

Cu₂O-Catalyzed Tandem Ring-Opening/ Coupling Cyclization Process for the Synthesis of 2,3-Dihydro-1,4-benzodioxins

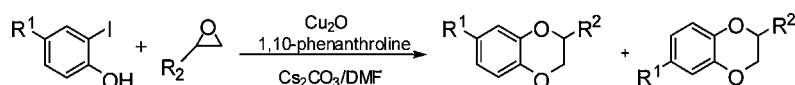
Weiliang Bao,* Yunyun Liu, Xin Lv, and Weixing Qian

Department of Chemistry, Zhejiang University, Xi Xi Campus, Hangzhou, Zhejiang
310028, P. R. of China

wlbao@css.zju.edu.cn

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ABSTRACT



2, 3-Dihydro-1, 4-benzodioxins can be prepared in a tandem one-pot procedure by reaction of *o*-iodophenols with epoxides catalyzed by Cu₂O/1, 10-phenanthroline/Cs₂CO₃ system. The reaction is suggested to occur via a novel ring-opening/coupling mechanism, giving moderate to good yields. Moreover, both aryl and aliphatic epoxides are tolerated under these conditions.

Compounds containing 1, 4-benzodioxane structures have attracted considerable interest during the past few years due to their interesting biological activities.¹ For example, fluparoxan (Figure 1, **1**) is claimed to have potent antidepressant properties,² the mesylate salt of doxazosin (**2**) is an effective antihypertension agent,³ piperoxan (**3**), an α -adrenergic blocking agent with considerable stimulating activity, has been used to diagnose pheochromocytoma and served as an antihypertension agent,⁴ and WB 4104 (**4**) is recognized as a selective α -adrenoceptor antagonist.⁵ Moreover, they are found in a variety of natural products, such as silybin,⁶ isosilybin,⁷ haedoxan A,⁸ eusiderin,⁹ purpureanol,¹⁰ and so

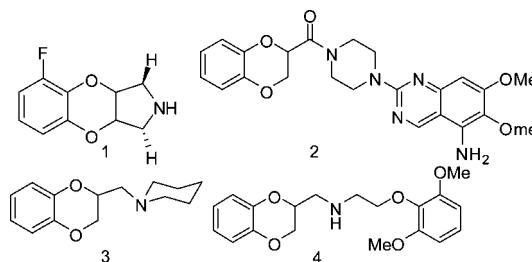


Figure 1. Structures of some biologically important 1,4-benzodioxanes.

(1) (a) Merlini, L.; Zamarotti, A.; Pelter, A.; Rochefort, M. P.; Haensel, R. *J. Chem. Soc., Chem. Commun.* **1979**, 695. (b) Bosseray, P.; Guillaumet, G.; Coudert, G.; Wasserman, H. *Tetrahedron Lett.* **1989**, 30, 1387. (c) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *Tetrahedron* **1994**, 50, 13583. (d) Achari, B.; Mandal, S. B.; Dutta, P. K.; Chowdhury, C. *Synlett* **2004**, 2449.

(2) Pinder, R. M.; Wieringa, J. H. *Med. Res. Rev.* **1993**, 13, 2509.

(3) Fang, Q. K.; Grover, P.; Han, Z.; McConville, F. X.; Rossi, R. F.; Olsson, D. J.; Kessler, D. W.; Wald, S. A.; Senanayake, C. H. *Tetrahedron: Asymmetry* **2001**, 12, 2169.

(4) Zhou, R.; Luo, G.; Ewing, A. G. *J. Neuroscience* **1994**, 14, 2402.

(5) Takano, Y.; Takano, M.; Yaksh, T. L. *Eur. J. Pharmacol.* **1992**, 219, 465.

(6) Hansel, R.; Schulz, J.; Pelter, A. *J. Chem. Soc., Chem. Commun.* **1972**, 195.

(7) Pelter, A.; Hansel, R. *Chem. Ber.* **1975**, 108, 790.

on.¹¹ These compounds could also be used as intermediates for further synthetic transformations.¹²

Several methods for the assembly of 1,4-benzodioxanes have developed in recent years. One of the typical approaches employs catechols as substrates, which can react with various

(8) (a) Taniguchi, E.; Oshima, Y. *Agric. Biol. Chem.* **1972**, 36, 1013, and references cited therein. (b) Ishibashi, F.; Taniguchi, E. *Phytochemistry* **1998**, 49, 613.

(9) Hobbs, J. J.; King, F. E. *J. Chem. Soc.* **1960**, 4732.

