RSC Advances

RSC Publishing

COMMUNICATION

View Article Online
View Journal | View Issue

A simple and efficient approach to 2-alkynylbenzofurans under mild copper(I)-catalyzed conditions†

Cite this: *RSC Advances*, 2013, **3**, 3865

Received 8th January 2013,
Accepted 10th January 2013

DOI: 10.1039/c3ra00093a

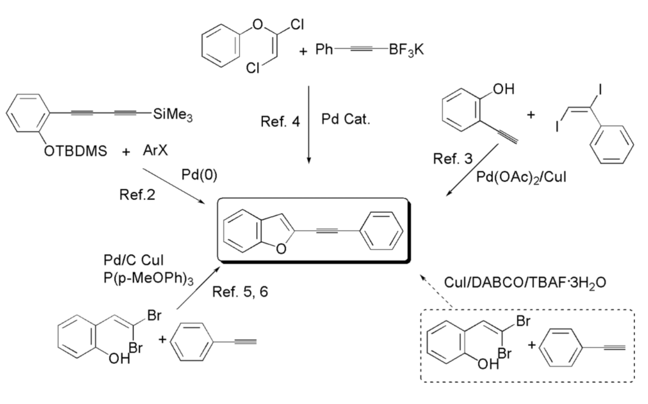
www.rsc.org/advances

Jianming Liu,[a] Ningfei Zhang,[a] Yuanyuan Yue,[a] Dong Wang,[b] Yuanli Zhang,[a] Xin Zhang[a] and Kelei Zhuo*[a]

The copper(I)-catalyzed synthetic method for the preparation of 2-alkynylbenzofurans from *gem*-dihaloolefins has been established using DABCO and TBAF·3H$_2$O as a cocatalyst. This methodology relies on a simple reaction system and inexpensive Cu salts as catalysts. It is generally applicable to *gem*-dihaloolefins and phenylacetylenes.

2-Alkynylbenzofuran derivatives have attracted much attention in biological and material sciences as ubiquitous building blocks with wide-ranging pharmaceutical and pharmacological properties.[1] Thus, a number of synthetic strategies have been reported for the construction of these privileged molecular entities. Previously developed approaches for the preparation of members of this family include a Pd-catalyzed intramolecular coupling reaction with 2-(4-trimethylsilyl-1,3-butadiyn-1-yl)-*tert*-butyldimethylsilylphenol,[2] Pd- and Cu-catalyzed cascade reaction of 2-ethynylphenols with (*E*)-1,2-diiodoalkenes and the one-pot Suzuki coupling/direct arylation of (*E*)-1,2-dichlorovinyl ethers and alkynyl trifluoroborates.[3] An alternative procedure includes a transition metal-catalyzed sequential Suzuki–Miyaura coupling/intra-molecular direct arylation between dichlorovinyl ethers and organoboronic acids.[4] Despite the existence of several methods for the synthesis of 2-alkynylbenzofuran derivatives, versatile and flexible methods to construct the target compounds are still desired. Recently, Lautens *et al.* described a novel and practical method of alkynyl benzofuran synthesis *via* tandem CuI and Pd-catalyzed cross-couplings.[5] Meanwhile, Wang *et al.* reported a similar Pd-catalyzed process involving 2-bromobenzofuran and phenylacetylene to generate the corresponding cross-coupling products in high yields under the Sonogashira reaction conditions.[6] These approaches to prepare 2-alkynylbenzofuran are summarized in Scheme 1.

The *gem*-dihaloolefins, owing to their simple and readily available starting materials,[7] broad functional group tolerance, mild reaction conditions, facile operation, and high regioselectivity, could be used for the construction of heterocyclic compounds. Following the pioneering efforts, this strategy has been applied to the preparation of a variety of heterocycles, such as indoles,[8] benzothiophenes,[9] benzofurans,[5] and isocoumarins[10] through tandem reactions. Therefore, the transition metal-catalyzed tandem reaction serves as an atom-economical and environmentally benign alternative for C–C and C–heteroatom bond formation.[11] In the reactions mentioned above, Pd is used extensively because of its tolerance of many functional groups, its low toxicity and regioselectivity. However, in recent years copper-catalyzed reactions have received considerable attention because of their high efficiency and low costs.[12] Inspired by recently reported advantages of the Cu-catalyzed tandem reaction, we hypothesized that inexpensive Cu catalysts should be capable of promoting intramolecular cross-coupling reactions and Sonogashira reactions of *gem*-dihaloolefins. Herein, we describe a novel catalytic system which is not dependent phosphine ligand or precious metal to mediate this reaction with an efficient performance. This methodology relies on a simple reaction system and inexpensive Cu salts as catalysts.



