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Copper-catalysed amidation of 2-chloro-pyridines†

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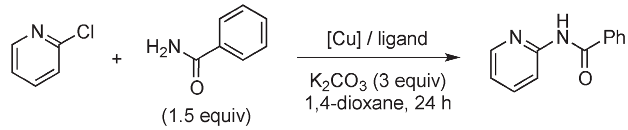
The simple and inexpensive *N*,*N*-dimethylcyclohexane-1,2-diamine/CuI catalytic system provides a versatile, easy and efficient access to an array of *N*-(2-pyridin-2-yl)-amides from 2-chloro-pyridine derivatives.

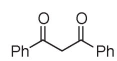
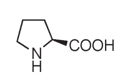
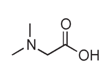
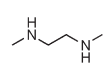
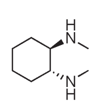
Amide formation is ubiquitous in organic chemistry as many biologically-relevant synthetic and natural products incorporate an amide moiety. Among amides, *N*-heteroaryl amides constitute one important class of pharmacophores used in medicinal chemistry and, recently, *N*-(2-pyridin-2-yl)-amide derivatives were reported to block sodium channels which are involved in neuronal regulation with potential applications in the treatment of pain, arrhythmia or epilepsy.[1] Non-catalytic amidations of 2-amino heterocycles as well as metal-catalysed amidations of aryl halides are existing to access amide derivatives.[2] However, despite considerable progresses in palladium- and copper-catalysed C–N bond formation,[3–5] broadening the scope of electrophiles and nucleophiles that can be used in these reactions, only a few methods are able to achieve the amidation of aryl chlorides, and a few examples are reported for the amidation of 2-chloro-pyridine derivatives which are less reactive than their brominated counterparts.[6] Herein, we would like to report a general method for the catalytic amidation of chloro-pyridine derivatives involving a cheap and simple catalytic system based on CuI and *trans*-*N*,*N*-dimethyl-cyclohexane-1,2-diamine.[6b–c,f,7,8,9]

Initially, a catalytic amidation of 2-chloropyridine with benzamide was examined to tune up the reaction conditions (Table 1). Initial trials involving CuI (50 mol%) and 1,3-diphenylpropan-1,3-dione, proline or *N*,*N*-dimethylglycine as ligands (50 mol%) did not lead to any conversion of the starting materials (Table 1, entries 1–3). However, the use of *N*,*N*-dimethylethylenediamine as a ligand (50 mol%) provided *N*-(pyridin-2-yl)benzamide in 48% yield (Table 1, entry 4), and the yield was increased to 82% when *N*,*N*-dimethylcyclohexane-1,2-diamine (50 mol%) was used (Table 1, entry 5).

Having identified *N*,*N*-dimethylcyclohexane-1,2-diamine (**L**) as the best ligand, the optimisation of the amidation of 2-chloropyridine with benzamide was achieved (Table 2). Other copper sources such as CuO, CuBr, Cu_2O or $Cu(OAc)_2{\cdot}H_2O$ were evaluated

Table 1 Ligand screening in the amidation of 2-chloropyridine



Entry[a]	[Cu] (mol%)	Ligand (mol%)	T (°C)	Yield[b]
1	CuI (50)	 (50)	100	—
2	CuI (50)	 (50)	100	—
3	CuI (50)	 (50)	100	—
4	CuI (50)	 (50)	100	48%
5	CuI (50)	 **L** (50)	100	82%

[a] c = 1 M. [b] Isolated yield.

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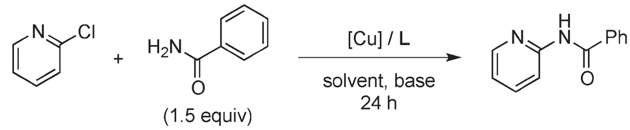
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data and NMR spectra for amide compounds. See DOI: 10.1039/c3ra43368d

Table 2 Optimisation of the catalyst for the amidation of 2-chloropyridine



Entry	[Cu] (mol%)	**L** (mol%)	Base (equiv.)	Solvent[a]	*T* (°C)	Yield[b]
1	CuO (50)	(50)	K_2CO_3 (3)	1,4-dioxane	100	11%
2	CuBr (50)	(50)	K_2CO_3 (3)	1,4-dioxane	100	23%
3	Cu_2O (50)	(50)	K_2CO_3 (3)	1,4-dioxane	100	38%
4	$Cu(OAc)_2 \cdot H_2O$ (50)	(50)	K_2CO_3 (3)	1,4-dioxane	100	26%
5	CuI (50)	(50)	K_3PO_4 (3)	1,4-dioxane	100	74%
6	CuI (50)	(50)	Cs_2CO_3 (3)	1,4-dioxane	100	36%
7	CuI (50)	(50)	K_2CO_3 (3)	DMF	150	38%
8	CuI (50)	(50)	K_2CO_3 (3)	DME	85	85%
9	CuI (25)	(25)	K_2CO_3 (3)	1,4-dioxane	100	71%
10	CuI (10)	(10)	K_2CO_3 (3)	1,4-dioxane	100	28%
11	CuI (10)	(10)	K_2CO_3 (2)	1,4-dioxane	170[c]	81%
12	CuI (5)	(5)	K_2CO_3 (2)	1,4-dioxane	170[c]	69%
13	CuI (2)	(2)	K_2CO_3 (2)	1,4-dioxane	170[c]	60%[d]
14	—	—	K_2CO_3 (2)	1,4-dioxane	170[c]	—
15	CuI (10)	—	K_2CO_3 (2)	1,4-dioxane	170[c]	—
16	—	(10)	K_2CO_3 (2)	1,4-dioxane	170[c]	—

