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Cu-mediated selective O-arylation on C-6 substituted pyridin-2-ones

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ABSTRACT

A practical and mild strategy has been developed for the selective O-arylation on C-6 substituted pyridin-2-ones with a series of arylboronic acids, using $Cu(OTf)_2$ as the catalyst, DABCO as the ligand, Et_3N as the base, and K_2HPO_4 as the additive. This method affords O-arylated pyridin-2-ones with good selectivity and yields

Transition metal-mediated carbon–carbon and carbon–heteroatom coupling reactions are important tools in organic synthesis and have been widely used in the synthesis of natural products and pharmaceutical agents. Compared to palladium and other transition metals, copper salts are less toxic, less expensive, earth-abundant, and stable in air. Thus, copper-catalyzed cross-coupling has attracted many chemists' interest. The traditional Ullmann and Goldberg procedures played an important role in the synthesis of biaryl ethers. However, vigorous reaction conditions, such as high temperature, stoichiometric amounts of catalysts, and specific halide substrates, limited the use of this methodology. In 1998, Chan,[1] Evans,[2] and Lam[3] developed a new copper-catalyzed N/O-arylation methodology, using aryl boronic acids as the substrates. This method has been soon proven to be a powerful and attractive synthetic tool to construct carbon–heteroatom bond and widely used in the synthesis of many biologically active compounds.[4,5]

To date, many compounds with the 2-aryloxypyridine moiety have been reported to show various biological activities, such as herbicidal activity,[6] antispasmodic activity,[7] anti-bacterial activity,[8] M5 positive allosteric modulators activity,[9] anti-mycobacterial activity,[10] obesity-induced insulin resistance inhibitive activity, and anticancer activity.[11] Since 2-aryloxypyridine derivatives widely occur in biologically active molecules and chemical products, it is highly desired to develop a practical and efficient approach to diverse 2-aryloxypyridine derivatives.

Although several accounts of N-arylation of pyridin-2-ones with aryl halides[12,13] or arylboronic acids[14] have been reported, few literatures exist on the selective O-arylation of pyridin-2-ones.[15] Herein, we present a selective O-arylation method on C-6 substituted pyridin-2-ones, using Chan–Evans–Lam cross-coupling reaction.

To screen suitable reaction conditions, we focused on the coupling of 6-methyl pyridin-2-ones (**1**) and phenylboronic acid (**2**). As shown in Table 1, among the six copper catalysts screened, $Cu(OTf)_2$ gave a 30% yield of O-arylated compound **3**. Although the N/O selectivity was not satisfactory (41% yield of N-arylated compound **4** obtained), $Cu(OTf)_2$ was still the most effective catalyst. $Cu(NO_3)_2{\cdot}3H_2O$ (entry 4) could also produce the desired product **3**, nevertheless the yield was slightly lower than that of $Cu(OTf)_2$. Thus, $Cu(OTf)_2$ was determined as the appropriate catalyst and was used in the subsequent screening.

Secondly, different solvents were surveyed as shown in entries 7–11. It was found that both the yield and the selectivity of O-arylation were dramatically improved by using DMSO as the solvent (entry 8).

Subsequently, different ligands were investigated (entries 12–16). The most surprising results were obtained when DABCO was used as the ligand, which produces only O-arylated compound **3** without N-arylated product in 28% yield.

Recently, some literatures clarified[16,17] the significance of base and K_2HPO_4 in Cu(II)-mediated couplings. Bases, such as Et_3N could capture hydrogen proton and thus promote the formation of the

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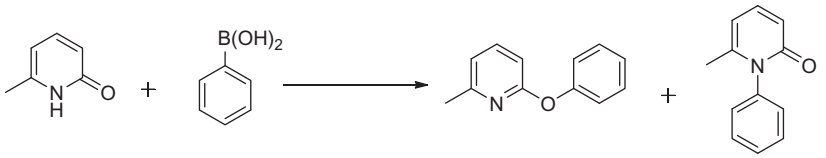
Table 1
Survey of copper salts with TMEDA[a]