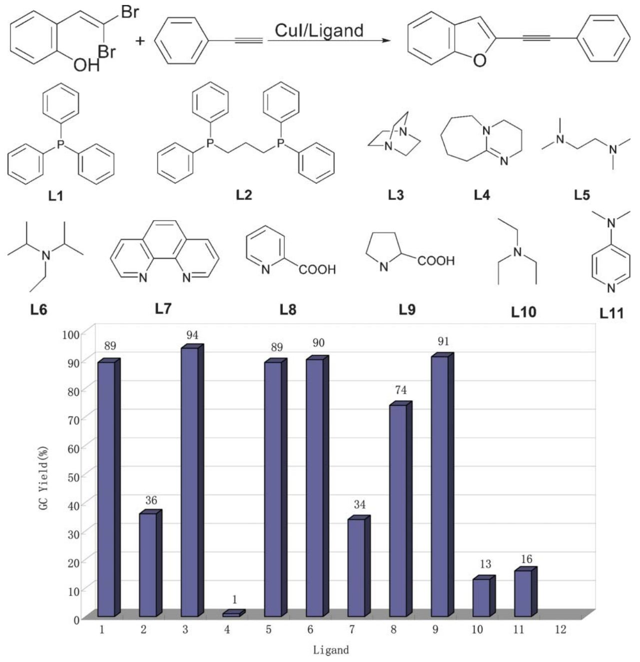
Scheme 1 Direct approaches to 2-alkynylbenzofuran.

---

[a] *Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry nd Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, P. R. China. E-mail: klzhuo@263.net; Fax: (+86)-373-3326336*

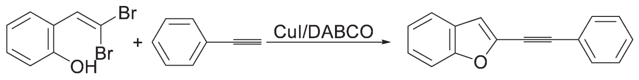
[b] *Department of Bio-Health Technology, College of Biomedical Science, Kangwon National University, Chuncheon, Gangwon-Do, 200-701, Korea*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra00093a



Scheme 2 Ligands screened in the tandem reaction.

Table 1 Influence of the base, catalyst, and solvent on the cross-coupling between 2-(2, 2-dibromovinyl)phenol and phenylacetylene[a]



Entry	Catalyst	Base	Solvent	T/°C	Yield (%)[b]
1	CuI[c]	Cs_2CO_3	DMF	140	73
2	CuI[d]	Cs_2CO_3	DMF	140	trace
3	CuI[e]	Cs_2CO_3	DMF	140	80
4	CuI	Cs_2CO_3	DMF	140	94(86)[c]
5	CuI	Cs_2CO_3	DMF	140	73
6	CuBr	Cs_2CO_3	DMF	140	82
7	$Cu(OAc)_2 \cdot H_2O$	Cs_2CO_3	DMF	140	59
8	$Cu(acac)_2$	Cs_2CO_3	DMF	140	74
9	CuCl	Cs_2CO_3	DMF	140	53
10	CuI	K_2CO_3	DMF	140	92
11	CuI	KOH	DMF	140	48
12	CuI	Na_2CO_3	DMF	140	86
13	CuI	$K_3PO_4 \cdot 3H_2O$	DMF	140	31
14	CuI	Cs_2CO_3	Dioxane	140	66
15	CuI	Cs_2CO_3	THF	140	88
16	CuI	Cs_2CO_3	Toluene	140	trace
17	CuI	Cs_2CO_3	DMF	120	87
18	CuI	Cs_2CO_3	DMF	100	67

[a] Reaction conditions: CuI (0.15 mmol), DABCO (0.30 mmol), *gem*-dihaloolefin (1.0 mmol), phenylacetylene (1.5 mmol), $TBAF \cdot 3H_2O$ (1.0 mmol), base (2.0 mmol), solvent (5.0 mL). [b] Yields were determined by GC with *n*-dodecane as an internal standard. [c] Yield of isolated product. [d] DABCO and $TBAF \cdot 3H_2O$ were not added. [e] $TBAF \cdot 3H_2O$ was not added.

