highly functionalized polysubstituted furans (Scheme 2).[15] Unfortunately, this domino process cannot take place when ethyl phenylpropionate was employed as the substrate to replace diethyl but-2-ynedioate (Scheme 3). In addition, it is needful to probe the proposed mechanism. To solve these problems, we first broadened the range of catalysts to investigate their activity, and we found that Cu_2O nanoparticles can be utilized as an effective heterocatalyst to accomplish the reaction through the formation of carbon–carbon and carbon–oxygen bonds. Herein, we report the successful extension of the scope of this new catalytic system to various electron-deficient alkynes with 2-yn-1-ols by using air oxidation under atmospheric pressure and we disclose a novel and effective method for the synthesis of α-carbonyl furans.



Scheme 2. CuI-catalyzed synthesis of an α-carbonyl furan. DABCO: 1,4-diazabicyclo[2.2.2]octane; DMF: *N*,*N*-dimethylformamide.

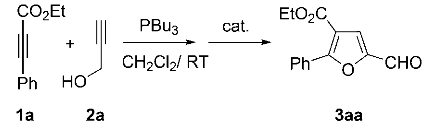


Scheme 3. Synthesis of the furan from **1a** and **2a** cannot be completed.

Results and Discussion

Based on our previous work, we focused on searching for different catalysts and suitable reaction conditions (Table 1) by using **1a** and **2a** as the starting materials. In a typical procedure, **1a** (0.5 mmol), **2a** (0.5 mmol), and PBu_3 were stirred in CH_2Cl_2 at room temperature.[16] The solution was then evaporated to dryness under reduced pressure. Subsequently, a variety of catalysts were examined. As shown in Table 1, the desired product **3aa** could not be formed by using CuI as the catalyst (Table 1, entry 1). It was found that the desired product was detected when CuI was substituted by Cu_2O (Table 1, entry 2). We then assumed that an increase of temperature may influence the production of **3aa**. However, it was observed that the yield of **3aa** did not

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Air/O_2 (pressure [atm])	*T* [°C]	Yield [%][b]
1	5 mol% CuI	air	80	–
2	5 mol% Cu_2O	air	80	<5
3	5 mol% Cu_2O	air	120	<5
4	5 mol% $Ru_3(CO)_{12}$	air	80	–
5	5 mol% $PdCl_2$	air	80	–
6	5 mol% $Pd(OAc)_2$	air	80	–
7	5 mol% $Pd(dba)_2$	air	80	–
8	5 mol% $NiSO_4$	air	80	trace
9	5 mol% nano-Cu_2O	air	80	62
10	5 mol% nano-Cu_2O	O_2 (1)	80	67
11	5 mol% nano-Cu_2O	O_2 (3)	80	46
12	5 mol% nano-Cu_2O	O_2 (5)	80	41
13	10 mol% nano-Cu_2O	O_2 (5)	80	58
14	10 mol% nano-Cu_2O	O_2 (1)	80	69
15	10 mol% nano-Cu_2O	air	80	68
16	10 mol% nano-Cu_2O	air	100	65
17	10 mol% nano-Cu_2O	air	50	75
18	10 mol% nano-Cu_2O	air	RT	–

[a] dba: *trans*,*trans*-dibenzylideneacetone. [b] Yields determined by GC analysis.

change significantly, even at 120 °C (Table 1, entry 3). Other late-transition-metal catalysts, such as $Ru_3(CO)_{12}$, $PdCl_2$, $Pd(OAc)_2$, $Pd(dba)_2$, and $NiSO_4$ (Table 1, entries 4–8), were employed; no conversion was observed in these cases. Stimulated by the result that Cu_2O could catalyze the reaction, we attempted to prepare Cu_2O nanoparticles. According to previous reports,[17] Cu_2O microcrystals were synthesized by a simple hydrothermal method. The formation of the nano-Cu_2O particles was confirmed by XRD (Figure 1 a) and SEM analysis (Figure 2).