(10) Debenedetti, S. L.; Nadinic, E. L.; Coussio, J. D.; De Kimpe, N.; Dupont, J. F.; Declercq, J. P. *Phytochemistry* **1991**, 30, 2757.

reagents, such as epoxides, α -haloalkene, 1,4-bis(methoxycarbonyloxy)but-2-ene or 3,4-bis(methoxycarbonyloxy)but-1-ene, and so on.¹³ Another approach uses the cycloaddition of a variety of *o*-quinones with dienophile, either directly or via a two-step process involving a hetero-Diels–Alder reaction followed by a [3,3] sigmatropic rearrangement.¹⁴ More recently, a method for the synthesis of 1,4-benzodioxanes from halo alcohols through a Pd-catalyzed intramolecular etherification has been reported.¹⁵ However, these methods have some limitations with respect to the availability of the starting materials and the higher costs of Pd catalysts, as well as tedious multistep sequence.

Thus, a general and practical method to prepare 1,4-benzodioxanes is still required.

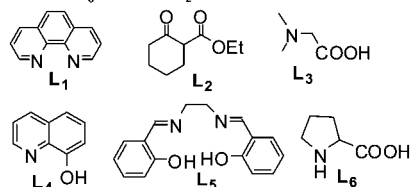
In the past few years, the formation of aryl C–X bonds (X = N, O, S, etc.) via copper-catalyzed Ullmann coupling between aryl halides and heteroatom-centered nucleophiles has drawn considerable attention.¹⁶ More recently, the Ullmann coupling was successfully extended to the preparation of many heterocycles via copper-mediated cyclization.¹⁷ Li and co-workers reported a copper-catalyzed tandem double-alkenyl C–N bond formation by the reaction of (1*Z*,3*Z*)-1,4-diiodo 1,3-dienes with amides to form di- or trisubstituted *N*-acylpyrroles.¹⁸ Ma and co-workers developed a novel protocol for the elaboration of *N*-substituted 1,3-dihydrobenzimidazol-2-ones from methyl *o*-haloarylcarbamates via a CuI/amino acid catalyzed coupling with amines and subsequent condensative cyclization.¹⁹ Copper-catalyzed tandem C–N bond formation for the synthesis of *N*-

alkylbenzimidazoles in regioisomerically pure form starting from *o*-haloanilines has been recently reported by Buchwald and co-workers.²⁰ The above reports developed a simple and convenient method for synthesis of various heterocycles in an efficient process. Here we would like to describe a new general and practical methodology to synthesize 1,4-benzodioxanes from *o*-iodophenols and epoxides catalyzed by a Cu₂O/1,10-phenanthroline system via cascade ring-opening/coupling cyclization reactions.

In our initial screening experiment, the reaction of *o*-iodophenol **5a** with styrene oxide **6a** mediated by cesium carbonate was chosen as a model for exploring the suitable reaction conditions (Table 1). It was found that the reaction

Table 1. Optimization of Experimental Conditions for **7a**^a

entry	ratio	ligand	catalyst	solvent	temp (°C)	yield (%) ^b
1	1:1	L ₁	CuI	PhMe	90	43
2	1:1	L ₁	CuI	PhMe	110	48
3	1:1.2	L ₁	CuI	PhMe	110	50
4	1:1.2	L ₁	CuBr	PhMe	110	53
5	1:1.2	L ₁	Cu ₂ O	PhMe	110	54
6	1:1.2	L ₁	Cu ₂ O	DMSO	110	43
7	1:1.2	L ₁	Cu ₂ O	DMF	110	61
8	1:1.2	L ₁	Cu ₂ O	NMP	110	48
9	1:1.2	L ₁	Cu ₂ O	<i>n</i> C ₃ H ₇ CN	110	50
10	1:1.5	L ₁	Cu ₂ O	DMF	110	89
11	1:1.5	L ₂	Cu ₂ O	DMF	110	30
12	1:1.5	L ₃	Cu ₂ O	DMF	110	15
13	1:1.5	L ₄	Cu ₂ O	DMF	110	57
14	1:1.5	L ₅	Cu ₂ O	DMF	110	15
15	1:1.5	L ₆	Cu ₂ O	DMF	110	57



^a Reaction conditions: CuX (15 mol %), Ligand (30 mol %), Cs₂CO₃ (2 mmol), solvent (2 mL), 48 h, ratio based on *o*-iodophenol. ^b Isolated yield.

