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Copper-Catalyzed Tandem Aryl-Halogen Hydroxylation and CH_2Cl_2-Based *N,O*-Acetalization Toward the Synthesis of 2,3-Dihydrobenzoxazinones

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The concise synthesis of 2,3-dihydro-4H-benzo[e][1,3]oxazin-4-ones has been accomplished by copper-catalyzed tandem reactions of o-halobenzamides, LiOH and dichloromethane. The aryl-halogen bond hydroxylation and subsequent *N,O*-acetalization on CH_2Cl_2 are enabled under the catalytic conditions which allowed the generation of C(sp2)-O, C(sp3)-O and C(sp3)-N bond to the target products.

Copper-catalyzed Ullmann C-O cross-coupling reaction has been known as highly efficient and powerful tool in the construction of aryl/vinyl C-O bonds. By employing such transformation, a massive number of oxygen-containing molecules such as aryl/vinyl ethers and *O*-containing heterocycles have been successfully synthesized.[1] As the specific version of Ullmann C-O cross coupling reaction, the aryl-halogen bond hydroxylation providing phenol products has also received broad concern, which has led to the development of many practical catalytic approaches toward the hydroxylation of aryl halides.[2] However, while most known efforts have been made in discovering alternative catalytic methods, the limit on the synthetic application of this hydroxylation transformation has been ignored. Actually, in many cases, simply synthesizing phenols from corresponding aryl halides are not industrially economical. In this regard, exploring extended application of the aryl-halogen bond hydroxylation in the synthesis of organic products with increased structural complexity is of high significance in terms of disclosing the synthetic potential of this specific cross-coupling process.[3] In 2009, You and co-workers have reported the copper-catalyzed synthesis of ethers via the in situ aryl-halogen bond hydroxylation and subsequent intermolecular Williamson etherification.[4] Similar copper-catalyzed hydroxylation and tandem reactions for the synthesis of functional ether products have also been delevoped.[5] More recently, Wang et al developed the aryl-halogen hydroxylation-based tandem reactions for the synthesis of ethers and benzofurans in water.[6] Regardless the notable achievement reflected by these seminal works, the overall models of tandem reactions initiated by the aryl-halogen bond hydroxylation, especially the reactions providing heterocyclic products, are still rather rare.

2,3-Dihydro-4H-benzo[e][1,3]oxazin-4-ones (2,3-dihydrobenzoxazinones) are a class of heterocyclic compounds with enriched biological profiles,[7] these heterocyclic compounds have also been extensively employed as key building blocks in the synthesis of many other important organic products.[8] Conventionally, 2,3-dihydrobenzoxazinones can be accessed via the condensation reactions of *o*-hydrozxyl benzamides with aldehydes and ketones.[9] In order to expand the compound diversity of the synthesis on the basis of the condensation protocol, some complementary methodologies have been disclosed in recent years. For example, Taylor et al developed the tandem deacetalisation–bicyclisation reactions employing *o*-hydroxyl benzoic acids and acetal functionalized alkyl amines,[10] and later on the tandem reactions of *o*-hydroxyl benzoic acids with imines.[11] Coates and Mulzer reported the synthetic methods employing cobalt-mediated reactions based on the hydroformylation of dihydroxazines.[12] Recently, Maiti et al reported another interesting route to these heterocyclic products via copper-catalyzed intramolecular dehydrogenative coupling of *N,N*-dialkyl functionalized *o*-hydroxyl benzamides.[13] Interesting, all these known method, as happened in the conventional condensation approach with *o*-hydroxyl benzamides, rely on the transformation of the pre-installed hydroxyl group in the substrates. Alternative synthetic method without using hydroxylated starting materials, to our knowledge, is not yet available. In the process of our work in exploring both new synthetic methods based on the copper-catalyzed cross-coupling[14] and synthesis using dichloromethane as methylene donor,[15] we wish to report herein a new synthetic protocol toward 2,3-dihydrobenzoxazinones by means of the tandem aryl-halogen

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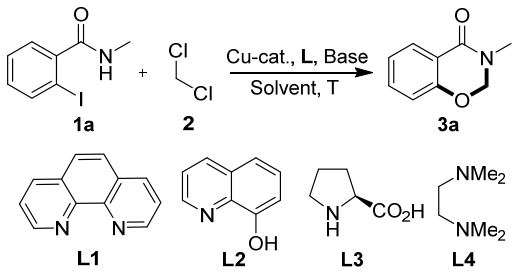
hydroxylation and CH_2Cl_2-based *N,O*-acetalization using *o*-halobenzamides and CH_2Cl_2.