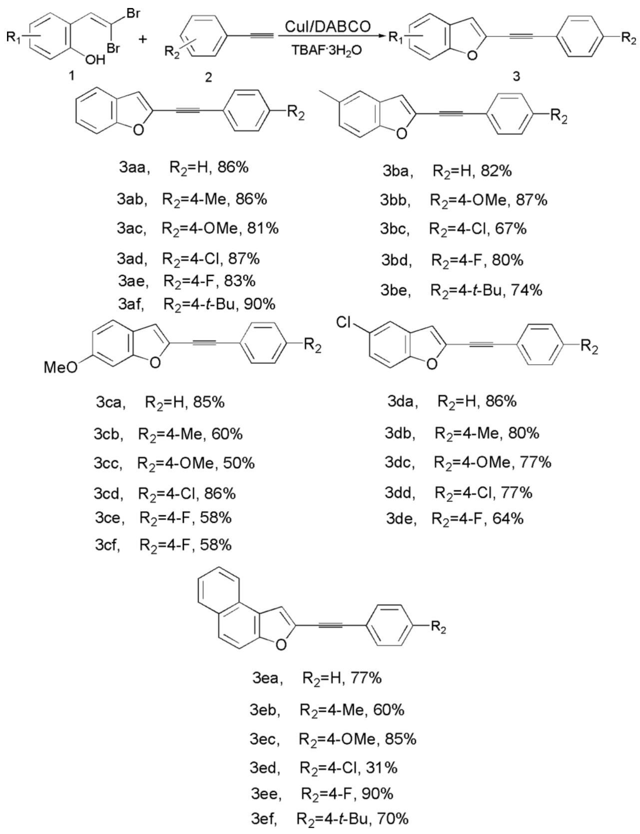
We initially tested the tandem reaction of 2-(2,2-dibromovinyl)-phenol with phenylacetylene using 15 mol% CuI in *N,N*-dimethyl formamide at 140 °C in a N_2 atmosphere. The reaction parameters including various ligands, copper catalysts, solvents and bases were investigated. The ligands screened are shown in Scheme 2. Ligand **L1** was prepared in 89% yield by a catalytic tandem reaction, while Ligand **L2** was prepared in 36% yield. We believe that the most promising preliminary results were obtained using **L5**, **L6**, **L8**, and **L9** as the supporting ligand. We observed that the latter provided a superior yield (91%). We postulated that the key point to achieve this transformation is the excellent coordination of **L3** to the Cu catalyst and its high solubility in the DMF system.

The development of an applicable tandem reaction procedure requires further assessment of the catalyst activity. These studies revealed that the reactions conducted with Cu(I) catalysts could result in high reactivities in DMF. It was found that CuI was the most efficient catalyst, producing the corresponding alkynyl benzofuran in 94% yield (Table 1, entry 4). Bases have an insignificant influence on the catalyst activity (Table 1, entries 10 and 13), while solvents play an important role in the chemical process (Table 1, entries 14–16). DMF turns out to be the most efficient solvent amongst the solvents DMF, THF, dioxane, and toluene. A low reaction temperature leads to a low yield in forming the tandem coupling reaction product (Table 1, entries 17 and 18).

