



Cite this: *RSC Adv.*, 2017, 7, 41723

Received 2nd July 2017  
 Accepted 21st August 2017

DOI: 10.1039/c7ra07306b

rsc.li/rsc-advances

# Cu-catalyzed intermolecular oxyalkylation of styrenes under air: access to diverse iminolactones†

Yunhe Lv,<sup>ID</sup>\* Weiya Pu, Shukuan Mao, Xiaoran Ren, Yingtao Wu and Hao Cui

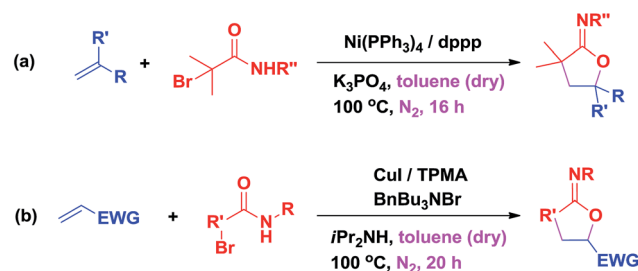
A practical, simple, and efficient copper-catalyzed highly regioselective oxyalkylation of styrenes and readily available  $\alpha$ -bromoacetamides under air is realized. This reaction exhibits a wide range of functional group tolerance in styrenes and  $\alpha$ -bromoacetamides to afford iminolactones.

Difunctionalization of alkenes is a powerful tool for the synthesis of heterocycles through tandem two same or different C–X (X = C, N, O, *etc.*) bond formations in organic synthesis. Although metal-free as well as transition-metal-catalyzed aminocarbonylation, aminoarylation, aminovinylolation, aminoalkynylation, and aminoxygenation reactions of alkenes have been significant developments in recent decades,<sup>1</sup> the selective oxyalkylation reactions of alkenes for their efficiency in synthesizing different types of oxygen-containing heterocycles remains challenging.<sup>2</sup> N-Substituted iminolactones, which can be easily converted to  $\gamma$ -lactones, are prevalently used as antibacterial agents, aldosterone inhibitors, and proper precursors for the preparation of a wide spectrum of natural compounds.<sup>3</sup> However, the selective oxyalkylation of alkenes for the synthesis of N-substituted iminolactones are still rare. In this context, Lei and coworkers developed Ni-catalyzed cyclization of  $\alpha$ -haloamides with alkenes through carbon-centered radical addition to the carbonyl oxygen of amides or esters (Scheme 1a).<sup>4</sup> Recently, Nishikata and coworkers reported copper-catalyzed oxyalkylation of alkenes to afford iminolactone by controlling the reactivity of the oxygen nucleophile of the amide group (Scheme 1b).<sup>5</sup> However, these methods require long reaction time, anhydrous solvent, inert atmosphere protection and sometimes even special apparatuses such as the glovebox to manipulate the reactions. Therefore, a practical and simple methodology towards effective intermolecular oxyalkylation of alkenes is highly desirable. Recently, we developed selectfluor-mediated highly selective radical dioxygenation of alkenes and metal-free catalyzed C–O bond formation reactions directly from C–H bonds.<sup>6</sup> As part of our ongoing study on difunctionalization of alkenes<sup>6a,d</sup> and C–O bond formation reactions, we present herein our recent progress in copper-catalyzed

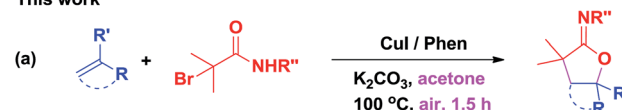
highly regioselective oxyalkylation of styrenes and readily available  $\alpha$ -bromoacetamides under air.

We started our investigation by applying styrene **1a** and 2-bromo-2-methyl-N-phenylpropanamide **2a** in a model reaction to optimize the reaction conditions. To our delight, in the preliminary experiment of using 10 mol% of CuI as catalyst, the desired oxyalkylation proceeded to give the desired product **3a** in 45% yield in the presence of 1,10-phenanthroline (Phen) and K<sub>2</sub>CO<sub>3</sub> at 100 °C in CH<sub>3</sub>CN (Table 1, entry 1). Product **3a** was obtained in 83% yield when acetone was employed as the solvent (Table 1, entry 2). In contrast, other solvents such as CH<sub>2</sub>Cl<sub>2</sub>, DMF, and EtOAc did not perform well (Table 1, entries 3–5). Further investigation on different copper salts revealed that CuBr, CuCl and Cu(OTf)<sub>2</sub> were also efficient catalyst for this transformation, affording product **3a** in a satisfying 80%, 79% and 81% yield, respectively (Table 1, entries 6–8). Other ligand such as PPh<sub>3</sub> and 2,2'-bipyridine (bipy) were less effective than Phen (Table 1, entries 9 and 10). Other bases such as NaOAc and Et<sub>3</sub>N gave the desired product in lower yield (Table 1, entries 11 and 12). Control experiments demonstrated that CuI, Phen and K<sub>2</sub>CO<sub>3</sub> were all important (entries 13–15). In addition, trace

### Previous works



### This work



Scheme 1 Oxyalkylation of alkenes with  $\alpha$ -bromoacetamides.

