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Efficient Cu-catalyzed intramolecular *O*-arylation for synthesis of benzoxazoles in water†

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An efficient method was developed for synthesis of benzoxazoles by Cu-catalyzed intramolecular *O*-arylation of *o*-halobenzanilides in water. This strategy provides several advantages, such as high yields, water as a green solvent and functional groups tolerance.

Benzoxazole derivatives not only exist in several important natural products, but are also present in many important classes of organic compounds due to their biological, pharmaceutical and catalytic properties, which have attracted more and more attention from pharmaceutical and synthetic chemists (Fig. 1).[1,2] Commonly, the preparation of benzoxazoles has attracted considerable attention. Traditional methods to construction of 2-aryl benzoxazoles involve the condensation of 2-aminophenol with carboxylic acids or aldehydes under oxidative conditions, which unfortunately often suffer from the use of harsh reaction conditions involving strong acids or highly toxic reagents in combination with high temperatures.[3]

In the last decades, some of these drawbacks have been overcome by the development of transition-metal-catalyzed processes for C–O bond formations under comparatively milder reaction conditions.[4] Until now, there are various reactions reported for the construction of benzoxazoles by intramolecular *O*-arylation of orthohaloanilides under milder reaction conditions.[5] Evindar *et al.* have improved the formation of benzoxazoles *via* a CuI/1,10-phenanthroline-catalyzed cyclization of *o*-haloanilides in the presence of Cs_2CO_3 in DMF.[6a] Saha *et al.* have reported cobalt(II)/1,10-phenanthroline-catalyzed the intramolecular C–O cross-couplings of *o*-halobenzanilides to give benzoxazoles in DMSO.[6b] Dai *et al.* have prepared 2-substituted benzoxazoles *via* Cu-catalysed intramolecular coupling cyclization reactions using methyl 2-methoxybenzoate (MMB) as the ligand in DMF.[7a] Bonnamour *et al.* have obtained benzoxazole derivatives by iron-catalyzed intramolecular *O*-arylation reaction and 2,2,6,6-tetramethyl-3,5 heptanedione (TMHD) as the cocatalyst in DMF.[7b] Tapia *et al.* described an efficient synthesis of 2-aryl-benzoxazoles using (IPr)CuCl *via* intramolecular coupling cyclization of 2-haloanilides in DMF.[8] Although many improvements have been achieved for the synthesis of 2-substituted benzoxazoles from *o*-halobenzanilides through intramolecular *O*-arylation by transition-metal-catalyzed processes, many approaches reported so far were harsh conditions, such as long reaction time, costly and toxic solvents.[3,9]

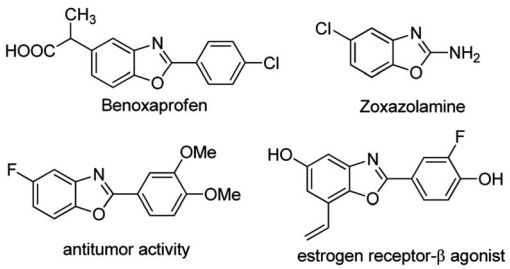
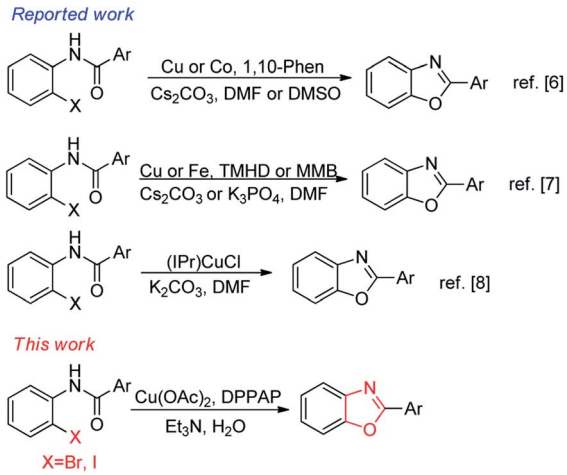


Fig. 1 Examples of biologically and pharmaceutically benzoxazoles.