At the beginning, the reactions of *N*-methyl *o*-iodobenzamide **1a**, dichloromethane (DCM) **2** and KOH was conducted in the presence of CuBr and 1,10-phenanthroline wherein the target product **3a** was obtained in 31% yield (entry 1, Table 1). Control experiment in the absence of copper catalyst did not yield **3a** (entry 2, Table 1). On the other hand, the entry without using ligand provided **3a** with lower yield (entry 3, Table 1). The variation on the DCM amount indicated that 0.2 mL was the most appropriate (entries 4-5, Table 2). A class of different Cu(I) and Cu(II) catalysts were also screened, but no copper catalyst better than CuBr was identified (entries 6-10, Table 1). In addition, the results from the entries with different catalyst loading suggested that 5 mol% catalyst was favored by the reaction (entries 11-12, Table 1). In order to improve the product yield, some different ligands **L2**-**L4** were also tested, but no positive result was observed (entries 13-15, Table 1). However, the attempts in using different metal hydroxides (base) led to the discovery that LiOH was a better hydroxyl source by providing **3a** with much higher yield (entries 16-17, Table 1). Subsequent work in varying the reaction medium and temperature failed to afford further improved results (entries 18-21, Table 1).

After the efforts in optimizing reaction conditions, the scope of this new synthetic approach was consequently investigated. According to the reaction process, the synthesis of different 2,3-dihydrobenzoxazinones was performed mainly by varying the *o*-halobenzamide substrates. It was noteworthy that the present catalytic method exhibited general tolerance to the *o*-halobenzamides since the substrates containing functional substituent in the phenyl ring and *N*-atom (both aryl and alkyl) all displayed tolerance to the tandem reaction. The employment of both *o*-iodo- and *o*-bromobenzamides in the reactions showed smooth tolerance to the expect transformation. On the other hand, the for the reactions using N-alkylated benzamides, longer alkyl chain in the N-atom afforded corresponding products with higher yiels (**3a**, **3b**, **3e**, **3f** and **3h**, Table 2). On the other hand, *N*-allyl and *N*-benzyl benzamides took part in the reaction to provide *N*-allyl and *N*-benzyl products with similar yields as those entries using *N*-methyl and *N*-ethyl benzamides (**3j**-**3o**, Table 2), and much lower yield was observed in the reaction of *N*-cyclohexyl benzamide (**3p**, Table 2), suggesting that both the electron and steric effect were crucial in determining the synthetic efficiency. *N*-Aryl benzamides were also applicable starting materials for the synthesis of *N*-arylated products (**3q** and **3r,** Table 2), but with even lower yield probably because of the

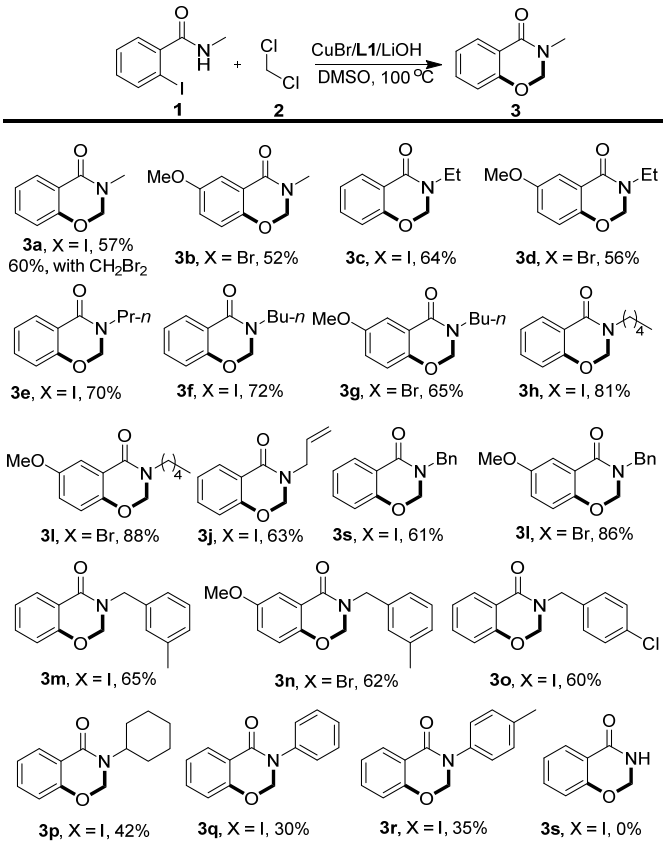
Table 1 Optimization on reaction conditions[a]



