Efficient synthesis of aminopyridine derivatives by copper catalyzed amination reactions†

Mohammed K. Elmkaddem,[a] Cédric Fischmeister,*[a] Christophe M. Thomas*[b] and Jean-Luc Renaud*[c]

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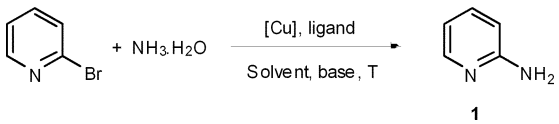
A copper(I) catalyzed amination reaction utilizing aqueous ammonia and operating under mild conditions is presented. This method was employed for the efficient synthesis of various aminopyridine derivatives bearing electron withdrawing and electron donating groups.

Amine substituted aromatic and heteroaromatic derivatives are important building blocks in pharmacology[1] and materials science.[2] As a consequence, synthetic methods for the efficient formation of C–N bonds are strongly desired. Since the pioneering work by Ullmann and Goldberg on copper promoted formation of C–N bonds at the beginning of the 20th century,[3] it was almost one century later that a major breakthrough was achieved by Buchwald *et al.*[4] and Hartwig and Louie,[5] who reported very efficient palladium based amination catalysts.[6,7] More recently, copper complexes have enjoyed a renewal and several efficient copper catalyzed C–N bond formations have been mentioned.[8] Recently, we reported the synthesis of various sterically hindered dipyridylamine (dpa) ligands of potential interest in homogeneous catalysis.[9] These compounds were efficiently prepared using a Cu_2O catalysed amination of bromopyridine derivatives with ammonia at 100 °C in ethylene glycol.[10] As part of our continuing efforts into the synthesis of dpa ligands we were interested in using the easy to handle and inexpensive aqueous ammonia. Until now, only a few examples on the use of aqueous ammonia in copper catalyzed amination reactions have been reported. In 2008, Chang and Kim used a CuI/L-proline system, allowing the arylation of various derivatives with aqueous ammonia.[11] This catalytic system could also be employed with ammonium chloride as the ammonia source, however, the use of iodine derivatives was necessary to obtain efficient transformations. In 2007 and 2009, Taillefer and Xia[12] reported several examples of



Scheme 1 Copper catalyzed amination of bromopyridine.

$NH_3{\cdot}H_2O$ arylation using CuI/2,4-pentadione as the catalytic system, whereas Ma *et al.*[13] described one example using a catalytic system based on CuI/4-hydroxyproline. In addition, an efficient system based on Cu_2O allowing the amination of aryl chloride derivatives under microwave irradiation was disclosed by Wolf and Xu.[14]

Here we wish to report on a copper(I) based catalytic system for the efficient amination of bromopyridine derivatives operating under very mild conditions *i.e.* 60 °C. The method makes use of cheap Cu_2O and takes advantage of the easy to handle aqueous ammonia.

As a starting point we used the amination of 2-bromopyridine to screen several reaction parameters such as temperature, ligands, metals and solvents (Scheme 1).

We initially chose the experimental conditions successfully employed for the amination using ammonia. 2-Bromopyridine was thus reacted with an excess of $NH_3{\cdot}H_2O$ (40 equiv.) and 5 mol% of Cu_2O in ethylene glycol at 100 °C. Under these conditions, we were pleased to observe 61% conversion of 2-bromopyridine after 16 h reaction time. Although ethylene glycol can be regarded as a bidentate ligand for such reactions,[15] we next considered the use of several *N*,*N*-bidentate ligands (Fig. 1).

As depicted in Table 1, the best result was obtained with DMEDA (dimethylethylenediamine). Both the unsymmetrical and symmetrical DMEDA provided similar results and the study was pursued with the unsymmetrical derivative **B**.

Following these preliminary results, the use of an additional base was also evaluated. As observed with DMEDA, the addition of 20 mol% of K_2CO_3 resulted in a major improvement

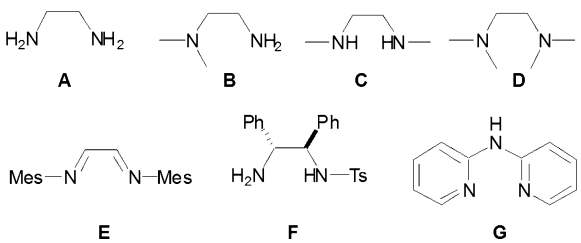


Fig. 1 Additives in the Cu_2O amination of 2-bromopyridine.