Scheme 1 Intramolecular *O*-arylation for the synthesis of benzoxazoles.

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† Electronic supplementary information (ESI) available: Experimental details and spectra data. See DOI: 10.1039/d0ra00570c

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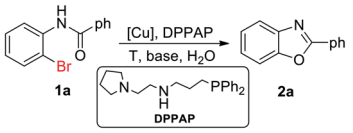
Therefore, there is still worthwhile to develop an economic, efficient and eco-friendly catalytic system (Scheme 1).

To the best of our knowledge, no report on the synthesis of benzoxazoles from *o*-halobenzanilides in water has been reported so far. In initiatory work, we have found that 1-[2-(*N*-(3-diphenylphosphinopropyl))aminoethyl]pyrrolidine (DPPAP) could promoted transition metal-catalyzed reactions as NNP-type pincer ligand, which accelerated Cu-catalyzed intramolecular *O*-arylation of *o*-halobenzanilides to form benzoxazoles in water. In present work, we optimum reaction conditions based on initiatory study, and report a new, efficient and green Cu-catalyzed synthesis of benzimidazoles in water.

Reaction between *N*-(2-bromophenyl)benzamide (**1a**) was selected as a model substrate and various copper sources were tested including CuI, $CuSO_4$, $Cu(OAc)_2$ and $Cu(OTf)_2$ to check and identify optimization of reaction conditions. As shown in Table 1, the reaction results were distinguishable catalyzed by various copper sources. In general, CuI could lead to product in low yield, and $CuSO_4$ was not active to this action and no product was obtained (Table 1, entries 1–6). To our surprise, $Cu(OTf)_2$ and $Cu(OAc)_2$ enhanced the reaction yields obviously (Table 1, entries 7–15). In order to study the effects of different types of bases on the reaction, 4 bases were employed including inorganic and organic base such as K_3PO_4, K_2CO_3, TMEDA and Et_3N. We could see that compound **2a** was formed in the presence of TMEDA and Et_3N in better yields than that of K_3PO_4 and K_2CO_3, and there was nearly no difference.

Furthermore, we examined the effects of temperature and time on the reaction. With the increasing of temperature from

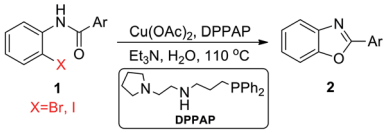
Table 1 Optimization of reaction conditions for the synthesis of **2a**[a,b]



Entry	[Cu]	Base	T (°C)	Time (h)	Yield (%)
1	CuI	K_2CO_3	100	12	22
2	CuI	K_3PO_4	100	12	20
3	CuI	TMEDA	100	12	38
4	CuI	Et_3N	100	12	36
5	$CuSO_4$	TMEDA	100	12	Trace
6	$CuSO_4$	Et_3N	100	12	Trace
7	$Cu(OTf)_2$	TMEDA	100	12	64
8	$Cu(OTf)_2$	Et_3N	100	12	62
9	$Cu(OAc)_2$	TMEDA	100	12	84
10	$Cu(OAc)_2$	Et_3N	100	12	83
11	$Cu(OAc)_2$	Et_3N	90	12	70
12	$Cu(OAc)_2$	Et_3N	110	12	89
13	$Cu(OAc)_2$	Et_3N	110	6	62
14	$Cu(OAc)_2$	Et_3N	110	24	81
15	$Cu(OAc)_2$	Et_3N	120	12	72

[a] All reactions were performed using **1a** (1 mmol), [Cu] (5 mol%), DPPAP (10 mol%), base (2 mmol) in water (3 mL). [b] Isolated yield after chromatographic purification.