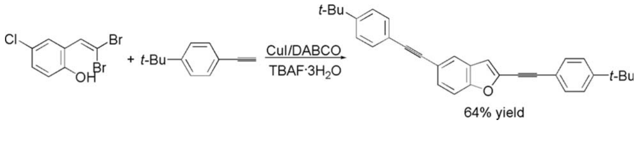
Under optimized conditions, various electron-rich and electron-poor phenylacetylenes were investigated in their reaction with *gem*-dibromovinylphenol (**3aa–3af**, Table 2). The results indicated that the scope of the reaction was quite broad given that alkyl, methoxyl, fluoro and halo substituents were tolerated. The desired products were obtained in high yields up to 86% and the reactions were highly regioselective. To our delight, the *p-tert*-butyl substituted compounds were formed in excellent yields. Furthermore, various functional groups can be tolerated both in the *gem*-dibromovinylphenol and the phenyl fragment, including a large range of methyl, methoxyl, and halo substituents (**3ba–3ef**). It was found that both electron-rich groups and electron-poor groups at the *para*- and *meta*- positions of the *gem*-dibromovinylphenol gave higher yields from 50% to 88%. Meanwhile, the tandem coupling reaction of 1-(2, 2-dibromovinyl)naphthalen-2-ol and phenylacetylenes with various electron releasing and withdrawing groups also proceeded smoothly to give the corresponding alkynyl benzofurans in high yields.

Under similar conditions, we were able to extend this copper-catalytic protocol to the coupling of 4-chloro-2-(2, 2-dibromovinyl)-phenol with 1-(*tert*-butyl)-4-ethynylbenzene. We found that the electronic and steric effects of the groups attached to 4-chloro-2-(2, 2-dibromovinyl)phenol can not be ignored for either the initial tandem coupling reaction or the sequential Sonogashira reaction. The target product was obtained in moderate yield up to 64% (Scheme 3). In addition, benzyl derivatives which are valuable compounds, are found as a substructure of natural products, and are utilized as corrosion inhibitors of mild steel and photosensitive agents in photocurable coatings. Under similar conditions to those reported by Sajiki,[13] we have established a Pd/C-catalyzed environmentally benign process for the oxidation of 2-alkynylbenzofuran to corresponding benzil derivatives using DMSO and oxygen as dual oxidizing agents. The 2-(phenylethynyl)benzofuran underwent the oxidation to give 1-(benzofuran-2-yl)-2-phenylethane-1,2-dione in good yield to 70% (Scheme 4).

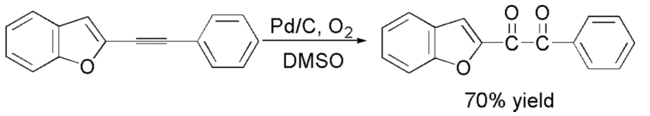
Table 2 Tandem coupling products from *gem*-dibromovinylphenols and phenylacetylenes[a,b]



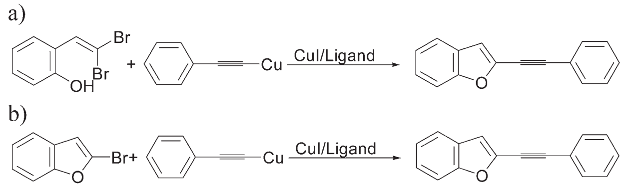
[a] Reaction conditions: CuI (0.15 mmol), DABCO (0.30 mmol), *gem*-dihaloolefin (1.0 mmol), phenylacetylene (1.5 mmol), TBAF·$3H_2O$ (1.0 mmol), Cs_2CO_3 (2.0 mmol), DMF (5.0 mL). [b] Yield of isolated product.



Scheme 3 Cu(I)-catalyzed tandem coupling products from 4-chloro-2-(2, 2-dibromovinyl)phenol with 1-(*tert*-butyl)-4-ethynylbenzene.



Scheme 4 Pd/C-catalyzed environmentally benign process for the oxidation of 2-alkynylbenzofuran.



Scheme 5 Control experiment confirming the CuI-catalyzed tandem reactions of *gem*-dihaloolefins.