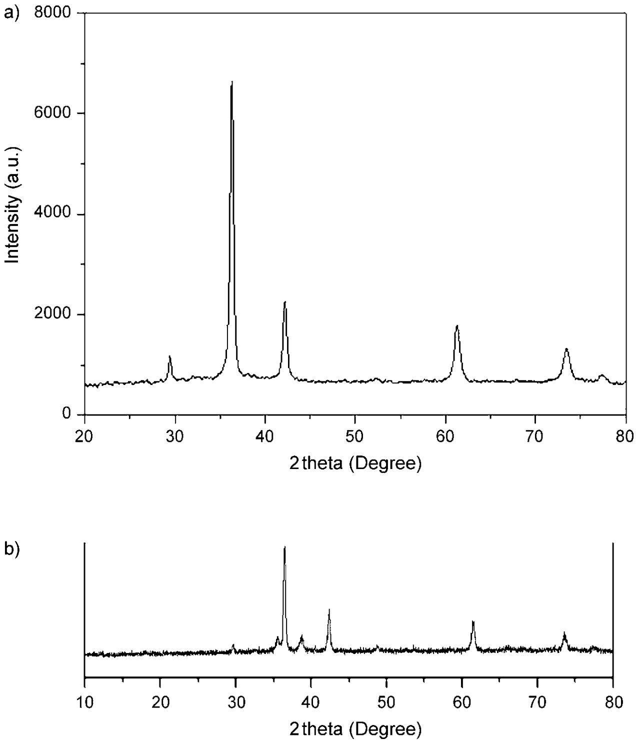


Figure 1. a) XRD pattern of Cu_2O particles. b) XRD pattern of nano-Cu_2O particles after undergoing the reaction twice.

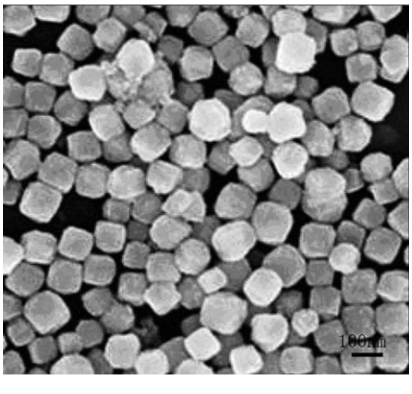


Figure 2. SEM image of the nano-Cu_2O particles.

Surprisingly, the yield of **3aa** dramatically increased to 62 % (Table 1, entry 9) when nano-Cu_2O particles (5 mol %) were tested in DMF under atmospheric pressure. We then tried to improve the yields by using oxygen instead of air and by increasing the oxygen pressure (Table 1, entries 10–12). It was found that the yield increased to 67 % when O_2 at 1 atm was used (Table 1, entry 10). However, when higher pressure O_2 was used (Table 1, entries 11 and 12), the yield decreased gradually, which indicated that the nano-Cu_2O particles were oxidized to CuO at high oxygen pressure. Inspired by the above results, we attempted to change the amount of catalyst to improve the yield of **3aa**. The results showed that moderate yields were obtained by using 10 mol % of nano-Cu_2O particles (Table 1, entries 13–16). Interestingly, a good yield was achieved by using 10 mol % of nano-Cu_2O particles under 1 atm of air at 50 °C (Table 1, entry 17). Subsequently, we turned our attention to catalyst reuse. It is noteworthy that 65 % yield was maintained even when the catalyst was reused twice.

Next, under the optimized reaction conditions (Table 1, entry 17), the reactions of a number of electron-deficient alkynes with 2-yn-1-ols were examined (Table 2). We discovered that the reactions between ethyl phenylpropionate (**1a**) and differently substituted 2-yn-1-ols (R^3 is H, CH_3, phenyl, *m*-tolyl, 4-methoxyphenyl, 4-nitrophenyl, 2-pyridyl, 2-thiophenyl) were successful, and the corresponding products (**3aa**–**3ah**) were obtained in good yields in most cases (Table 2, entries 1–8). These results indicated that this domino reaction tolerates functional groups at different positions of the aromatic ring. There was no effect on this transformation from either electron-rich or electron-withdrawing groups on the aromatic ring. Notably, no other regioisomers were detected, which indicated that this cyclization was regioselective and chemoselective. To further expand the scope of this methodology, other electron-deficient alkynes, **1b**–**1d**, were surveyed. The results showed that ethyl but-2-ynoate and aryl alkynyl ketones were also tolerated under the reaction conditions and afforded the corresponding products in good yields (Table 2). The molecular structure of representative product **3cc** was determined by X-ray crystallography (Figure 3).