Table 2 Cu-catalyzed synthesis of benzoxazoles from 2-iodo/bromophenylbenzanilides using DPPAP as the ligand[a,b]



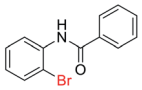
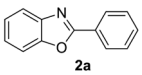
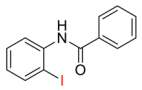
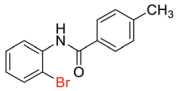
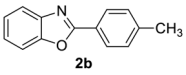
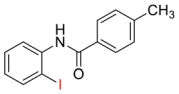
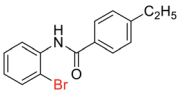
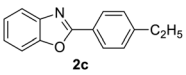
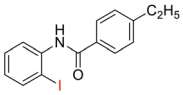
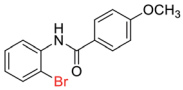
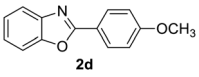
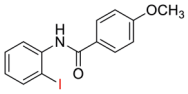
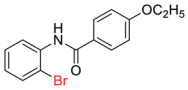
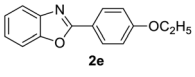
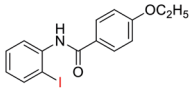
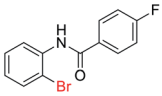
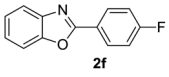
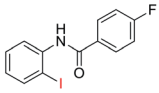
Entry	1	2	Yield[c] (%) present	Yield[c] (%) reported
1		 **2a**	89	78 (ref. 7*a*)
2			92	87 (ref. 7*a*)
3		 **2b**	90	79 (ref. 8)
4			92	87 (ref. 8)
5		 **2c**	81	—
6			87	—
7		 **2d**	88	75 (ref. 8)
8			93	82 (ref. 8)
9		 **2e**	82	—
10			85	—
11		 **2f**	74	80 (ref. 7*a*)
12			81	91 (ref. 7*a*)

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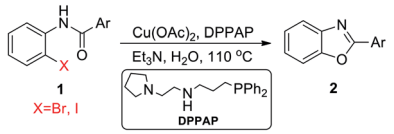
Table 2 (*Contd.*)



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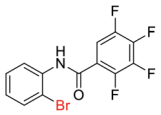
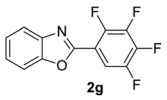
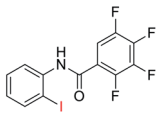
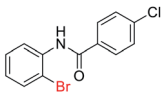
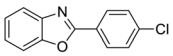
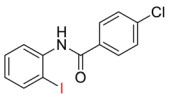
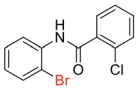
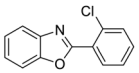
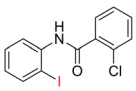
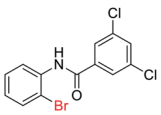
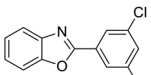
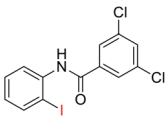
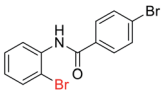
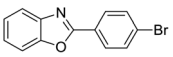
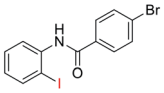
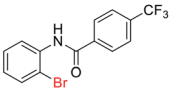
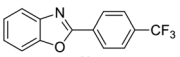
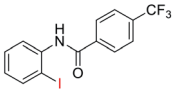
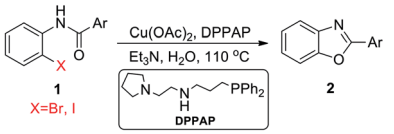
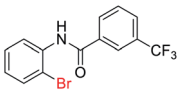
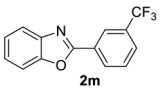
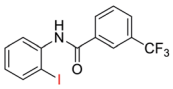
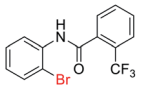
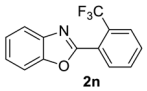
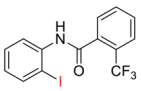
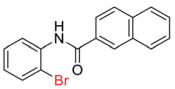
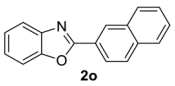
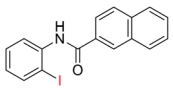
13		 2g	70	—
14			77	—
15		 2h	79	77 (ref. 8)
16			85	86 (ref. 8)
17		 2i	74	—
18			83	—
19		 2j	86	—
20			89	—
21		 2k	83	92 (ref. 6*a*)
22			90	—
23		 2l	76	—
24			88	—