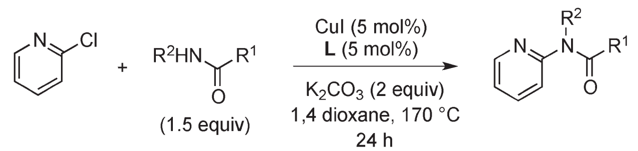
[a] *c* = 1 M. [b] Isolated yield. [c] Reaction performed in a sealed tube. [d] After 60 h of reaction.

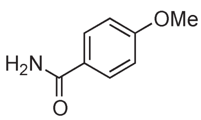
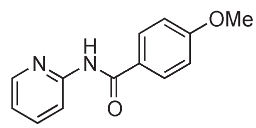
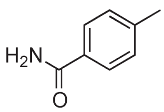
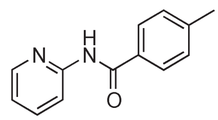
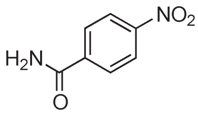
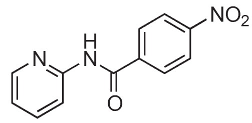
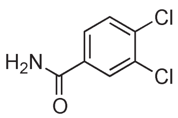
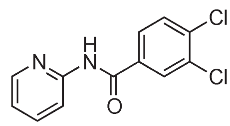
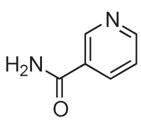
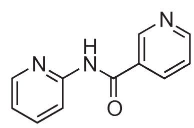
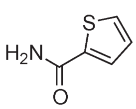
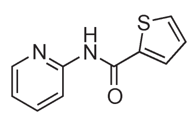
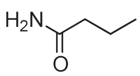
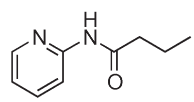
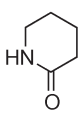
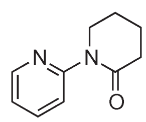
(Table 2, entries 1–4), however they displayed lower catalytic activities than CuI (Table 1, entry 5). The use of K_3PO_4 as a base, instead of K_2CO_3, led to a slightly decreased yield (74%) whereas the use of Cs_2CO_3 lowered the yield to 36% (Table 2, entries 5–6). When DMF was used as the solvent, *N*-(pyridin-2-yl)benzamide was isolated in 48% yield, and when DME was utilised, the yield was similar to the one obtained with 1,4-dioxane (85%) (Table 2, entries 7–8). A decrease of the catalytic loading in both CuI and ligand **L** from 50 mol% to 10 mol% dramatically decreased the yield in the cross-coupling; *N*-(pyridin-2-yl)benzamide was isolated in 71% yield with 25 mol%, and in 28% yield with a 10 mol% catalytic loading (Table 2, entries 9–10). Gratifyingly, when the reaction was performed with 10 mol% CuI and 10 mol% **L** in 1,4-dioxane in a sealed tube at 170 °C, *N*-(pyridin-2-yl)benzamide was isolated in 81% yield (Table 2, entry 11) and, at this temperature, the amount of K_2CO_3 could be reduced to 2 equivalents. It was possible to decrease the catalytic charge to 5 mol% of CuI and 5 mol% of **L** as *N*-(pyridin-2-yl)benzamide was still obtained in good yield (69%) (Table 2, entry 12). With 2 mol% of CuI and 2 mol% of **L**, the yield was 60% however, after 60 h of reaction (Table 2, entry 13). We have to point out that in the absence of either CuI or **L**, no conversion of the starting material was observed under the reaction conditions (Table 2, entries 14–16).[10]

Having obtained optimized conditions for the cross-coupling of 2-chloropyridine with benzamide (5 mol% CuI and 5 mol% **L**, 2 equiv., K_2CO_3, 170 °C, 1,4-dioxane, 24 h), the reaction of 2-chloropyridine was evaluated with several aromatic, heteroaromatic and aliphatic amides, and the results are reported in Table 3. Aromatic amides such as 4-methoxybenzamide, 4-methylbenzamide or 4-nitrobenzamide provided the corresponding cross-coupling products in 72–57% yield (Table 3, entries 1–3), the electron-poor 4-nitrobenzamide leading to the lowest yield (57%) (Table 3, entry 3). When 3,4-dichlorobenzamide was engaged in the amidation of 2-chloropyridine, the cross-coupling was chemoselective and the expected amide was obtained in 69% yield (Table 3, entry 4). Heteroaromatic amides such as nicotinamide or thiophene-2-carboxamide are suitable in the cross-coupling with 2-chloropyridine as the corresponding amides were isolated with good yields of 83% and 75% respectively (Table 3, entries 5 and 6). Aliphatic amides such as a primary amide, butyramide, or a secondary amide, piperidin-2-one, provided the expected *N*-(pyridin-2-yl)amides in 96% and 78% yields respectively (Table 3, entries 7–8).