As an extension of the above study, we continued to investigate the scope of this transformation by using diethyl

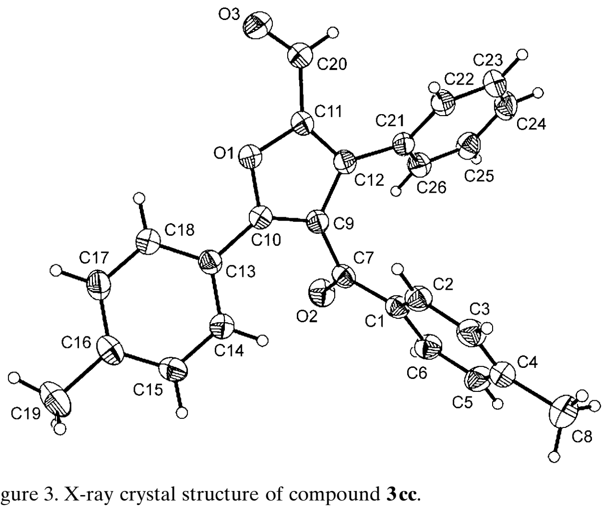
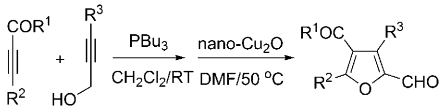
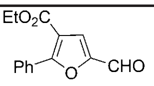
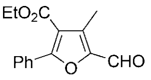
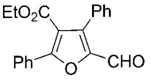
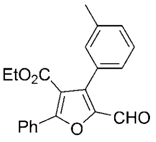
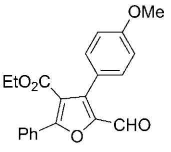
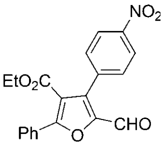
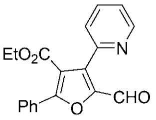
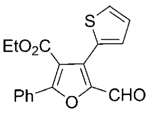
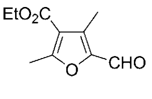
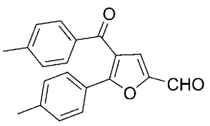
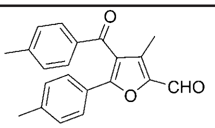
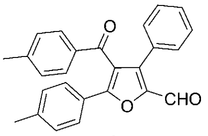
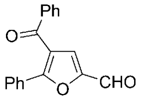
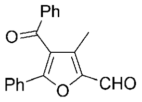
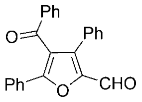
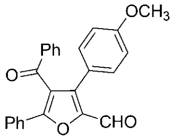
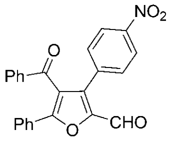
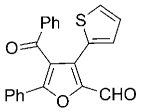


Figure 3. X-ray crystal structure of compound **3cc**.

Table 2. Nano-Cu_2O-catalyzed synthesis of α-carbonyl furans.

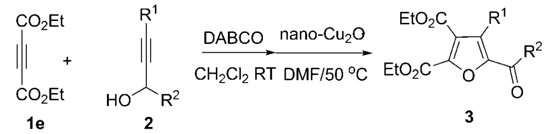


Entry	Alkyne	2-Yn-1-ol	Product	Yield [%][a]
1	ethyl 3-phenylpropionate (**1a**)	prop-2-yn-1-ol (**2a**)	 **3aa**	71
2	**1a**	but-2-yn-1-ol (**2b**)	 **3ab**	67
3	**1a**	3-phenylprop-2-yn-1-ol (**2c**)	 **3ac**	63
4	**1a**	3-*m*-tolyl-prop-2-yn-1-ol (**2d**)	 **3ad**	68
5	**1a**	3-(4-methoxyphenyl)-prop-2-yn-1-ol (**2e**)	 **3ae**	65
6	**1a**	3-(4-nitrophenyl)-prop-2-yn-1-ol (**2f**)	 **3af**	66
7	**1a**	3-(pyridin-2-yl)-prop-2-yn-1-ol (**2g**)	 **3ag**	69
8	**1a**	3-(thiophen-2-yl)-prop-2-yn-1-ol (**2h**)	 **3ah**	62
9	ethyl but-2-ynoate (**1b**)	**2b**	 **3bb**	60
10	1,3-di-*p*-tolyl-prop-2-yn-1-one (**1c**)	**2a**	 **3ca**	67
11	**1c**	**2b**	 **3cb**	73
12	**1c**	**2c**	 **3cc**	70
13	1,3-diphenyl-prop-2-yn-1-one (**1d**)	**2a**	 **3da**	68
14	**1d**	**2b**	 **3db**	73
15	**1d**	**2c**	 **3dc**	71
16	**1d**	**2e**	 **3de**	71
17	**1d**	**2f**	 **3df**	67
18	**1d**	**2h**	 **3dh**	61

[a] Yields of isolated products.