Table 2 (*Contd.*)



Entry	1	2	Yield[c] (%) present	Yield[c] (%) reported
25		 2m	76	—
26			85	—
27		 2n	73	—
28			78	—
29		 2o	89	—
30			92	—

[a] All reactions were carried out using *o*-halobenzanilides (1 mmol), $Cu(OAc)_2$ (0.05 mmol), DPPAP (0.1 mmol), Et_3N (2 mmol) in water (3 mL) for 12 h at 110 °C. [b] Isolated yield. [c] '—' presented no report yield from *o*-halobenzanilides.

90 °C to 110 °C, the yield had increased to 89% (Table 1, entry 12). However, further increasing temperature led to decline of yield(Table 1, entry 15). In addition, reaction time from 6 h to 12 h was favorable to reaction obviously. However, further increase of reaction time to 24 h had negative effect on the yield of benzoxazole (Table 1, entry 14). Therefore, it was clear that the best reaction was performed taking $Cu(OAc)_2$ (5 mol%) and DPPAP (10 mol%) as the catalyst in water in present of Et_3N (2 eq.) for 12 h at 110 °C.

With the optimal reaction conditions in hand, a series of *o*-halobenzanilides were investigated to study the scope of Cu-catalyzed intramolecular *O*-arylation. As shown in Table 2, to our delight, the *O*-arylation of various substituted 2-bromobenzanilides or 2-iodobenzanilides under standard reaction condition gave the corresponding title products in good to high yields, and 2-iodobenzanilides were more active than 2-bromobenzanilides (Table 2). In order to study the influence of substituted groups, various substituted *o*-halobenzanilides were performed including electron donating groups (CH_3, C_2H_5, CH_3O, F, Cl, Br) and withdrawing group (CF_3). From the results,

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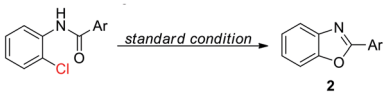
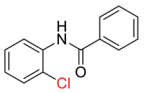
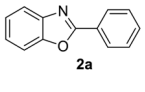
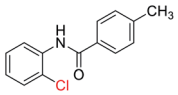
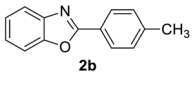
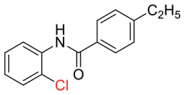
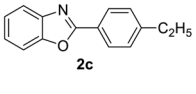
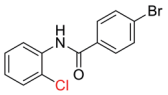
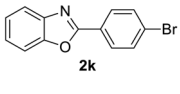
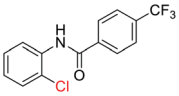
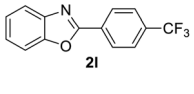
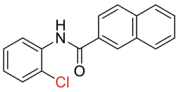
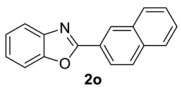
Table 3 Cu-catalyzed synthesis of benzoxazoles from *N*-(2-chloro phenyl)benzanilides using standard condition[a,b]



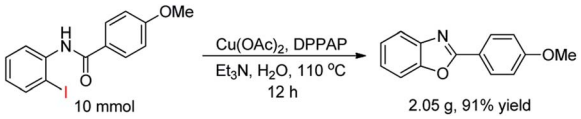
Entry	1	2	Yield (%)
1		 **2a**	22
2		 **2b**	28
3		 **2c**	13
4		 **2k**	25
5		 **2l**	Trace
6		 **2o**	15

[a] All reactions were carried out using *o*-chlorobenzanilides (1 mmol), $Cu(OAc)_2$ (0.05 mmol), DPPAP (0.1 mmol), Et_3N (2 mmol) in water (3 mL) for 12 h at 110 °C. [b] Isolated yield.