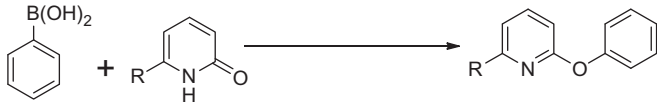


1 2 3 4

Entry	Copper source	Solvent	Ligand	Additive	**3**/Yield[b] (%)	**4**/Yield[b] (%)
1	$Cu(OTf)_2$	CH_2Cl_2	TMEDA	—	30	41
2[c]	$Cu(OAc)_2$	CH_2Cl_2	TMEDA	—	/	/
3[d]	$CuSO_4$	CH_2Cl_2	TMEDA	—	/	/
4	$Cu(NO_3)_2{\cdot}3H_2O$	CH_2Cl_2	TMEDA	—	20	10
5[c]	$CuCl_2$	CH_2Cl_2	TMEDA	—	/	/
6[c]	CuI	CH_2Cl_2	TMEDA	—	/	/
7[c]	$Cu(OTf)_2$	CH_3CN	TMEDA	—	/	/
8	$Cu(OTf)_2$	DMSO	TMEDA	—	45	9
9[c]	$Cu(OTf)_2$	DMF	TMEDA	—	10	/
10[c]	$Cu(OTf)_2$	CH_3OH	TMEDA	—	/	/
11[c]	$Cu(OTf)_2$	H_2O	TMEDA	—	/	/
12[c]	$Cu(OTf)_2$	DMSO	1,2-Ethanediamine	—	/	/
13[c]	$Cu(OTf)_2$	DMSO	*N*,*N*′-Dimethyl-1,2-ethanediamine	—	/	/
14[c]	$Cu(OTf)_2$	DMSO	Cyclohexane-1,2-diamine	—	/	/
15[c]	$Cu(OTf)_2$	DMSO	DABCO	—	28	/
16[c]	$Cu(OTf)_2$	DMSO	1,10-Phenanthroline	—	/	/
17[c]	$Cu(OTf)_2$	DMSO	DABCO	Et_3N/K_2HPO_4	44	/
18[c,d]	$Cu(OTf)_2$	DMSO	DABCO	Et_3N/K_2HPO_4	85	/

[a] Unless otherwise indicated, the reaction conditions were as following: compound **1** (1 equiv), compound **2** (2 equiv), copper source (20 mol %), ligand (20 mol %), additive (2 equiv), 2 mL solvent, rt, air, 5 h.
[b] Isolated yields.
[c] Compound **3** or **4** is trace.
[d] Under 50 °C.

Table 2
Expansion of the C-6 substituted pyridin-2(1*H*)-one



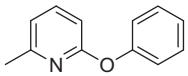
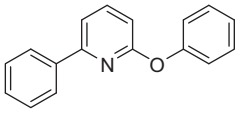
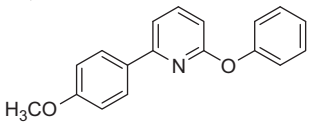
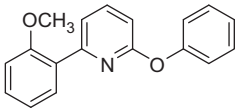
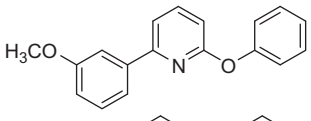
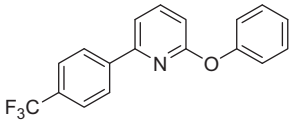
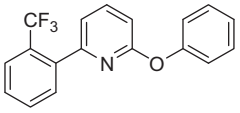
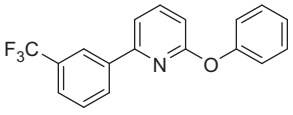
Entry	Product	Yield[a] (%)
1		65
2		74
3		40
4		50
5		61
6		58

Table 2 (*continued*)

Entry	Product	Yield[a] (%)
7		50
8		81

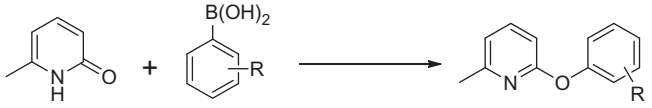
General reaction conditions: 0.2 mmol of 2-hydroxypyridines, 0.4 mmol of phenylboronic acid, 0.04 mmol of $Cu(OTf)_2$ 0.04 mmol of triethylenediamine, 0.4 mmol Et_3N, 0.4 mmol of K_2HPO_4, 2 mL DMSO, 50 °C for 5 h in air.
[a] Isolated yields.

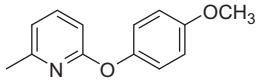
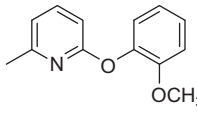
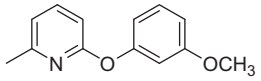
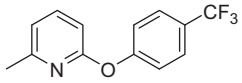
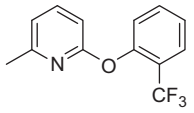
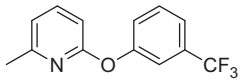
$Cu(II)$ complex, while K_2HPO_4 could avoid the decomposition of phenylboronic acid (**2**) to some extent. Thus, addition of Et_3N and K_2HPO_4 into the reaction was attempted (entry 17), which gave a slightly improved yield (44%). When the temperature was elevated to 50 °C, the yield was improved up to 65% (entry 18). Unfortunately, the yield could not be further improved because of the inevitability of the decomposition of phenylboronic acid.