To explore the mechanism for this reaction, control experiments were conducted under the standard reaction conditions (Scheme 5). The tandem cross coupling of 2-(2, 2-dibromovinyl)-phenol, 2-bromobenzofuran with (phenylethynyl)copper was also carried out smoothly in a good yield (up to 86%). A working mechanism was proposed as an outline in Fig. 1 for the Cu-catalyzed tandem cross coupling reaction.[14] The reaction of intermediate Cu complexes (a four-center transition state proposed by Castro and Stephens) with phenylacetylene afforded a copper(I)-complex intermediate. The latter occurs to form a four-coordinated copper(III) complex by oxidative addition with 2-bromobenzofuran, followed by reductive elimination of the copper(III) intermediate (in neutral or cationic type), giving the tandem coupling product and regenerating the active copper(I) complex.

In conclusion, we have explored the convenient and efficient synthesis of 2-alkynylbenzofurans from *gem*-dihaloolefins *via* a sequential cyclization and Sonogashira reaction. By applying this elegant protocol, a wide range of electron-rich and electron-poor 2-alkynylbenzofurans were obtained. We believe that such a simple and effective catalyst system could provide good insight into the synthesis of related 2-alkynylbenzofurans.

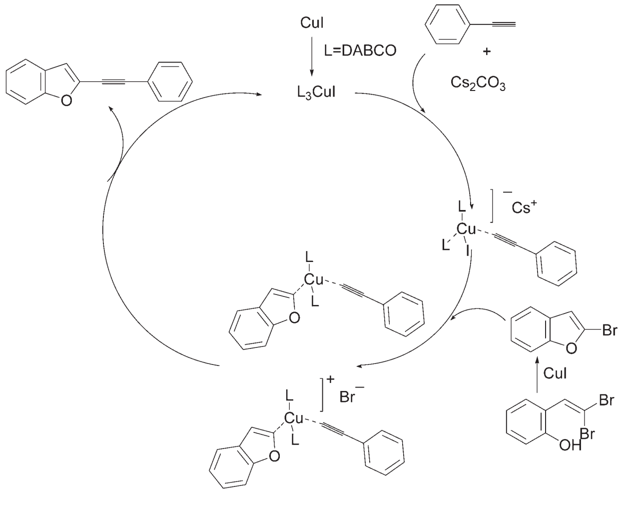


Fig. 1 Possible mechanism for the CuI-catalyzed tandem reactions of 2-(2,2-dibromovinyl)phenol.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (No. 21103044, 21173070, 21205029), Ph.D. Programs Foundation of Ministry of Education of China (No. 20114104120003), and Foundation of Henan Educational Committee (12B150013) for generous financial support.

Notes and references

1 (*a*) I. Muhammad, X. C. Li, M. R. Jacob, B. L. Tekwani, D. C. Dunbar and D. Ferreira, *J. Nat. Prod.*, 2003, **66**, 804; (*b*) M. Lounasmaa and A. Tolvanen, *Nat. Prod. Rep.*, 2000, **17**, 175; (*c*) R. S. Ward, *Nat. Prod. Rep.*, 1997, **14**, 43; (*d*) A. Gangjee, R. Devrai, J. J. Mc Guire and R. L. Kisliuk, *J. Med. Chem.*, 1995, **38**, 3798.