Entry	Catalyst	Ligand	Base	Solvent	T (°C)	Yield[b](%)
1	CuBr	**L1**	KOH	DMSO	100	31
2	no	**L1**	KOH	DMSO	100	nr
3	CuBr	no	KOH	DMSO	100	21
4[c]	CuBr	**L1**	KOH	DMSO	100	14
5[d]	CuBr	**L1**	KOH	DMSO	100	17
6	CuCl	**L1**	KOH	DMSO	100	trace
7	CuI	**L1**	KOH	DMSO	100	17
8	$CuSO_4$	**L1**	KOH	DMSO	100	11
9	$Cu(OAc)_2$	**L1**	KOH	DMSO	100	13
10	CuO	**L1**	KOH	DMSO	100	nr
11[e]	CuBr	**L1**	KOH	DMSO	100	16
12[f]	CuBr	**L1**	KOH	DMSO	100	22
13	CuBr	**L2**	KOH	DMSO	100	21
14	CuBr	**L3**	KOH	DMSO	100	nr
15	CuBr	**L4**	KOH	DMSO	100	nr
16	CuBr	**L1**	NaOH	DMSO	100	35
17	CuBr	**L1**	LiOH	DMSO	100	57
18	CuBr	**L1**	LiOH	DMF	100	25
19	CuBr	**L1**	LiOH	DMA	100	33
20	CuBr	**L1**	LiOH	DMSO	90	36
21	CuBr	**L1**	LiOH	DMSO	110	42

[a]General conditions: **1a** (0.3 mmol), **2** (0.3 mL), copper catalyst (0.015 mmol), ligand (0.03 mmol), base (2.7 mmol) in solvent (2 mL), stirred at 100 °C in sealed tube for 12h. DMA = *N,N*-dimethyl acetamide; nr = no reaction. [b]Yield of isolated product based on **1a**. [c]CH_2Cl_2 (0.2 mL) was used. [d]CH_2Cl_2 (0.4 mL) was used. [e]CuBr (0.01 mmol) was used. [f]CuBr (0.02 mmol) was used.

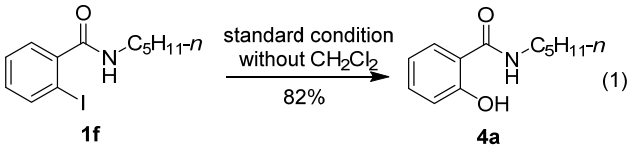
Table2 Synthesis of of different 2,3-dihydrobenzoxazinones



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.3 mL, ~16 equiv.), LiOH (2.7 mmol), CuBr (0.015 mmol), **L1** (0.03 mmol) in DMSO (2 mL), stirred at 100 °C in sealed tube for 12h. [b]Yield of isolated product based on **1**.

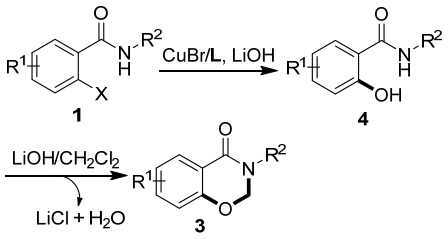
significantly weaker nucleophilicity of the *N*-atom therein. Additionally, the entry using unsubstituted *o*-iodobenzamide failed to provide the target *NH*-heterocyclic product **3s**. Notably, **3a** was provided with also fair yield when CH_2Br_2 was used as alternative substrate of CH_2Cl_2, indicating that the halogen source in the dihalomethane did no impact much to the reaction result. Finally, when a different gem-dichloroalkane, the 1,1-dichloroethane was employed to reaction with **1a** and LiOH, the expect 2,3-dihydrobenzoxazinone was not formed.

To gain information on the possible reaction process, a control experiment without employing DCM has been conducted under standard conditions. As shown in Eq (1), the o-iodobenzamide **1f** was found to be smoothly transformed into the hydroxylated benzamide **4a**, indicating that the hydroxylation of the aryl-halogen bond is a key transformation in the product formation.



1f **4a** (1)

From the mechanistic point of view, the tandem reaction is proposed to proceed via the well documented copper-catalyzed Ar-X hydroxylation with the assistance of ligand, which provides *o*-hydroxyl benzamides **4**. With the promotion of a base, the double nucleophilic substitution involving NH and OH group enables the annulation to give products **3** (Scheme 1).