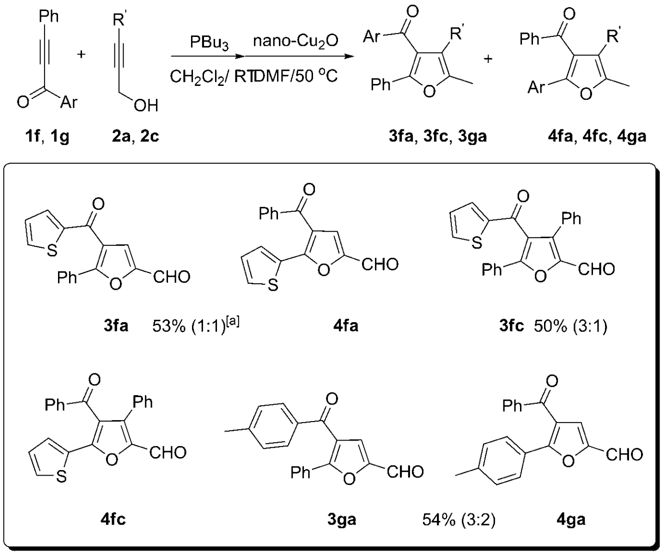
but-2-ynedioate (**1e**) as a substrate. As indicated in Table 3, in contrast to **1a**–**1d**, diethyl but-2-ynedioate (**1e**) gave the corresponding rearrangement products with good yields only upon initiation by DABCO. Interestingly, more sterically hindered *ortho*-substituted substrates such as **2i** or **2j** afforded the corresponding products in relatively higher yields when the nano-Cu_2O particles were employed as the catalytic system to substitute CuI in DMF (Table 3, entries 4 and 5).[15] Other substrates can also obtain good yields under the

Table 3. Nano-Cu_2O-catalyzed formation of furans from diethyl but-2-ynedioate (**1e**) with different 2-yn-1-ols.



Entry	2-Yn-1-ol	Product	Yield [%][a]
1	**2a**	**3ea**	80
2	**2d**	**3ed**	67
3	**2h**	**3eh**	72
4	3-*o*-tolylprop-2-yn-1-ol (**2i**)	**3ei**	65 (52)[b]
5	3-(2-methoxyphenyl)-prop-2-yn-1-ol (**2j**)	**3ej**	63 (45)[b]
6	methyl 4-(3-hydroxyprop-1-ynyl)-benzoate (**2k**)	**3ek**	72
7	3-(2-fluorophenyl)-prop-2-yn-1-ol (**2l**)	**3el**	66
8	3-(4-ethylphenyl)-prop-2-yn-1-ol (**2m**)	**3em**	73
9	hept-4-yn-3-ol (**2n**)	**3en**	65
10	1-phenylhex-1-yn-3-ol (**2o**)	**3eo**	66

[a] Yields of isolated products. [b] See reference [15].



Scheme 4. Synthesis of regioisomeric furans. [a] Isolated yields and the ratio was determined by ^1H NMR spectroscopy.

optimal conditions. It was evident that the nano-Cu_2O particles were an effective catalyst for this domino reaction.

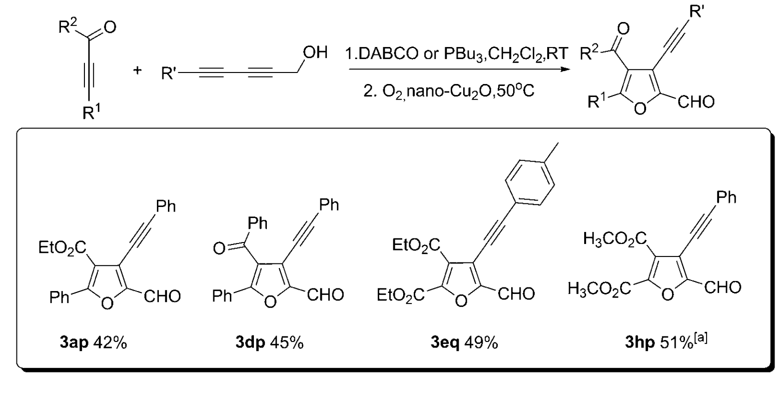
The ketone substrates 3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-one (**1f**) and 3-phenyl-1-*p*-tolylprop-2-yn-1-one (**1g**) were also examined and this sequence ran very well (Scheme 4). Interestingly, we found that a pair of isomeric furans was observed and high yields of products were obtained under the optimized reaction conditions. This result demonstrated that regioisomers would be produced because the two carbonyl groups in complex **D** (see below) were both active in the following cyclization reaction.