worked at 90 °C in toluene under the action of 15% CuI and 30% 1,10-phenanthroline giving the corresponding product **7a** (entry 1). Raising the reaction temperature to 110 °C resulted in an improved yield (entry 2). When the copper(I) source was switched to CuBr or Cu₂O, the product yield was enhanced (entries 4 and 5). From an economic point of view, Cu₂O was a better catalyst than CuBr. Several solvents such as toluene, DMSO, NMP, butyronitrile, and DMF were tested. DMF was superior to the other solvents (entries 5–9). A brief study of the effect of the ligand was also carried out; 1,10-phenanthroline **L**₁ provided good

(11) (a) Woo, W. S.; Kang, S. S.; Wagner, H.; Chari, V. M. *Tetrahedron Lett.* **1978**, 19, 3239. (b) Woo, W. S.; Kang, S. S.; Seligmann, O.; Chari, V. M.; Wagner, H. *Tetrahedron Lett.* **1980**, 21, 4255. (c) Chin, Y. W.; Kim, J. *Tetrahedron Lett.* **2004**, 45, 339.

(12) (a) Lee, T. V.; Leigh, A. J.; Chapleo, C. B. *Tetrahedron* **1990**, 46, 921. (b) Mata, E. G.; Suarez, A. G. *Synth. Commun.* **1997**, 27, 1291.

(13) (a) Koo, J.; Avakian, S.; Martin, J. G. *J. Am. Chem. Soc.* **1955**, 77, 5373. (b) Willard, A. K.; Smith, R. L.; Cragoe, E. J., Jr. *J. Org. Chem.* **1981**, 46, 3846. (c) Procopiou, P. A.; Brodie, A. C.; Deal, M. J.; Hayman, D. F. *Tetrahedron Lett.* **1988**, 29, 3671. (d) Massacret, M.; Lhoste, P.; Lakhmiri, R.; Parella, T.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 2665, and references therein. (e) Harrak, y.; Guillaumet, G.; Pujol, M. D. *Synlett* **2003**, 813.

(14) (a) Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. C* **1969**, 1692. (b) Ansell, M. F.; Leslie, V. J. *J. Chem. Soc. C* **1971**, 1423. (c) Dondoni, A.; Fogagnolo, M.; Mastellari, A.; Pedrini, P.; Ugozzoli, F. *Tetrahedron Lett.* **1986**, 27, 3915. (d) Takada, M.; Oshima, R.; Yamauchi, Y.; Kumanotani, J.; Seno, M. *J. Org. Chem.* **1988**, 53, 3073. (e) Takuwa, A. *Chem. Lett.* **1989**, 5. (f) Nair, V.; Mathew, B.; Radhakrishnan, K. V.; Rath, N. P. *Tetrahedron* **1999**, 55, 11017. (g) Cameron, D. W.; Heisey, R. M. *Aust. J. Chem.* **2000**, 53, 109. (h) Xu, D. W.; Chiaroni, A.; Largeron, M. *Org. Lett.* **2005**, 7, 5723.

(15) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, 123, 12202, and references therein.

(16) For reviews, see: (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, 42, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 248, 2337. (d) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973.

(17) For the latest selected example, see: (a) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, 5, 3843. (b) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, 7, 4781. (c) Evinder, G.; Batey, R. A. *J. Org. Chem.* **2006**, 71, 1802. (d) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, 71, 6427. (e) Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, 9, 3379. (f) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, 73, 3452. (g) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, 10, 625.

(18) (a) Yuan, X.; Xv, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, 72, 1510.

(19) Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, 9, 4291.

(20) Zheng, N.; Buchwald, S. L. *Org. Lett.* **2007**, 9, 4749.

Table 2. Scope of the Sequential One-Pot Ring-Opening/Coupling Protocol^a

entry	ortho-iodophenol	epoxide	product	yield ^b (%) / regioisomer ratio (7:8) ^c
1	5a	6a	7a	90
2	5a	p-Cl-C ₆ H ₄ -epoxide 6b	7b	70
3	5a	Ph-CH ₂ -epoxide 6c	7c	71
4	5a	o-Me-C ₆ H ₄ -epoxide 6d	7d	62
5	5a	cyclohexene oxide 6e	7e	63
6	t-C ₄ H ₉ -substituted 5b	6e	7f	76
7	Cl-substituted 5c	6e	7g	74
8	H ₃ C-substituted 5d	6a	7h , 8h	71 (92:8)
9	5b	6a	7i , 8i	75 (87:13)
10	5c	6a	7j , 8j	58 (75:25)
11	5d	6c	7k	68
12	5b	6c	7l	61
13	5c	6c	7m , 8m	57 (78:22)
14	5b	6b	7n , 8n	62 (94:6)
15	5d	H ₂ C=HC(H ₂ C) ₆ -epoxide 6f	7o	49
16	5e	6a	7p , 8p	81 (75:25)