College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang, 455000, P. R. China. E-mail: luyh086@nenu.edu.cn; lvyunhe0217@163.com

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra07306b



Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Metal	Ligand	Additive	Solvent	Yield <sup>b</sup> (%)
1	CuI	Phen	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	45
2	<b>CuI</b>	<b>Phen</b>	<b>K<sub>2</sub>CO<sub>3</sub></b>	<b>Acetone</b>	<b>83</b>
3	CuI	Phen	K <sub>2</sub> CO <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	Trace
4	CuI	Ph <sub>3</sub> P	K <sub>2</sub> CO <sub>3</sub>	DMF	18
5	CuI	Phen	K <sub>2</sub> CO <sub>3</sub>	EtOAc	Trace
6	CuBr	Phen	K <sub>2</sub> CO <sub>3</sub>	Acetone	80
7	CuCl	Phen	K <sub>2</sub> CO <sub>3</sub>	Acetone	79
8	Cu(OTf) <sub>2</sub>	Phen	K <sub>2</sub> CO <sub>3</sub>	Acetone	81
9	CuI	PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	Acetone	37
10	CuI	bipy	K <sub>2</sub> CO <sub>3</sub>	Acetone	41
11	CuI	Phen	NaOAc	Acetone	45
12	CuI	Phen	Et <sub>3</sub> N	Acetone	40
13	None	Phen	K <sub>2</sub> CO <sub>3</sub>	Acetone	Trace
14	CuI	None	K <sub>2</sub> CO <sub>3</sub>	Acetone	Trace
15	CuI	Phen	None	Acetone	0
16 <sup>c</sup>	CuI	Phen	K <sub>2</sub> CO <sub>3</sub>	Acetone	Trace

<sup>a</sup> Reactions were carried out with **1a** (0.45 mmol), **2a** (0.3 mmol), metal (10 mol%), ligand (10 mol%) and additive (2.0 equiv.) in 3 mL solvent under air atmosphere at 100 °C for 1.5 h, unless noted otherwise. <sup>b</sup> Yield of the isolated product. <sup>c</sup> The reaction was performed at 70 °C. Phen = 1,10-phenanthroline, Tf = trifluoromethanesulfonyl, bipy = 2,2'-bipyridine.

amounts of **3a** was obtained when the reaction was performed at 70 °C (Table 1, entry 16).

The scope of the oxyalkylation of styrenes was then investigated under the optimized reaction conditions (Table 1, entry 5). As described in Table 2, a broad range of styrene derivatives were investigated. Generally, styrene substrates bearing electron-donating substituents provided higher yields than those containing electron-withdrawing substituents on the aromatic ring (**3b–3h**). Halo-substituted styrene derivatives (**1b–1d**, **1i–1m**) were tolerated in the oxyalkylation reaction of styrenes, allowing for further functionalization through a cross-coupling manifold. Starting from disubstituted styrene 1,4-dimethyl-2-vinylbenzene, **3n** was obtained in 71% yield. In addition, the cyclic alkene substrates such as indene also provided the desired oxyalkylation product **3o** in 70% yield. Notably, 1,1-disubstituted styrenes such as **1p–1r** were also effective to provide **3q–3s** in 80–86% yields. In addition, starting from methyl acrylate (**1s**), the corresponding product **3s** could be obtained in 78% yields. Remarkably, in all cases, the reactions proceeded smoothly under air, and the desired imino-lactones (**3a–3r**) were consistently obtained in 60–93% yields with high regioselectivity.

This oxyalkylation of styrenes was further expanded to a range of  $\alpha$ -bromoacetamides, and the results are shown in Table 3. The results indicate that reactions of  $\alpha$ -bromoacetamides with different substituents on the aromatic ring, such as F, Cl, Br, nitril, methyl, ethyl, *tert*-butyl, and