[a] *UMR 6226-CNRS-Université de Rennes 1, Sciences Chimiques de Rennes, Catalyse et Organométalliques, Campus de Beaulieu, avenue du général Leclerc, 35042 Rennes cedex, France. E-mail: cedric.fischmeister@univ-rennes1.fr; Fax: +33(0)223236939; Tel: +33(0)223235998*
[b] *ENSCP, UMR CNRS 7223, 11 rue Pierre et Marie Curie, 75005 Paris, France. E-mail: christophe-thomas@enscp.fr; Fax: +33(0)143260061; Tel: +33(0)144276721*
[c] *Laboratoire de Chimie Moléculaire et Thioorganique, UMR 6507, INC3M, FR 3038, ENSICAEN-Université de Caen, 14050 Caen, France. E-mail: jean-luc.renaud@ensicaen.fr; Fax: +33(0)231452877; Tel: +33(0)231452842*

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Table 1 $Cu_2O/NH_3{\cdot}H_2O$ amination of 2-bromopyridine[a]

	Additive[b]	Conversion (%)[c]	Yield (%)[d]
1	—	61	57
2	**A**	66	63
3	**B**	86	83
4	**C**	94	86
5	**D**	64	61
6	**E**	57	54
7	**F**	19	19
8	**G**	72	70

[a] 2-Bromopyridine (0.5 mmol), Cu_2O (5 mol%), $NH_3{\cdot}H_2O$ (28% solution, 40 equiv.), ethylene glycol (1 mL), 100 °C, 16 h. [b] 10 mol%. [c] Determined by ^{1}H NMR spectroscopy. [d] Isolated yield.

Table 2 $Cu_2O/NH_3{\cdot}H_2O$ catalysed amination of 2-bromopyridine at low temperature[a]

	T/°C	t/h	Conversion (%)[b]	Yield (%)[c]
1	80	4	100	96
2	60	8	88	80
3	60	12	98	86
4	60	16	100	90

[a] 2-Bromopyridine (0.5 mmol), Cu_2O (5 mol%), $NH_3{\cdot}H_2O$ (28% solution, 40 equiv.), K_2CO_3 (20 mol%), DMEDA (10%), ethylene glycol (1 mL). [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

in the reaction efficiency, affording 76% conversion of 2-bromopyridine in only 4 h. Finally, the simultaneous use of K_2CO_3 (20 mol%) and DMEDA (10%) was found to be the best combination, providing 100% conversion of 2-bromopyridine in 4 h. It is noteworthy that this catalytic system remained very efficient at 60 °C, affording good yields of **1** in a reasonable 16 h reaction time (Table 2, entry 4).

Various copper(I) and copper(II) complexes were then tested under the optimized conditions but none of them showed a higher performance than Cu_2O (Table 3, entries 1–6). Solvent effects were also screened but again our initial choice, *i.e.* ethylene glycol, was found to be superior to the solvents tested

Table 3 Copper catalyzed amination of 2-bromopyridine with $NH_3{\cdot}H_2O$ using various copper sources and solvents[a]

	[Cu][b]	Solvent[d]	Conversion (%)[e]	Yield (%)[f]
1	—[c]	EG	0	—
2	Cu_2O	EG	100	90
3	CuI	EG	9	—
4	$Cu(OTf){\cdot}C_6H_6$	EG	60	58
5	$CuCl_2$	EG	24	22
6	$Cu(OAc)_2{\cdot}H_2O$	EG	10	—
7	Cu_2O	DME	70	68
8	Cu_2O	DMF	68	65
9	Cu_2O	NMP	92	83
10	Cu_2O	Dioxane	86	83
11	Cu_2O	PC	25	22

[a] 2-Bromopyridine (0.5 mmol), $NH_3{\cdot}H_2O$ (28% solution, 40 equiv.), DMEDA (10%), K_2CO_3 (20 mol%), 60 °C, 16 h. [b] [Cu] (5 mol%). [c] Blank test realised in the absence of Cu_2O and DMEDA. [d] Solvent (1 mL), EG = ethylene glycol, DME = dimethoxyethane, DMF = dimethylformamide, NMP = *N*-methylpyrrolidinone, PC = propylene carbonate. [e] Determined by ^{1}H NMR spectroscopy. [f] Isolated yield.