1 **4** **3**

Scheme 1 The general process of the copper-catalyzed tandem reaction

In conclusion, we have realized for the first time the copper-catalyzed tandem synthesis of 2,3-dihydrobenzoxazinones using *o*-halobenzamides, dichloromethane and LiOH as starting materials. The formation of three new chemical bonds, including a C(Ar)-O bond, a C(sp^3)-O bond and a C(sp^3)-N takes place during the whole reaction process. Besides providing a facile and new tactic for the synthesis of these important heterocyclic compounds, the significance of the presence work also lies in exemplifying the potential of the Ar-halogen hydroxylation in the designation of diverse tandem transformation-based organic synthesis.

Experimental Section

General procedure for the synthesis of products 3. In a 25 mL tube were located *o*-halobenzamide **1** (0.3 mmol), dichloromethane **2** (0.3 mL), LiOH (2.7 mmol), CuBr (0.015 mmol), ligand **L1** (0.03 mmol) and DMSO (2 mL). The vessel was then sealed with Teflon cap and heated up to 100 °C and stirred at the same temperature for 12 h. After completion (TLC), the vessel was cooled down to room temperature, and water (5 mL) was added. The resulting suspension was extracted with ethyl acetate (10 mL × 3). The organic layer was combined and dried with anhydrous Na_2SO_4. After filtration, the solvent in the acquired solution was removed under reduced pressure. The residue obtained therein was subjected to silica gel column chromatography to give pure product by using mixed ethyl acetate and petroleum ether as eluent (v / v = 1 : 5).

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Notes and references

1 (a) C. Sambiagio, S. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.,* 2014, **43**, 3525. (b) F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed.,* 2009, **48**, 6954. (c) K. Kunz, U. Scholz and D. Ganzer, *Synlett,* 2003, 2428.

2 For selected references, see (a) S. Xia, L. Gan, K. Wang, Z. Li and D. Ma, *J. Am. Chem. Soc.,* 2016, **138**, 13493. (b) B. K. Singh and R. Jana, *J. Org. Chem.,* 2016, **81**, 831. (c) G.-L. Song, Z. Zhang, Y.-X. Da and X.-C. Wang, *Tetrahedron,* 2015, **71**, 8823. (d) Y. Wang, C. Zhou and R. Wang, *Green Chem.,* 2015, **17**, 3910. (e) G. Ding, H. Han, T. Jiang, T. Wu and B. Han, *Chem. Commun.,* 2014, **50**, 9072. (f) D. Wang, D. Kuang, F. Zhang, S. Tang and W. Jiang, *Eur. J. Org. Chem.,* 2014, 315. (g) F. Ke, X. Chen, Z. Li, H. Xiang and X. Zhou, *RSC Adv.,* 2013, **3**, 22873. (h) K. Yang, Z. Li, Z. Wang, Z. Yao and S. Jiang, *Org. Lett.,* 2011, **13**, 4340. (i) K. G. Thakur and G. Sekar, *Chem. Commun.,* 2011, **47**, 6692. (j) A. Tlili, N. Xia, F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed.,* 2009, **48**, 8725.

3 For reviews and examples on tandem reactions initiated by copper-catalyzed coupling, see (a) Y. Liu and J.-P. Wan, *Org. Biomol. Chem.,* 2011, **9**, 6973. (b) Y. Liu and J.-P. Wan, *Chem. Asian J.,* 2012, *7*, 1488. (c) Q. Liao, X. Yang and C. Xi, *J. Org. Chem.,* 2014, **79**, 8507. (d) P. Sang, M. Yu, H. Tu, J. Zou and Y. Zhang, *Chem. Commun*., 2013, **49**, 701.

4 D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan and J. You, *Angew. Chem. Int. Ed.,* 2009, **48**, 8729.

5 (a) Y. Xiao, Y. Xu, H.-S. Cheon and J. Chae, *J. Org. Chem.,* 2013, **78**, 5804. (b) P. Rajesh, A. M. Ashif and P. Tharmalingam, *Synthesis,* 2010, 4268.

