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Cu-catalyzed amidation of halogenated imidazoles†

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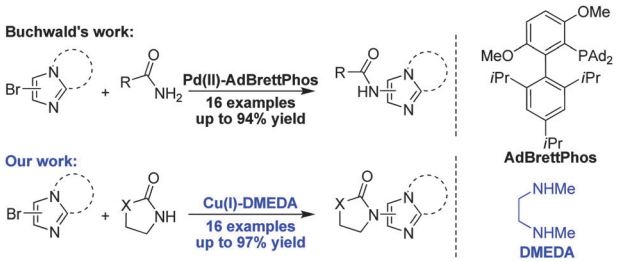
Mo Wang,[a] Zhenfeng Zhang,*[b] Fang Xie[a] and Wanbin Zhang*[ab]

An efficient methodology involving the Cu-catalyzed amidation of halogenated imidazoles has been successfully developed. The amidated product of 5-bromo-1-alkylimidazole was further applied to the synthesis of a new chiral imidazole nucleophilic catalyst for the kinetic resolution of secondary alcohols.

Amido and amino group-substituted imidazoles have been widely utilized as bioactive compounds, especially for kinase inhibitors.[1] The most commonly utilized method for the synthesis of amido-imidazoles and aminoimidazoles is *via* cyclization to construct specific imidazole rings.[2] For the introduction of an amido or amino group onto an already established imidazole ring, an indirect method involves reduction of a nitro group substituted imidazole followed by acylation or reductive amination.[3] A direct approach utilizes the aromatic nucleophilic substitution of halogenated imidazoles by amides or amines.[4] However, these traditional routes usually require harsh reaction conditions and suffer from limited substrate scope, often being applicable to only nitro-substituted halogenated imidazoles or 2-halogenated imidazoles. The development of a general methodology for the amidation or amination of halogenated imidazoles is thus highly desired.

Transition-metal catalyzed C–N cross-coupling reactions have the potential to overcome the aforementioned limitations.[5–7] Following pioneering work by Buchwald and Hartwig on Pd-catalyzed C–N cross-couplings, the amidation and amination of a variety of aryl halides and pseudohalides have been realized.[6] However, these protocols are not amenable to five-membered heterocyclic substrates possessing two heteroatoms such as halogenated imidazoles.[6i,8] Recently, Buchwald successfully applied a bulky biaryl phosphine ligand to the Pd-catalyzed amidation of this class of substrate (Scheme 1).[6i] However, reactions using substrates possessing stronger coordination ability such as 5-halogenated-1-alkyl-imidazoles have not been reported.



Scheme 1 Comparison with Buchwald's work.

Compared to Pd, Cu is inexpensive and has been widely used in C–N cross-coupling reactions.[7] However, to the best of our knowledge, no work has been reported on the Cu-catalyzed amidation of halogenated imidazoles. Herein, we report our results concerning the Cu-catalyzed amidation of halogenated imidazoles (Scheme 1). It is also worth mentioning that this methodology is applicable to other halogenated five-membered heterocycles containing two heteroatoms. Furthermore, we used this methodology for the synthesis of an efficient chiral imidazole nucleophilic catalyst which showed higher catalytic activity than the previously developed **DPI**.[9] This represents the first synthesis of such an amino group activated imidazole nucleophilic catalyst.[10]

We first optimized the cross-coupling reaction conditions between 5-bromo-1-methylimidazole and pyrrolidin-2-one (Table 1). Several types of ligands (10 mol%) were investigated using 10 mol% CuI as Cu salt, 4.0 eq. of K_2CO_3 as base, and reacting at the reflux temperature of dioxane (entries 1–8). Using ethane-1,2-diol (**L1**) as a ligand, no reaction occurred (entry 1). Increasing the coordinating ability of the ligand by using a more acidic hydroxyl group (**L2** or **L4**) or a greater electron-donating amino group (**L3** or **L5**) improved the yield (entries 2–5). The electron-donating methyl groups on both N atoms (**L6**) can significantly improve the coordinating ability of the diamine ligand resulting in a higher yield (entry 6 *vs.* 5). However, tetramethylethane-1,2-diamine (**L7**) only gave the desired product in 18% yield, presumably due

[a] *School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China.*
E-mail: wanbin@sjtu.edu.cn; Fax: +86 02154743265; Tel: +86 02154743265
[b] *School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China*