Finally, the generality of this transformation was also investigated by using 5-phenylpenta-2,4-diyn-1-ol (**2p**) and 5-*p*-tolylpenta-2,4-diyn-1-ol (**2q**; Scheme 5). Interestingly, the desired products **3ap**, **3cp**, **3eq**, and **3hp** were formed in 42, 45, 49, and 51 % yields, respectively, when **1a**, **1c**, **1e**, and **1h** reacted with **2p** or **2q**. It was especially noteworthy that these novel 2,4,5-trisubstituted 3-ynylfurans were formed in an extremely direct manner without tedious stepwise synthesis.

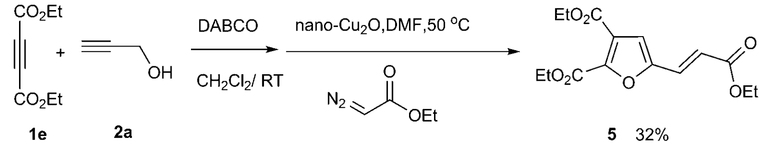
Mechanism

To gain further insight into the mechanism of this novel conversion, we envisioned the possibility of trapping the intermediates of the reaction. Recently, Hofmann et al.[18] have reported the carbene dimer through the reaction of the copper(I) carbene with nucleophilic diazo compounds. Stimulated by this novel result, we tried to trap copper carbene by using ethyl 2-diazoacetate (EDA; Scheme 6). **1a** (0.5 mmol), **2a** (0.5 mmol), and DABCO (0.05 mmol) in CH_2Cl_2 were stirred for 15 min at room temperature. The solution was then evaporated and DMF (3 mL) containing nano-Cu_2O particles (0.3 mmol) was added at 50 °C. Subsequently, EDA (0.8 mmol) was added. Interestingly, vinyl furan **5** was observed. However, when **3ea** was used as a substrate, compound **5** could not be detected by GC–MS (Scheme 7). These results indicated that a copper carbene complex was possibly formed during this domino process.

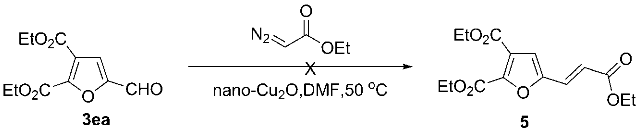
To investigate the possible hydrogen migration of the reaction, an experiment was performed with deuterium-labeled prop-2-yn-1-ol at 50 °C catalyzed by nano-Cu_2O particles (Scheme 8). Compounds **3aD and 4aD** were not observed as the products, which indicated that the D atom can't migrate to the C4 and C6 positions and is only eliminated by water.



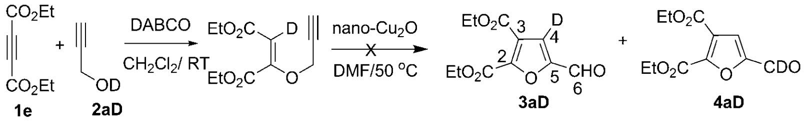
Scheme 5. Synthesis of 2,4,5-trisubstituted 2-ynylfurans from 2,4-diyn-1-ols. [a] Isolated yields.



Scheme 6. Formation of compound **5**.