Table 2 Reactions of alkenes **1** with **2a**<sup>a,b</sup>

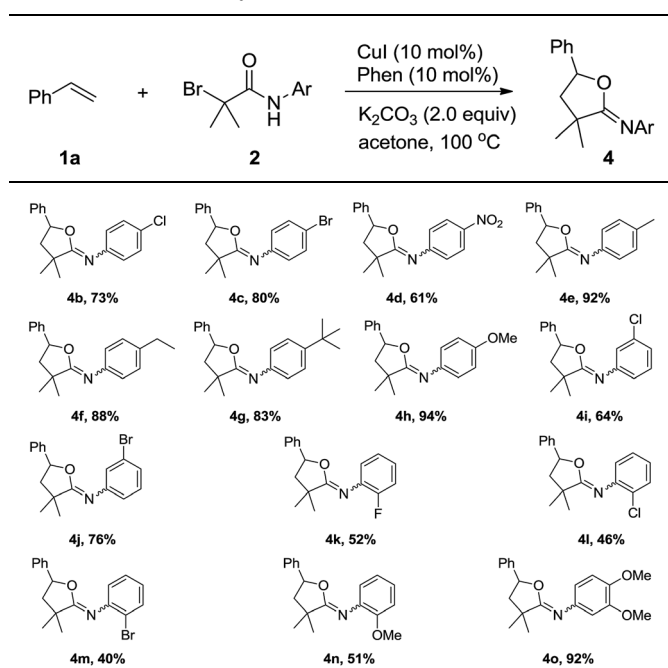
Product	Yield (%)
<b>3b</b>	74%
<b>3c</b>	82%
<b>3d</b>	78%
<b>3e</b>	92%
<b>3f</b>	82%
<b>3g</b>	93%
<b>3h</b>	60%
<b>3i</b>	76%
<b>3j</b>	78%
<b>3k</b>	75%
<b>3l</b>	90%
<b>3m</b>	85%
<b>3n</b>	71%
<b>3o</b>	70%
<b>3p</b>	86%
<b>3q</b>	84%
<b>3r</b>	80%
<b>3s</b>	78%

<sup>a</sup> Reactions were carried out with **1** (0.45 mmol), **2a** (0.3 mmol), CuI (10 mol%), Phen (10 mol%) and K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) in acetone (3 mL) under air atmosphere at 100 °C for 1.5 h. <sup>b</sup> Yield of the isolated product.

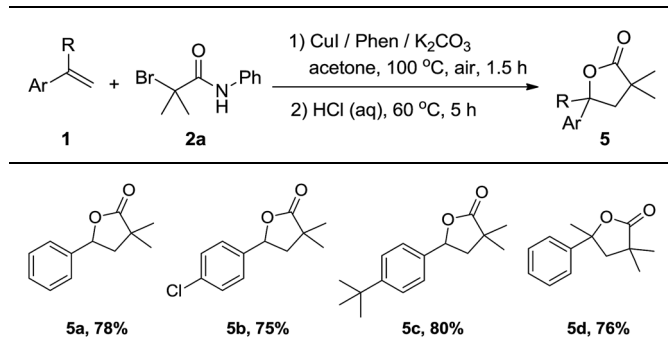
methoxy, proceeded well with moderate to good yields. This reaction trend is also consistent with the electronic effect of styrenes. In addition, the steric hindrance on the aryl ring also influence the reaction. Slightly decreased yields were achieved for *ortho*-substituted  $\alpha$ -bromoacetamides (**2k–2n**).

Furthermore, a sequential one-pot two-step tandem reaction for efficient synthesis of  $\gamma$ -lactones was investigated (Table 4). For example, the  $\gamma$ -lactone **5a** was obtained in 78% yield when the reaction system of **1a** with **2a** was quenched *in situ* by HCl (2 M aqueous solution). Starting from **1c** and **1f**, the corresponding compounds **5b** and **5c** could be obtained in 75% and 80% yields, respectively. In addition, 1,1-disubstituted styrenes such as prop-1-en-2-ylbenzene **1p** was also effective to provide **5d** in 76% yield. The present method was applied to citronellol derivatives 3,7-dimethyloct-6-en-1-yl acrylate **6**, and the corresponding product **7** was obtained in 56% yield [eqn (1)].

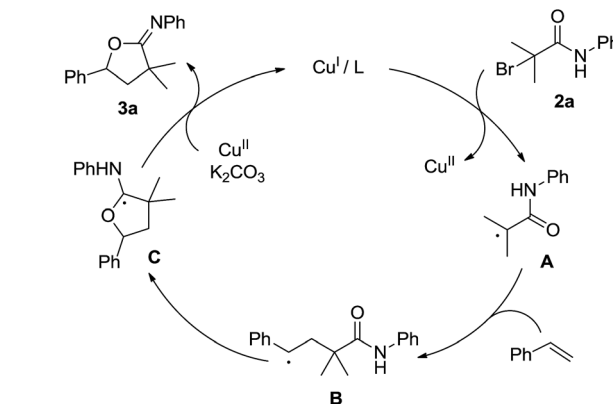
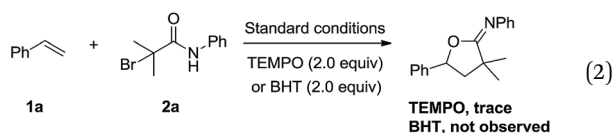
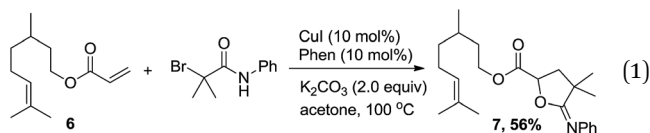