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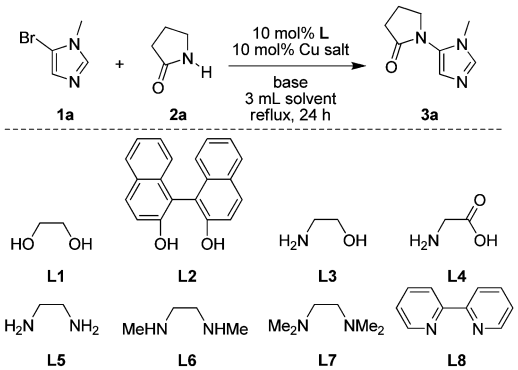
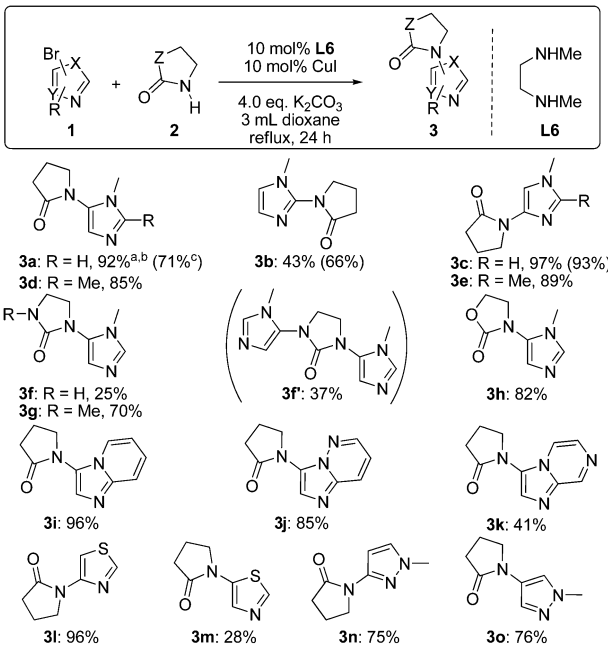
Table 1 The optimization of reaction conditions[a]



Entry	Ligand	Cu salt	Base	Solvent	Yield[b] (%)
1	**L1**	CuI	K_2CO_3	Dioxane	NR
2	**L2**	CuI	K_2CO_3	Dioxane	23
3	**L3**	CuI	K_2CO_3	Dioxane	9
4	**L4**	CuI	K_2CO_3	Dioxane	38
5	**L5**	CuI	K_2CO_3	Dioxane	9
6	**L6**	CuI	K_2CO_3	Dioxane	94
7	**L7**	CuI	K_2CO_3	Dioxane	18
8	**L8**	CuI	K_2CO_3	Dioxane	33
9	**L6**	CuBr	K_2CO_3	Dioxane	76
10	**L6**	CuCl	K_2CO_3	Dioxane	48
11	**L6**	Cu_2O	K_2CO_3	Dioxane	11
12	**L6**	$CuBr_2$	K_2CO_3	Dioxane	32
13	**L6**	$Cu(OAc)_2$	K_2CO_3	Dioxane	37
14[c]	**L6**	CuI	K_2CO_3	Dioxane	45
15[d]	**L6**	CuI	K_2CO_3	Dioxane	91
16	**L6**	CuI	Cs_2CO_3	Dioxane	NR
17	**L6**	CuI	K_3PO_4	Dioxane	NR
18[e]	**L6**	CuI	K_2CO_3	Dioxane	72
19[f]	**L6**	CuI	K_2CO_3	Dioxane	85
20[g]	**L6**	CuI	K_2CO_3	Dioxane	83
21	**L6**	CuI	K_2CO_3	Toluene	90
22	**L6**	CuI	K_2CO_3	DMF	11
23	**L6**	CuI	K_2CO_3	THF	7

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Cu salt (0.05 mmol, 10 mol%), **L** (0.05 mmol, 10 mol%, unless otherwise noted), base (2.0 mmol, 4.0 eq., unless otherwise noted), solvent (3 mL), reflux, and 24 h. [b] Yields were determined by ^{1}H NMR. [c] 5 mol% of **L6**. [d] 20 mol% of **L6**. [e] 1.0 eq. of K_2CO_3. [f] 2.0 eq. of K_2CO_3. [g] 6.0 eq. of K_2CO_3.

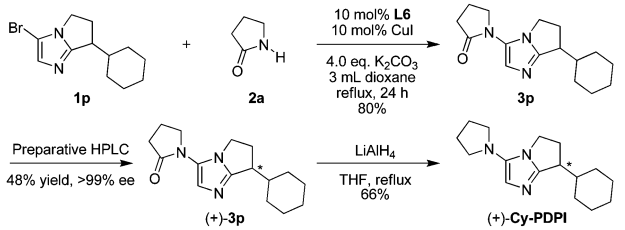
to the steric-hindrance around the two N atoms (entry 7). Use of the bipyridine ligand (**L8**) also gave the product in a low yield of 33% (entry 8). Using **L6** as a suitable ligand, different Cu salts were studied in this reaction (entries 9–13). A complex of CuBr and **L6** led to the formation of the desired product in 76% yield (entry 9). The yield was reduced to 48% when CuCl was used (entry 10). Cu_2O only afforded the product in 11% yield probably due to its poor solubility (entry 11). Cu(II) salts can also catalyze this reaction, but lower yields were obtained (entries 12 and 13). It was found that less loading of ligand (5 mol%) reduced the yield to 45% while higher loading of ligand (20 mol%) had no obvious effect on yield (entries 14 and 15). The influence of base was also examined (entries 16–20). Using K_2CO_3 provided the highest yield compared to other bases such as Cs_2CO_3 or K_3PO_4 (entries 16 and 17). Decreasing or increasing the amount of K_2CO_3 reduced the yield of this reaction (entries 18–20). Several other solvents were also utilized in this reaction. Toluene gave a high yield of 90% while others gave lower yields (entries 21–23).