At this stage, the amidation of other pyridyl halides with benzamide was examined, under the optimized conditions (5 mol% CuI and 5 mol% **L**, 2 equiv. K_2CO_3, 170 °C, 1,4-dioxane, 24 h), and the results are reported in Table 4. When 2-chloro-5-methoxypyridine was used, *N*-(5-methoxypyridin-2-yl)benzamide was obtained in 92% yield (Table 4, entry 1), whereas with 2-chloro-3-methoxypyridine, no cross-coupling product was isolated and the starting material was recovered (Table 4, entry 2). The reaction of 2-chloro-5-chloropyridine was chemoselective and the expected mono-amide was obtained selectively, however in 45% isolated yield for 75% conversion of the starting dihalopyridine (Table 3, entry 3). When 2,4-dichloropyridine was used, the corresponding mono-amide was obtained chemoselectively and, in this case, the isolated yield was 32%, for 72% conversion of the starting 2,4-dichloro-pyridine (Table 3, entry 4). In contrast, the use of 2-chloro-4-iodopyridine led to the expected diamide in 32% yield and only traces of the mono-amide were observed (Table 3, entry 5). Concerning 2-chloro-4-bromopyridine, the diamide product was isolated in only 21% yield, and only traces of the mono-amide were

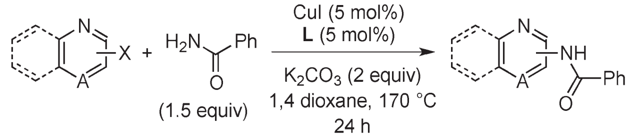
Table 3 Amidation of 2-chloropyridine with various amides

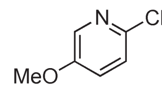
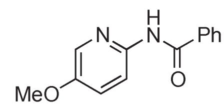
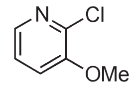
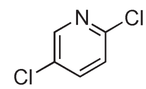
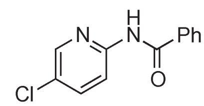
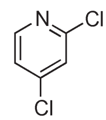
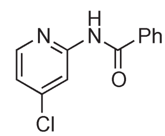
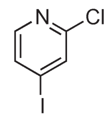
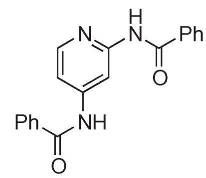
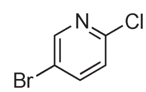
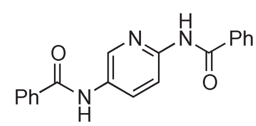
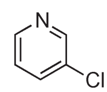
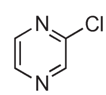
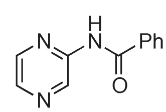
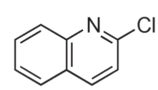
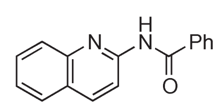


Entry[a,b]	Amide	Product	Yield[c]
1			72%
2			66%
3			57%
4			69%
5			83%
6			75%
7			96%
8			78%

[a] c = 1 M. [b] Reaction performed in a sealed tube. [c] Isolated yield.

Table 4 Amidation of various halogeno-heteroaromatics



Entry[a,b]	Halogeno pyridine	Product	Yield[c]
1			92%
2		—	—
3			45%[d]
4			32%[e]
5			32%[f]
6			21%[f]
7		—	—
8			67%
9			88%

[a] c = 1 M. [b] Reaction performed in a sealed tube. [c] Isolated yield. [d] 25% of starting material recovered. [e] 28% of starting material recovered. [f] Only traces of mono-amide product were observed.

observed (Table 3, entry 6). Worthy of note is the reaction of 3-chloropyridine which was unreactive under the reaction conditions (Table 3, entry 7). Finally, 2-chloropyrazine and 2-chloroquinoline successfully reacted with benzamide, and the corresponding amides were produced in 67% and 88% yield respectively (Table 3, entries 8–9).

Conclusions

In summary, we have described a straightforward method for the amidation of 2-chloropyridine derivatives with a cheap and convenient CuI/*N*,*N*-dimethylcyclohexane-1,2-diamine catalytic system, which constitutes an interesting alternative to both the reported Pd-centered methods and Cu-catalysed amidation of 2-bromo-pyridine derivatives. This C–N bond formation is general and can involve aromatic, heteroaromatic or aliphatic amides, and various pyridine derivatives such as 2-chloropyridines, as well as 2-chloropyrazine and 2-chloroquinoline.

Acknowledgements

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