Table 3 Reactions of styrene **1a** with  $\alpha$ -bromoacetamides **2**<sup>a,b</sup>

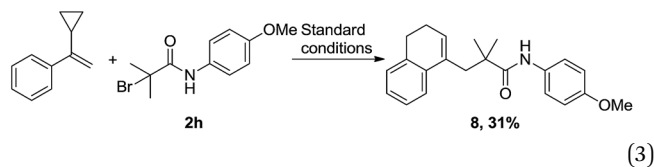
<sup>a</sup> Reactions were carried out with **1a** (0.45 mmol), **2** (0.3 mmol),  $\text{CuI}$  (10 mol%),  $\text{Phen}$  (10 mol%) and  $\text{K}_2\text{CO}_3$  (2.0 equiv.) in acetone (3 mL) under air atmosphere at  $100^\circ\text{C}$  for 1.5 h. <sup>b</sup> Yield of the isolated product.

Table 4 Direct synthesis of  $\gamma$ -lactones from styrenes **1** and **2a**<sup>a,b</sup>

<sup>a</sup> Reactions conditions: (1) **1** (0.45 mmol), **2a** (0.3 mmol),  $\text{CuI}$  (10 mol%),  $\text{Phen}$  (10 mol%),  $\text{K}_2\text{CO}_3$  (2.0 equiv.) and acetone (3 mL), air,  $100^\circ\text{C}$ , 1.5 h; (2)  $\text{HCl}$  (2 M), air,  $60^\circ\text{C}$ , 5 h. <sup>b</sup> Yield of the isolated product.



Scheme 2 Proposed mechanism.



Some mechanistic experiments have been investigated to probe the mechanism of this transformation. When the radical scavenger such as 2,2,6,6-tetramethylpiperidine *N*-oxide ( $\text{TEMPO}$ , 2.0 equiv.) and 2,6-di-*tert*-butyl-4-methylphenol ( $\text{BHT}$ , 2.0 equiv.) were added to the oxyalkylation reaction of **1a** under the optimal conditions, no desired products were isolated [eqn (2)]. These results indicate that a radical pathway may be involved under the catalytic system. Further evidence for a radical mechanism was demonstrated by the radical clock experiment with (1-cyclopropylvinyl)benzene as the substrate. The reaction of (1-cyclopropylvinyl)benzene with **2h** under the standard reaction conditions produced the ring-expanded products **8** in 31% yield [eqn (3)].<sup>7</sup>

On the basis of the present experimental results, a possible mechanism was proposed in Scheme 2. The  $\text{CuI}$  catalyst reacts with **2a** to generate a tertiary-alkyl radical species **A**<sup>8</sup> and a  $\text{Cu}^{\text{II}}$  species.<sup>9</sup> Then, addition of **A** to styrene takes place to give benzyl radical **B**.<sup>9a,b,10</sup> The intramolecular addition of benzyl radical to a carbonyl group of amide produces **C**,<sup>11</sup> which then undergoes radical oxidation and deprotonation to give the oxyalkylation product **3a** and regenerate  $\text{Cu}^{\text{I}}$  in the presence of  $\text{Cu}^{\text{II}}$  and  $\text{K}_2\text{CO}_3$ . According to the hard and soft acid and base theory (HSAB), highly selective C–O bond formation may be due to an easier amide oxygen attack under weakly basic conditions in soft acid solvents acetone.<sup>12</sup>

## Conclusions

In conclusion, a novel copper-catalyzed intermolecular oxyalkylation of styrenes and readily available  $\alpha$ -bromoacetamides has been reported. This work provided an efficient route to synthesize iminolactones, which can be conveniently converted into  $\gamma$ -lactones. Moreover, this reaction features high regioselectivity, excellent functional-group tolerance, no extra oxidant,



no inert atmosphere protection and can greatly simplify the operation and workup procedures, which may be a good alternative for the existing methods. Further mechanistic investigations are underway in our lab.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We gratefully acknowledge the Science & Technology Foundation of Henan Province, the Henan province key laboratory of new opto-electronic functional materials and AYNUN-KP-A04 for financial support.

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