Scheme 2 The substrate scope. [a] All reactions were conducted under conditions: **1** (0.5 mmol), **2** (0.6 mmol), **L6** (0.05 mmol, 10 mol%), CuI (0.05 mmol, 10 mol%), K_2CO_3 (2.0 mmol, 4.0 eq.), dioxane (3 mL), reflux, and 24 h. [b] Isolated yields for all data. [c] The data in brackets are the yields using iodoimidazoles.

The substrate scope was investigated as listed in Scheme 2. Bromoimidazoles with bromine substituted at the 2-, 4-, and 5-positions showed significantly different activities. Amidation of 2-bromoimidazole afforded the corresponding product **3b** in a yield of 43%, while the 4- and 5-position coupled products **3c** and **3a** were obtained in yields of 97% and 92%, respectively. Changing the bromine group to an iodine group also gave good yield.[11] The same products **3a** and **3c** were obtained in yields of 71% and 93% using 5- and 4-iodo-1-methylimidazoles, respectively, while 2-iodo-1-methylimidazole afforded **3b** in a yield of 66%. The substrates possessing a 2-methyl substituent also gave **3d** and **3e** in good yields of 85% and 89%, respectively. Besides pyrrolidin-2-one, other lactams were also investigated using 5-bromo-1-methylimidazole as a substrate. Imidazolidin-2-one showed a complex result with both the desired product **3f** and a coupled product **3f** being obtained in yields of 25% and 37%, respectively. After protection of the free NH group with a methyl group, the relevant product **3g** was obtained in 70% yield. The analogous oxazolidin-2-one also afforded the product **3h** in a yield of 82%. Fused bromoimidazoles, which have also been investigated by Buchwald in Pd-catalyzed amidation reactions,[6i] gave coupled products **3i**, **3j**, and **3k** in yields of 96%, 85%, and 41%, respectively. This method was also applied to other five-membered heterocycles containing two heteroatoms such as bromothiazole and bromopyrazole. Coupling of 4-bromothiazole with pyrrolidin-2-one afforded **3l** in 96% yield while its 5-position isomer **3m** was obtained only in a yield of 28%. Bromo-1-methylpyrazoles were also tested in this reaction to give the corresponding products **3n** and **3o** in yields of 75% and 76%, respectively.

The success in the cross-coupling of 5-bromo-1-methylimidazole and pyrrolidin-2-one encouraged us to apply this methodology to the synthesis of the nucleophilic catalyst (+)-**Cy-PDPI**,[12]



Scheme 3 The synthesis of (+)-**Cy-PDPI**.

which possesses a pyrrolidin-1-yl substituent (Scheme 3). **3p** was conveniently synthesized in a good yield of 80% using the above mentioned Cu-catalyzed C–N cross-coupling. By means of preparative HPLC, both *S* and *R* isomers can be obtained in yields of 48% and with >99% ees. After reduction with $LiAlH_4$ in THF, the desired target compound (+)-**Cy-PDPI** was obtained in 66% yield. (+)-**Cy-PDPI** was further applied in kinetic resolution of secondary alcohols as a model reaction for testing a new chiral nucleophilic catalyst. The preliminary results showed that (+)-**Cy-PDPI** has high catalytic activity and good stereocontrol in the kinetic resolution of secondary alcohols.[13]

To summarize, an efficient synthetic procedure for the Cu-catalyzed amidation of halogenated imidazoles has been developed. Various substrates were tested to obtain the relative products with up to 97% yield. The amidated product of 5-bromo-1-alkylimidazole was further applied to the synthesis of a new chiral imidazole nucleophilic catalyst which showed high catalytic activity and good stereocontrol in the kinetic resolution of secondary alcohols.

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11 No reaction occurred using 5-chloro-1-methylimidazole as a substrate using the same conditions.

12 **Cy-PDPI** is the abbreviation of 7-cyclohexyl-3-(pyrrolidin-1-yl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole.

13 This work will be published in detail in due course.