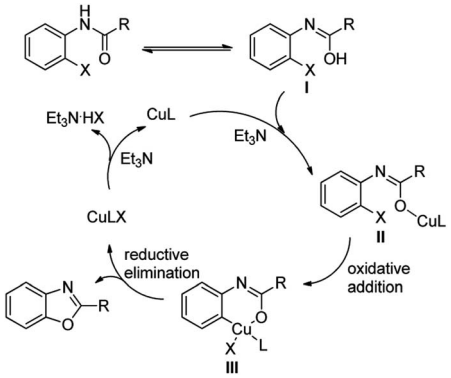
we could find that this reaction condition was beneficial to prepare 2-substituted benzoxazoles, and substitutions on amide were tolerated. In general, electron donating groups afforded the corresponding benzoxazoles in higher yields than that of CF_3. Especially, *N*-(2-iodophenyl)-4-methoxybenzamide formed **2d** in the best yield (93%), and *N*-(2-bromophenyl)-2,3,4,5-tetrafluorobenzamide formed **2g** in the lowest yield (70%).

In addition, the intramolecular *O*-arylation of various *ortho*, *meta* and *para* substituted *o*-halobenzanilides were carried out using the $Cu(OAc)_2$/DPPAP catalyst system. As shown in Table 2, all desired products were obtained in good yields, and position of both electron donating and withdrawing groups did not have obvious influence on applicability. It was gratified that *N*-(2-bromophenyl)-2,3,4,5-tetrafluorobenzamide, *N*-(2-iodophenyl)-2,3,4,5-tetrafluoro benzamide, *N*-(2-bromophenyl)-3,5-dichlorobenzamide and *N*-(2-iodophenyl)-3,5-dichlorobenzamide could afford the corresponding products **2g** and **2j** in good yields (70%, 77%, 86% and 89%, respectively) under optimal reaction conditions.

From above results, our improved protocol for synthesis of benzoxazoles by intramolecular *O*-arylation of *o*-halobenzanilides (Br, I) in water is significantly applicative under Cu/DPPAP catalyst system. Delighted with this results, we were



Scheme 2 Gram-scale synthesis of benzoxazole **2d**.



Scheme 3 Possible mechanism of intramolecular *O*-arylation.

eager to study *O*-arylation of 2-chlorobenzanilides. Therefore, six 2-chlorobenzanilides bearing different substituted groups were selected as the model reaction under standard conditions. As shown in Table 3, 2-chlorobenzanilides displayed poor reactivity under this conditions, and benzoxazoles were obtained in low yields (<30%), respectively.

In addition, we performed the reaction on a gram-scale by taking 10 mmol of *N*-(2-iodophenyl)-4-methoxybenzamide in 30 mL water at 110 °C for 12 h (Scheme 2). The reaction proceeded smoothly to form desired product **2d** (2.05 g, 91% yield).

Although the mechanism of the present reaction was not yet clear, based on experimental results mentioned and copper-catalyzed C–O bond formations in the literature,[6a,10] the most probable mechanism was proposed and depicted for the Cu-catalytic intramolecular *O*-arylation of *o*-halobenzanilides as shown in Scheme 3. Firstly, *o*-halobenzanilide converted to enol **I**, followed by coordination of the CuL catalyst and Et_3N to give **II**. Subsequently, intermediate **III** was formed by oxidative insertion. After that, **III** underwent reductive elimination to give benzoxazole as well as CuLX. Finally, CuLX was transformed into CuL catalyst for reuse in presence of Et_3N.

Conclusions

In conclusion, we have developed an efficient method for synthesis of benzoxazoles by Cu-catalyzed intramolecular *O*-arylation of *o*-halobenzanilides in water. This protocol is applicable to a wide variety of *o*-halobenzanilides bearing electron donating as well as electron withdrawing groups, which features high yields, water as green solvent and functional groups tolerable. The simple and green catalytic system provides a valuable synthetic approach for industrial applications.

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Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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