2 V. Fiandanese, D. Bottalico, G. Marchese and A. Punzi, *Tetrahedron*, 2008, **64**, 7301.

3 Y. Liang, L. M. Tao, Y. H. Zhang and J. H. Li, *Synthesis*, 2008, **24**, 3988.

4 L. M. Geary and P. G. Hultin, *Eur. J. Org. Chem.*, 2010, 5563.

5 M. Nagamochi, Y. Q. Fang and M. Lautens, *Org. Lett.*, 2007, **9**, 2955.

6 W. Chen, Y. C. Zhang, L. Zhang, M. Wang and L. Wang, *Chem. Commun.*, 2011, **47**, 10476.

7 (*a*) W. Shen and S. A. Thomas, *Org. Lett.*, 2000, **2**, 2857; (*b*) M. Lera and C. J. Hayes, *Org. Lett.*, 2000, **2**, 3873; (*c*) M. L. N. Rao, D. N. Jadhav and P. Dasgupta, *Org. Lett.*, 2010, **12**, 2048; (*d*) B. P. Berciano, S. Lebrequier, F. Besselièvre and S. Pigue, *Org. Lett.*, 2010, **12**, 4038; (*e*) A. Coste, G. Karthikeyan, F. Couty and G. Evano, *Angew. Chem., Int. Ed.*, 2009, **48**, 4381; (*f*) A. Coste, F. Couty and G. Evano, *Org. Lett.*, 2009, **11**, 4454; (*g*) S. Ye, G. Liu, S. Z. Pu and J. Wu, *Org. Lett.*, 2012, **14**, 70; (*h*) L. Ackermann, C. Kornhaass and Y. J. Zhu, *Org. Lett.*, 2012, **14**, 1824; (*i*) X. R. Qin, X. F. Cong, D. B. Zhao, J. S. You and J. B. Lan, *Chem. Commun.*, 2011, **47**, 5611.

8 (*a*) Y. Q. Fang, R. Karisch and M. Lautens, *J. Org. Chem.*, 2007, **72**, 1341; (*b*) Y. Q. Fang, Y. Yuen and M. Lautens, *J. Org. Chem.*, 2007, **72**, 5152; (*c*) Y. Q. Fang and M. Lautens, *J. Org. Chem.*, 2008, **73**, 538; (*d*) D. I. Chai and M. Lautens, *J. Org. Chem.*, 2009, **74**, 3054; (*e*) Y. Q. Fang and M. Lautens, *Org. Lett.*, 2005, **7**, 3549; (*f*) J. Yuen, Y. Q. Fang and M. Lautens, *Org. Lett.*, 2006, **8**, 653; (*g*) A. Fayol, Y. Q. Fang and M. Lautens, *Org. Lett.*, 2006, **8**, 4203; (*h*) M. Nagamochi, Y. Q. Fang and M. Lautens, *Org. Lett.*, 2007, **9**, 2955; (*i*) C. S. Bryan and M. Lautens, *Org. Lett.*, 2008, **10**, 4633; (*j*) T. O. Viera, L. A. Meaney, Y. L. Shi and H. Alper, *Org. Lett.*, 2008, **10**, 4899; (*k*) M. Arthuls, R. Pontikis and J. C. Florent, *Org. Lett.*, 2009, **11**, 4608.

9 (*a*) C. S. Bryan, J. A. Braunger and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 7064; (*b*) S. G. Newman, V. Aureggi, C. S. Bryan and M. Lautens, *Chem. Commun.*, 2009, 5236.

10 W. Shen and L. Wang, *Tetrahedron Lett.*, 1998, **39**, 7625.

11 (*a*) X.-Y. Liu and C. M. Che, *Angew. Chem., Int. Ed.*, 2008, **47**, 3805. For recent reviews, see: (*b*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*c*) J. M. Lee, Y. Na, H. Han and S. Chang, *Chem. Soc. Rev.*, 2004, **33**, 302; (*d*) A. Ajamian and J. L. Gleason, *Angew. Chem., Int. Ed.*, 2004, **43**, 3754; (*e*) J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*f*) A. de Meijere, P. von Zezschwitz and S. Brase, *Acc. Chem. Res.*, 2005, **38**, 413.

12 (*a*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*b*) C. Koradin, K. Polborn and P. Knochel, *Angew. Chem., Int. Ed.*, 2002, **41**, 2535; (*c*) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210; (*d*) A. Kondoh, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2007, **129**, 4099; (*e*) H. Isobe, K. Cho, N. Solin, D. B. Werz, P. H. Seeberger and E. Nakamura, *Org. Lett.*, 2007, **9**, 4611.

13 S. Mori, M. Takubo, T. Yanase, T. Maegawa, Y. Monguchi and H. Sajiki, *Adv. Synth. Catal.*, 2010, **352**, 1630.

14 (*a*) R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 2163; (*b*) J. H. Li, J. L. Li, D. P. Wang, S. F. Pi, Y. X. Xie, M. B. Zhang and X. C. Hu, *J. Org. Chem.*, 2007, **72**, 2053; (*c*) F. Monnier, F. Turtaut, L. Duroure and M. Taillefer, *Org. Lett.*, 2008, **10**, 3203.