6 Y. Wang, C. Zhou and R. Wang, *Green Chem.,* 2015, **17**, 3910.

7 (a) G. R. Madhavan, R. Chakrabarti, K. A. Reddy, B. M. Rajesh, V. Balraju, P. B. Rao, R. Rajagopalan and J. Iqbal, *Bioorg. Med. Chem.,* 2006, **14**, 584. (b) J. Magdalou, S. Fournel-Gigleux, B. Testa, M. Ouzzine, In *The Practice of Medicinal Chemistry*, 2nd. ed.; Wermuth, C. G., Ed.; Academic Press: London, 2003; pp 517−543. (c) A. Arai, M. Kessler, J. Ambros-Ingerson, A. Quan, E. Yigiter, G. Rogers and G. Lynch, *Neuroscience,* 1996, **75**, 573. (d) H. Jourdi, Y.-T. Hsu, M. Zhou, Q. Qin, X. Bi and M. Baudry, *J. Neurosci.,* 2009, **29**, 8688. (e) A. Arai, M. Kessler, G. Rogers and G. Lynch, *Mol. Pharmacol.,* 2000, **58**, 802.

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DOI: 10.1039/C7OB00625J

8 (a) O. K. Farat, V. I. Markov, S. A. Varenichenko, V. V. Dotsenko and A. V. Mazepa, *Tetrahedron,* 2015, **71**, 5554. (b) F. Ujjainwalla, T. F. Walsh, *Tetrahedron Lett.,* 2001, **42**, 6441. (c) R. A. Coburn, M. T. Clark, R. T. Evans and R. J. Genco, *J. Med. Chem.,* 1987, **30**, 205. (d) K. Kondo, M. Seki, T. Kuroda, T. Yamanaka and T. Iwasaki, *J. Org. Chem.,* 1995, **60**, 1096.
9 (a) B. W. Horrom and H. E. Zaugg, *J. Am. Chem. Soc.,* 1950, **72**, 721. (b) S. Vellalath, I. Čorić and B. List, *Angew. Chem. Int. Ed.,* 2010, **49**, 9749. (c) R. B. Gammill, *J. Org. Chem.,* 1981, **46**, 3340. (d) Y. Fang, D. Leysen and H. C. J. Ottenheijm, *Synth. Commun.,* 1993, **23**, 2303. (e) K. Kamei, N. Maeda, K. Nomura, M. Shibata, R. Katsuragi-Ogino, M. Koyama, M. Nakajima, T. Inoue, T. Ohno and T. Tatsuoka, *Bioorg. Med. Chem.,* 2006, **14**, 1978. (f) M. Kidwai and K. Singhal, *Heterocycles,* 2007, **71**, 1615.
10 A. N. Cayley, K. A. Gallagher, C. Ménard-Moyon, J. P. Schmidt, L. J. Diorazio and R. J. K. Taylor, *Synthesis,* 2008, 3846.
11 W. P. Unsworth, C. Kitsiou and R. J. K. Taylor, *Org. Lett.,* 2013, **15**, 258.
12 M. Mulzer and G. W. Coates, *Org. Lett.,* 2011, **13**, 1426.
13 A. Modak, U. Dutta, R. Kancherla, S. Maity, M. Bhadra, S. M. Mobin and D. Maiti, *Org. Lett.,* 2014, **16**, 2602.
14 (a) Y. Liu, H. Wang and J.-P. Wan, *J. Org. Chem.,* 2014, **79**, 10599. (b) B. Huang, D. Hu, J. Wang, J.-P. Wan and Y. Liu, *Tetrahedron Lett.,* 2015, **56**, 2551.
15 (a) X. Chen, C. Hu, J.-P. Wan and Y. Liu, *Tetrahedron Lett.,* 2016, **57**, 5116. (b) Y. Liu, Y. Du and L. Wei, *Curr. Org. Chem.,* 2016, **20**, 1656.

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DOI: 10.1039/C7OB00625J

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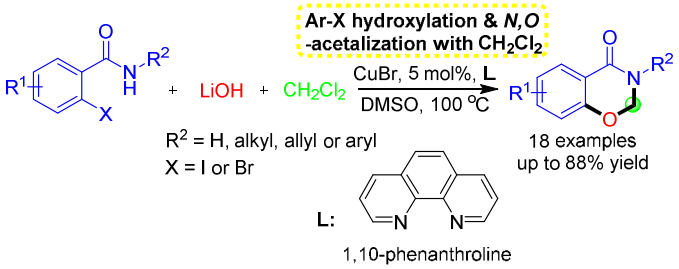

The copper-catalyzed tandem reactions consist of Ar-halogen hydroxylation and N,O-acetalization is designed for concise synthesis of 2,3-dihydrobenzoxazinones.