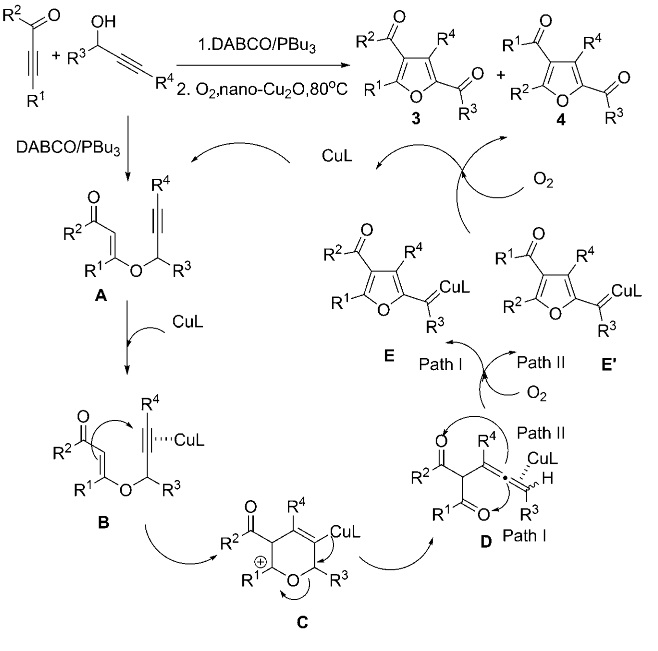


Scheme 7. Unsuccessful reaction of **3ea** with EDA.



Scheme 8. Deuterium labeling experiment.

On the basis of above experimental results, a plausible reaction mechanism is shown in Scheme 9. DABCO- or PBu_3-promoted nucleophilic addition of propargyl alcohol to electron-deficient alkynes formed enyne adduct **A**. A 6-*endo*-dig addition of the enol ether onto the copper(I)–alkyne complex **B** resulted in the formation of intermediate **C**, which collapsed into the β-allenic ketone **D**.[19] Complex **D** then underwent cyclization, a [1,3] hydrogen shift, and oxidation to form **E** and **E′**.[20] The two carbonyl groups in complex **D** were both active in the following cyclization reaction, so carbene complexes **E** and **E′** would be produced by different attack directions (paths I and II) in the presence of a copper catalyst and air. Subsequently, carbene complexes **E** and **E′** underwent carbene oxidation[21] with oxygen metathesis to give **3** and **4** as the desired products.



Scheme 9. Proposed mechanism.

Conclusion

In summary, we have reported an unprecedented nano-Cu_2O-catalyzed synthesis of α-carbonyl furans through a cyclization/rearrangement/oxidation sequence of 1,5-enynes. This catalytic system is environmentally benign and an effective domino process for the formation of C–C and C–O bonds in modern organic chemistry. It is especially noteworthy that this domino process is applicable to a number of electron-deficient alkynes. Furthermore, our findings open a convenient synthetic route to a variety of α-carbonyl furans, which are useful synthetic intermediates for bioactive and natural compounds. The domino reaction exhibits some unusual characteristics that are difficult to understand at this time and that will be an interesting subject of mechanistic studies in the future. Hopefully, this research has established a useful starting point for the investigation of future applications of the nanoparticle-catalyzed synthesis of furans.

Experimental Section

General procedure for the synthesis of ethyl 5-formyl-2-phenylfuran-3-carboxylate: Ethyl phenylpropionate (**1a**; 0.5 mmol), prop-2-yn-1-ol (**2a**; 0.5 mmol), and PBu_3 (0.05 mmol) were stirred in CH_2Cl_2 for 30 min at room temperature. The solution was then evaporated to dryness under reduced pressure. Subsequently, DMF and nano-Cu_2O particles were added at 50 °C. After completion of the reaction (monitored by TLC), water (8 mL) was added. The aqueous solution was extracted with diethyl ether (3 × 8 mL) and the combined extracts were dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give a pure sample of **3aa**: IR (KBr): $\tilde{\nu}$ = 2921, 2853, 1683, 1216, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 9.66 (s, 1H), 8.06–8.08 (m, 2H), 7.64 (s, 1H), 7.45–7.47 (m, 3H), 4.31 (q, J = 7.2 Hz, 2H), 1.33 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 177.4, 162.2, 161.5, 150.2, 131.0, 129.1, 128.3, 128.2, 123.8, 116.1, 61.2, 14.1 ppm; HRMS (EI): m/z calcd: 244.0736; found: 244.0732.

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[1] a) S. L. Schreiber, *Science* **2000**, *287*, 1964–1966; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; c) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; d) D. Enders, C. Grondal, M. R. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; e) S. Ikeda, *Acc. Chem. Res.* **2000**, *33*, 511–519; f) A. de Meijere, P. Zezschwitz, S. Bräse, *Acc. Chem. Res.* **2005**, *38*, 413–422; g) R. Stragies, S. Blechert, *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591; h) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; i) G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979; j) D. J. Cárdenas, B. Martín-Matute, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 5033–5040; k) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710–15711; l) Y. Luo, Z. Li, C. J. Li, *Org. Lett.* **2005**, *7*, 2675–2678.