^a Reaction conditions: *o*-iodophenol (1 mmol), epoxide (1.5 mmol), Cu₂O (15 mol %), 1, 10-phenanthroline (30 mol %), Cs₂CO₃ (2 mmol), in DMF (2 mL) at 110 °C for 48 h. ^b Isolated yield. ^c The regioisomer ratios were based on NMR spectrum and GC.

catalytic activity in this transformation (entries 9–15). In addition to the solvent and ligand, the ratio of *o*-iodophenol to styrene oxide was found to have a dramatic influence on the reaction outcome (compare entries 2 and 3 as well as entries 7 and 10).

On the basis of the above results, the reaction scope was explored with different epoxides and *o*-iodophenols. As indicated in Table 2, both aryl and aliphatic epoxides could react with *o*-iodophenols giving the corresponding products

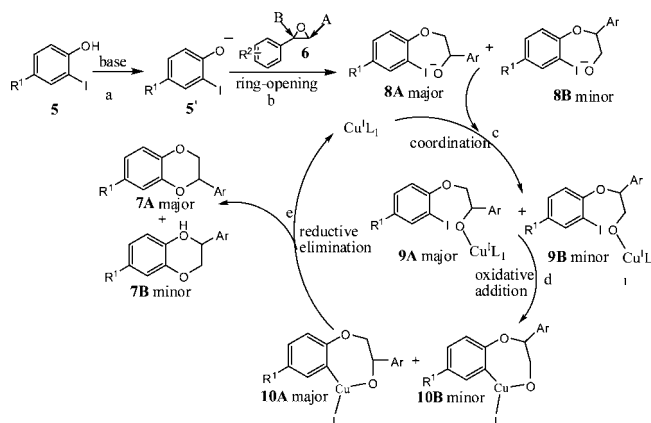
in moderate to good yield. No spectacular electronic effects were observed when cyclohexene oxide was submitted to reaction with para-substituted *o*-iodophenols (entries 6 and 7). When styrene oxide **6a** and 2-(phoxymethyl)oxirane **6c** were used as the substrates, the *o*-iodophenols with electron-rich substituents were generally superior to electron-deficient ones, as evidenced by giving better yields (compare entries 8–10 and 16, as well as entries 11–13). This result may be explained by the symmetry of the cyclohexene oxide.

2-(*o*-Tolyloxymethyl)oxirane **6d** proved to be a significantly less effective coupling partner due to its steric hindrance (compare entries 3 and 4). Condensation of substituted *o*-iodophenols with epoxides may afford a single regioisomer or a mixture of two regioisomers. The configuration of the isomers (**7p** and **8p**) was determined by ^1H NMR chemical shifts of H_a and H_b on the naphthalene ring (entry 16). Takuwa reported that H_a of **7p** resonated at lower field than H_b of **8p** probably due to a deshielding effect of the phenyl group at the position 2.^{14e} The NMR signals of our products **7p** and **8p** were in very good agreement with the chemical shifts provided by Takuwa, and **7p** was the major regioisomer. The phenate favored to attack the position of epoxide with less steric hindrance under basic conditions.

A plausible mechanism, which accounts for the formation of the 1,4-benzodioxane compounds from the *o*-iodophenols and epoxides, is shown in Scheme 1. First, in the presence of base, the *o*-iodophenol (**5**) transformed into phenate (**5'**) (step a), then it would attack onto electrophilic carbons of the styrene oxide **6** (the assault onto the position A would take priority) and the intermediates **8** would be formed (**8A** was major) (step b). Coordination of the oxygen to copper to give **9** (**9A** was major), followed by an oxidative addition to **10** (**10A** was major), and then a reductive elimination to release product **7** (**7A** was major) with concomitant regeneration of the catalyst/ligand (step e).

In conclusion, we have developed a novel, facile and practical protocol for the synthesis of 1,4-benzodioxanes through a $\text{Cu}_2\text{O}/1,10\text{-phenanthroline}$ -catalyzed tandem ring-opening/coupling cyclization reaction. This method allows the use of a wide range of *o*-iodophenols and epoxides to

Scheme 1. Plausible Mechanism



assemble various products in moderate to good yields. The readily accessible starting materials and relatively mild conditions should provide a useful tool for intramolecular C–O cyclization by copper catalysis in organic chemistry.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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