Finally, the optimal conditions for the selective O-arylation[18] were determined as following: 20 mol % of $Cu(OTf)_2$ as the catalyst, 20 mol % of DABCO as the ligand, Et_3N as the base and K_2HPO_4 as the additives and at 50 °C for no more than 5 h.

With the method[18] in hand, a series of C-6 substituted pyridin-2-ones was subjected to the coupling reaction with phenylboronic acid (**2**), as illustrated in Table 2, O-arylated compounds were obtained in moderate to good yields (40–81%). It was obvious that the C-6 substituent could influence the yield of this reaction. The

Table 3
Expansion of the substituted phenylboronic acid



Entry	Product	Yield[a] (%)
1		46
2		Trace
3		56
4		23
5		Trace
6		31

General reaction conditions: 0.2 mmol of 2-hydroxypyridines, 0.4 mmol of phenylboronic acid, 20 mol % of $Cu(OTf)_2$, 20 mol % of triethylenediamine, 2 equiv Et_3N, 2 equiv of K_2HPO_4, 2 mL DMSO, 50 °C for 5 h in air.
[a] Isolated yields.

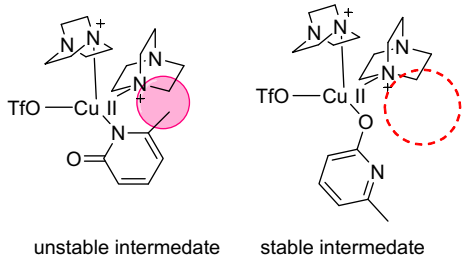
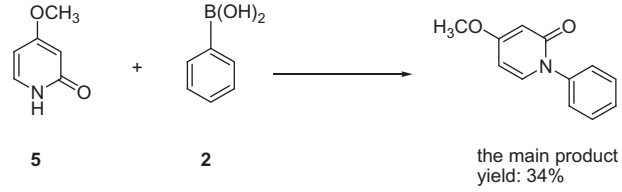


Figure 1. The plausible intermediate of Chan–Lam reaction.



Scheme 1. Substituent effect on other sites of pyridin-2-one. General reaction conditions: 0.2 mmol of 2-hydroxypyridines, 0.4 mmol of phenylboronic acid, 0.04 mmol of $Cu(OTf)_2$, 0.04 mmol of triethylenediamine, 0.4 mmol Et_3N, 0.4 mmol of K_2HPO_4, 2 mL DMSO, 50 °C for 5 h in air.

6-phenyl substituent was slightly better than 6-methyl one (entries 1 and 2). In addition, the presence of electron donating groups on the phenyl ring decreased the yield (entries 3–5), compared to that of electron withdrawing groups (entries 6–8). As desired, no N-arylated product was found in this way.

As shown in Table 3, the effect of different substituents on phenylboronic acid was also explored[18]. And, any substitution on the boronic acid would impede the coupling reaction accordingly. Among them, electron-rich phenylboronic acid with the electron-donating group facilitated the coupling reaction, when compared to the corresponding one with the electron-withdrawing group on the phenyl ring. However, no products were obtained with o-substituted phenylboronic acids, which implied that the reaction was very sensitive to steric effects for these substituted phenylboronic acids.

On the basis of the Chan–Lam coupling reaction mechanism and our experiment (Table 1, entries 1 and 18), we believed that there were two crucial factors to the regioselectivity. And as shown in Figure 1, the most important one is the steric hindrance of DABCO catalyst system which could impede the formation of N-Cu(II) unstable intermediate. The other is the steric hindrance of C6-substitution such as the methyl. As shown in Scheme 1, unfortunately, substituent effect on other sites of pyridin-2-one was investigated[18], this regioselectivity was not evident.

In conclusion, we have developed a mild and efficient method of selective O-arylation on C-6 substituted 2-hydroxypyridines using Chan–Evans–Lam cross-coupling reactions under very mild conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.126. These data include MOL files and InChiKeys of the most important compounds described in this article.

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17. Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528–1531.
18. *General procedure for O-arylation reaction:* A mixture of C-6 substituents of pyridin-2-one (0.2 mmol), related arylboronic acid (0.4 mmol), $Cu(OTf)_2$ (20 mol %), DABCO (20 mol %), Et_3N (0.4 mmol), K_2HPO_4 (0.4 mmol) followed by DMSO (2 mL) was stirred at in a 25 mL round bottom flask with calcium chloride tube for 5 h. The mixture was cooled to rt, water (12 mL) was added and extracted with dichloromethane (20 mL) for three times. The organic phases were combined, washed with brine, and dried over Na_2SO_4, and the solvent was distilled under reduced pressure. The residue was purified by column chromatography [CH_2Cl_2/petroleum ether (60–90 °C) 1:20] to afford the product.