[2] a) V. Polshettiwar, R. S. Varma, *Acc. Chem. Res.* **2008**, *41*, 629–639; b) W. Leitner, *Acc. Chem. Res.* **2002**, *35*, 746–756; c) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; d) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344.

[3] a) R. Martínez, D. J. Ramón, M. Yusa, *Adv. Synth. Catal.* **2008**, *350*, 1235–1240; b) G. S. Fonseca, E. T. Silveira, M. A. Gelesky, J. Dupont, *Adv. Synth. Catal.* **2005**, *347*, 847–853; c) M. Lakshmia Kantam, K. B. S. Kumar, C. Sridhar, *Adv. Synth. Catal.* **2005**, *347*, 1212–1214.

[4] a) V. Polshettiwar, R. S. Varma, *Org. Biomol. Chem.* **2009**, *7*, 37–40; b) A. Saha, D. Saha, B. C. Ranu, *Org. Biomol. Chem.* **2009**, *7*, 1652–1657; c) K. Sayo, S. Deki, S. Hayashib, *J. Mater. Chem.* **1999**, *9*, 937–942; d) B. M. Choudary, K. Jyothi, M. Roy, M. L. Kantam, B. Sreedhar, *Adv. Synth. Catal.* **2004**, *346*, 1471–1480.

[5] a) C. J. Mortko, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **2005**, *127*, 7994–7995; b) N. Yan, C. Zhao, C. Luo, P. J. Dyson, H. Liu, Y. Kou, *J. Am. Chem. Soc.* **2006**, *128*, 8714–8715.

[6] a) L. Lia, J. Shi, *Adv. Synth. Catal.* **2008**, *350*, 667–672; b) B. Z. Zhan, M. A. White, T. Sham, J. A. Pincock, R. J. Doucet, K. V. R. Rao, K. N. Robertson, T. S. Cameron, *J. Am. Chem. Soc.* **2003**, *125*, 2195–2199.

[7] a) V. Polshettiwar, R. S. Varma, *Chem. Soc. Rev.* **2008**, *37*, 1546–1557; b) V. Polshettiwar, R. S. Varma, *J. Org. Chem.* **2008**, *73*, 7417–7419; c) V. Polshettiwar, R. S. Varma, *J. Org. Chem.* **2007**, *72*, 7420–7422; d) Y. Ju, R. S. Varma, *J. Org. Chem.* **2006**, *71*, 135–141; e) V. Polshettiwar, B. Baruwati, R. S. Varma, *Green Chem.* **2009**, *11*, 127–131.

[8] a) M. D. Mullican, R. J. Sorenson, D. T. Connor, D. O. Thueson, J. A. Kennedy, M. C. Conroy, *J. Med. Chem.* **1991**, *34*, 2186–2194; b) B. L. Flynn, E. Hamel, M. K. Jung, *J. Med. Chem.* **2002**, *45*, 2670–2673; c) I. Francesconi, W. D. Wilson, F. A. Tanious, J. E. Hall, B. C. Bender, R. R. Tidwell, D. McCurdy, D. W. Boykin, *J. Med. Chem.* **1999**, *42*, 2260–2265; d) D. Giardinà, M. Crucianelli, R. Romanelli, A. Leonardi, E. Poggesi, C. Melchiorre, *J. Med. Chem.* **1996**, *39*, 4602–4607; e) S. M. Rahmathullah, J. E. Hall, B. C. Bender, D. R. McCurdy, R. R. Tidwell, D. W. Boykin, *J. Med. Chem.* **1999**, *42*, 3994–4000; f) K. T. Hopkins, W. D. Wilson, B. C. Bender, D. R. McCurdy, J. E. Hall, R. R. Tidwell, A. Kumar, M. Bajic, D. W. Boykin, *J. Med. Chem.* **1998**, *41*, 3872–3878; g) M. L. Bolognesi, R. Budriesi, A. Chiarini, E. Poggesi, A. Leonardi, C. Melchiorre, *J. Med. Chem.* **1998**, *41*, 4484–4853;h) D. S. Mortensen, A. L. Rodriguez, K. E. Carlson, J. Sun, B. S. Katzenellenbogen, J. Katzenellenbogen, *J. Med. Chem.* **2001**, *44*, 3838–3848.