Table 4 $Cu_2O/NH_3{\cdot}H_2O$ catalysed amination of 2-bromopyridine at low temperature[a]

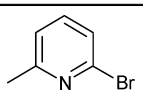
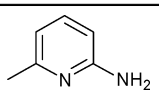
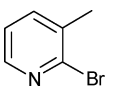
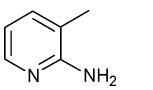
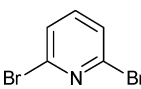
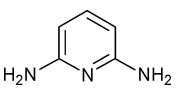
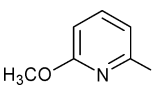
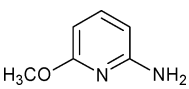
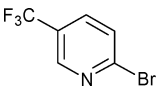
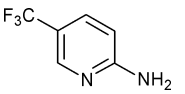
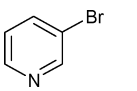
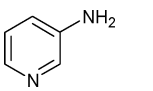
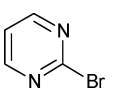
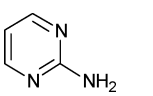
	NH_3 aq. (equiv.)	t/h	Conversion (%)[b]
1	40	16	100
2	20	16	100
3	10	16	92
4	10	24	100

[a] 2-Bromopyridine (0.5 mmol), Cu_2O (5 mol%), K_2CO_3 (20 mol%), DMEDA (10%), ethylene glycol (1 mL), 60 °C. [b] Determined by ^{1}H NMR spectroscopy.

(Table 3, entries 7–11). Furthermore, from an experimental point of view, the use of ethylene glycol facilitated the extraction by ethyl acetate of the organic products, the copper salt remaining immobilized in the reaction solvent. This prompted us to investigate the possibility of catalyst recycling but conversions were found to drop quickly after the second run. We believe that this result arises from the increased amount of water brought into the reaction mixture by the ammonia solution.

Finally, the amount of $NH_3{\cdot}H_2O$ was also screened and it was found that 20 equiv. were necessary to maintain a high activity, *i.e.* full conversion at 60 °C in 16 h, while the conversion dropped to 92% when 10 equiv. of $NH_3{\cdot}H_2O$ were employed (Table 4, entries 2 and 3). However, full conversion could be recovered by using longer reaction time (Table 4, entry 4). As also observed in

Table 5 Cu_2O catalysed amination of bromopyridine derivatives[a]

	Py–Br	Py–NH_2		Conversion (%)[b]	Yield (%)[c]
1			**2**	94	88
2			**3**	100	98
3			**4**	70[d]	68
4			**5**	46 100[e]	43 94
5			**6**	94 0[f]	86
6			**7**	81[e]	80
7			**8**	94	85

[a] Bromopyridine derivative (0.5 mmol), Cu_2O (5 mol%), $NH_3{\cdot}H_2O$ (28% solution, 20 equiv.), K_2CO_3 (20 mol%), DMEDA (10%), ethylene glycol (1 mL), 60 °C, 16 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] $NH_3{\cdot}H_2O$ (28% solution, 40 equiv.). [e] 80 °C. [f] Test realised in the absence of Cu_2O and DMEDA.

our previous work,[9] the product resulting from the *O*-arylation of the pyridine derivative by the solvent was detected in small quantity (8%).

With this efficient system in hand we next extended the scope of the reaction to various bromopyridine derivatives. We found that the reaction was applicable to a broad range of derivatives and was not strongly affected by electron-releasing or electron-withdrawing groups (Table 5, entries 1, 2, 4 and 5).

The efficiency of the reaction was not sensitive to the steric hindrance of an adjacent methyl group (Table 4, entry 2). Similarly, the catalytic system was also found to be suitable for the amination of 3-bromopyridine and 2-bromopyrimidine, yielding 3-aminopyridine **7** and 2-aminopyrimidine **8** in high yields (Table 2, entries 6 and 7).[16] It is noteworthy that the diamination of 2,6-dibromopyridine afforded **4** in good yield. However, the use of 20 equiv. of $NH_3{\cdot}H_2O$ (10 equiv./Py–Br) resulted in an incomplete reaction leading to a mixture of 2,6-diaminopyridine and 2-bromo-6-aminopyridine. To ensure good conversion and yield, 40 equiv. of $NH_3{\cdot}H_2O$ (20 equiv. per Br) have to be used, then the diaminopyridine **4** was isolated in 68% yield. Finally, as mentioned previously for the amination of 2-bromopyridine, the synthesis of products **2**, **5** and **8** were accompanied by the formation of *O*-arylation products in 5%, 6% and 7%, respectively. Finally, the amination reaction using 10 equiv. of $NH_3{\cdot}H_2O$ was still possible upon longer reaction time. For instance the transformation of 6-bromo-2-picoline and 2-bromo-6-methoxypyridine were performed over 24 h with high conversion (98%) providing **2** and **5** in 70 and 80% yield, respectively.

In summary, we have presented an efficient catalytic system for the amination of various bromopyridine and pyrimidine derivatives. The reaction proceeds with high conversions and yields under mild conditions regardless of the substitution by electron-donating or -withdrawing groups. The interest of the system is based on the use of a cheap copper complex and aqueous ammonia as a cheap and easy to handle ammonia source.

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