[9] a) S. Cacchi, *J. Organomet. Chem.* **1999**, *576*, 42–64; b) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955–2020.

[10] a) M. M. Bandurraga, F. William, S. F. Donovan, J. Clardy, *J. Am. Chem. Soc.* **1982**, *104*, 6463–6465; b) J. A. Marshall, L. M. McNulty, D. Zou, *J. Org. Chem.* **1999**, *64*, 5193–5200; c) J. A. Marshall, J. Liao, *J. Org. Chem.* **1998**, *63*, 5962–5970; d) J. A. Marshall, E. M. Wallace, *J. Org. Chem.* **1995**, *60*, 796–797.

[11] J. A. Marshall, W. J. DuBay, *J. Org. Chem.* **1994**, *59*, 1703–1708.

[12] a) K. Cheng, A. R. Kelly, R. A. Kohn, J. F. Dweck, P. J. Walsh, *Org. Lett.* **2009**, *11*, 2703–2706; b) J. N. Abrams, R. S. Babu, H. Guo, D. Le, J. Le, J. M. Osbourn, A. G. Doherty, *J. Org. Chem.* **2008**, *73*, 1935–1940; c) A. Fürstner, T. Nagano, *J. Am. Chem. Soc.* **2007**, *129*, 1906–1907.

[13] a) B. Xu, G. B. Hammond, *J. Org. Chem.* **2006**, *71*, 3518–3521; b) M. Zhang, H. F. Jiang, H. Neumann, M. Beller, P. H. Dixneuf, *Angew. Chem.* **2009**, *121*, 1709–1712; *Angew. Chem. Int. Ed.* **2009**, *48*, 1681–1684; c) S. M. Ma, J. L. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 12386–12387; d) C. Jung, J. C. Wang, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4118–4119; e) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165; f) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941–944; g) Y. Hu, Y. Zhang, Z. Yang, R. Fathi, *J. Org. Chem.* **2002**, *67*, 2365–2368; h) Y. Xiao, J. Zhang, *Angew. Chem.* **2008**, *120*, 1929–1932; *Angew. Chem. Int. Ed.* **2008**, *47*, 1903–1906.

[14] J. Barluenga, L. Riesgo, R. Vicente, L. A. López, M. Tomás, *J. Am. Chem. Soc.* **2008**, *130*, 13528–13529.

[15] H. Cao, H. F. Jiang, W. J. Yao, X. H. Liu, *Org. Lett.* **2009**, *11*, 1931–1933.

[16] J. Inanaga, Y. Baba, T. Hanamoto, *Chem. Lett.* **1993**, 241–244.

[17] a) H. L. Xu, W. Z. Wang, W. Zhu, *J. Phys. Chem. B* **2006**, *110*, 13829–13834; b) Y. Tan, X. Xue, Q. Peng, H. Zhao, T. Wang, Y. Li, *Nano Lett.* **2007**, *7*, 3723–3728; c) X. Liang, L. Gao, S. Yang, J. Sun, *Adv. Mater.* **2009**, *21*, 14; d) Z. Zheng, B. Huang, Z. Wang, M. Guo, X. Qin, X. Zhang, P. Wang, Y. Dai, *J. Phys. Chem. A* **2009**, *113*, 14448–14453.

[18] P. Hofmann, I. V. Shishkov, F. Rominger, *Inorg. Chem.* **2008**, *47*, 11755–11762.

[19] a) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979; b) J. W. Grissom, D. Kilingberg, B. J. Huang, *J. Org. Chem.* **1997**, *62*, 603–626; c) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627–2635.

[20] a) M. Gómez-Gallego, M. J. Mancheño, M. A. Sierra, *Acc. Chem. Res.* **2005**, *38*, 44–53; b) D. F. Harvey, D. M. Sigano, *Chem. Rev.* **1996**, *96*, 271–288; c) M. A. Sierra, *Chem. Rev.* **2000**, *100*, 3591–3637.

[21] a) B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.* **1999**, *121*, 11680–11683; b) D. Perdicchia, E. Licandro, S. Maiorana, B. Vandoni, C. Baldoli, *Org. Lett.* **2002**, *4*, 827–830; c) J. Barluenga, F. Andina, M. A. Fernández-Rodríguez, P. García-García, I. Merino, E. Aguilar, *J. Org. Chem.* **2004**, *69*, 7352–7354; d) C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838–5839; e) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

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