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Mild temperature amination of aryl iodides and aryl bromides with aqueous ammonia in the presence of CuBr and pyridyldiketone ligands

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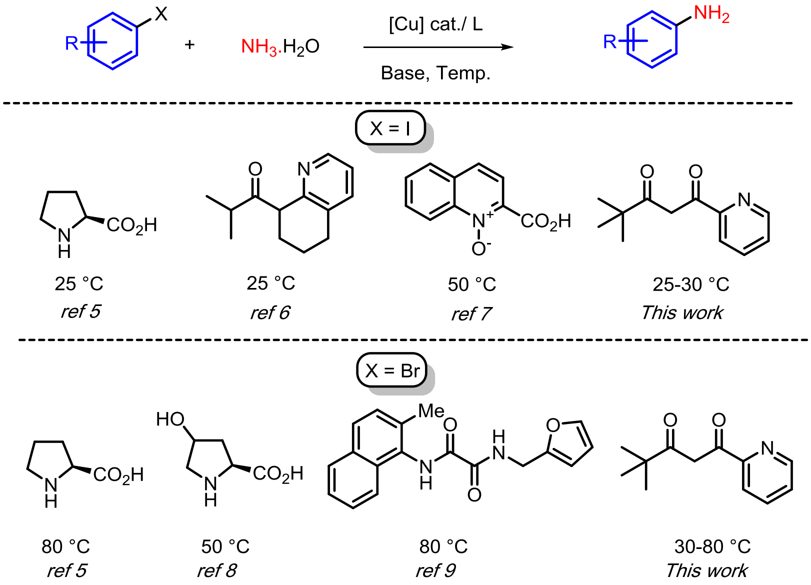
Catalytic systems based on copper and simple ligands of ambidentate pyridyldiketone type were used in direct amination of aryl iodides and bromides with aqueous ammonia in one of the mildest conditions described in the literature, with reaction temperature ranging beetween 25 and 80 °C.

The synthesis of primary aryl amines under mild conditions remained an challenging goal for synthetic chemist because of the importance of this class of compounds in fine chemicals production.[1] The coupling of ammonia and aryl halides catalyzed by transition metals is a method of choice to prepare aryl amines in a selective and cost-effective manner.[2] Efficient systems have been described with the assistance of palladium-based catalysts.[3] These methods nevertheless suffered from several drawbacks such as the use of relatively toxic and expensive metal, along with sophisticated ligands (bulky ferrocene, electron-rich phosphines), strong bases and in some cases the use of ammonia pressure.[3] In 2007, as part of our studies in the Cu-catalysed arylation of nucleophiles, we showed that amination of aryl iodides and bromides with the use of aqueous ammonia could be performed using a copper-based catalytic system.[4] Since then, a lot of related methods proceeding in the presence of various ligands have been reported in this field at temperature mainly ranging between 90 °C and 130 °C.[2] The use of proline[5] and 2-pyridinyl-β-ketone[6] as ligand allowed the coupling of aryl iodides with aqueous ammonia to be performed at room temperature, whereas acetylacetone permitted to proceed at 60-90 °C (Scheme 1, X = I).[4] Amination of aryl iodides could also be performed at 50 °C in the presence of Cu(I) and 2-carboxylic acid-quinoline-*N*-oxide as ligand.[7] There are relatively few examples reported for this transformation under mild temperature conditions (below 90 °C - Scheme 1, X = Br) in the presence of arylbromides.[2] Proline ligand was used to perform amination in good yields at 80 °C with ArBr bearing EW groups, but in poor yields with the aromatic cycle substituted by ED groups.[5] The coupling of ArBr with aqueous ammonia at 50 °C was also reported in the presence of 4-hydroxy-L-proline[8] and recently with a novel family of ligand (oxalic diamides) allowing the coupling of ArBr with $NH_3 \cdot H_2O$ at 80 °C with high turnovers.[9] In our previous report,[4] we showed that acetylacetone ligand in association with $Cu(acac)_2$ was able to perform amination of aryl bromides at 90 °C, and at 60 °C for activated aryl bromides bearing electron-withdrawing groups.



Scheme 1: Selected ligands for copper-catalyzed amination of ArI and ArBr under mild temperature conditions.

Under this context, we now report that simple ligands of ambidentate pyridyldiketone type can allow amination of aryl iodides and aryl bromides respectively at room temperature and at 30-80 °C.

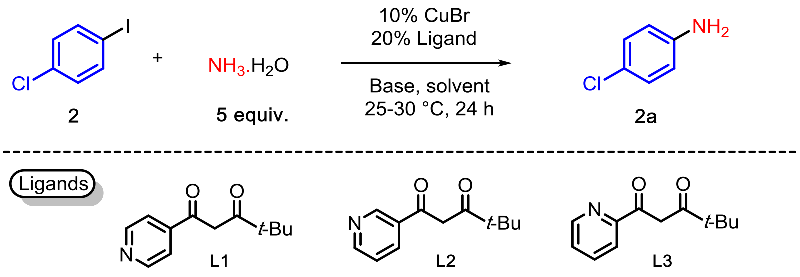
Ambidentate pyridyldiketones ligands containing two distinct coordination sites of different nature (i.e. anionic β-diketonate and neutral pyridine) despite their wide use for the construction of linkage isomers,[10] homo- and heteromultimetallic complexes[11] and large metallosupramolecular architectures[12] through coordination-driven self-assembly, have not been often employed in the Cu catalyzed arylation of nitrogen nucleophiles and never tested in the presence of aqueous ammonia.[13] Thus, isomeric compounds **L1**-**L3** (Table 1) are potential bifunctional ligands, that could be readily immobilized on a matrix of tetrahedral Cu(I) metal ion by means of acetylacetonate and pyridyl chelation. We have recently shown a first application for these ambidentate ligands, that the linkage isomers of the Pd(II) complexes of **L1** and **L2** are efficient catalyst precursors for the Suzuki-Miyaura reaction.[10] The ligands **L1** and **L2** as well as previously uncharacterised **L3**, were prepared according to the literature procedure,[10] by Claisen condensation of appropriate methyl ester with pinacolone in the presence of strong base (see supporting information for details).

A model was chosen for the reaction development study, and 4-chloro-iodobenzene **2** was engaged with 5 equivalents of $NH_3 \cdot H_2O$ using a combination of 10 mol % of CuBr and 20 mol % of ambidentate pyridyldiketones **L1**, **L2** or **L3** at 30 °C (Table 1). Bases such as Cs_2CO_3

and K_3PO_4 were tested with various solvents including DMF or DMSO (Table 1, entries 1-12). The majority of reactions studied in the presence of copper bromide and ligands **L1**, **L2** and **L3** occurred in high yields at this temperature and for the following of the study we used the couple DMSO/K_3PO_4 which allows whatever the ligand tested, the formation of the expected *p*-chloroaniline **2a** with excellent yields (Table 1 entries 10-12). Moreover DMSO and K_3PO_4 offer the advantage of being cheaper and less toxic than DMF and Cs_2CO_3. Noteworthy that decreasing reaction temperature to 25 °C slightly lowers the yield of **2a** (below this temperature the yields are very low).

We then explore the scope of this system in the best developed conditions (Table 1, entry 12). Combination of catalytic amounts of ligands **L1**, **L2** and **L3** and of CuBr allows the amination of various structurally distinct aryl iodides (Scheme 2).

Table 1: Amination of 4-chloroiodobenzene **2** using ligands **L1**, **L2**, **L3**.[a]

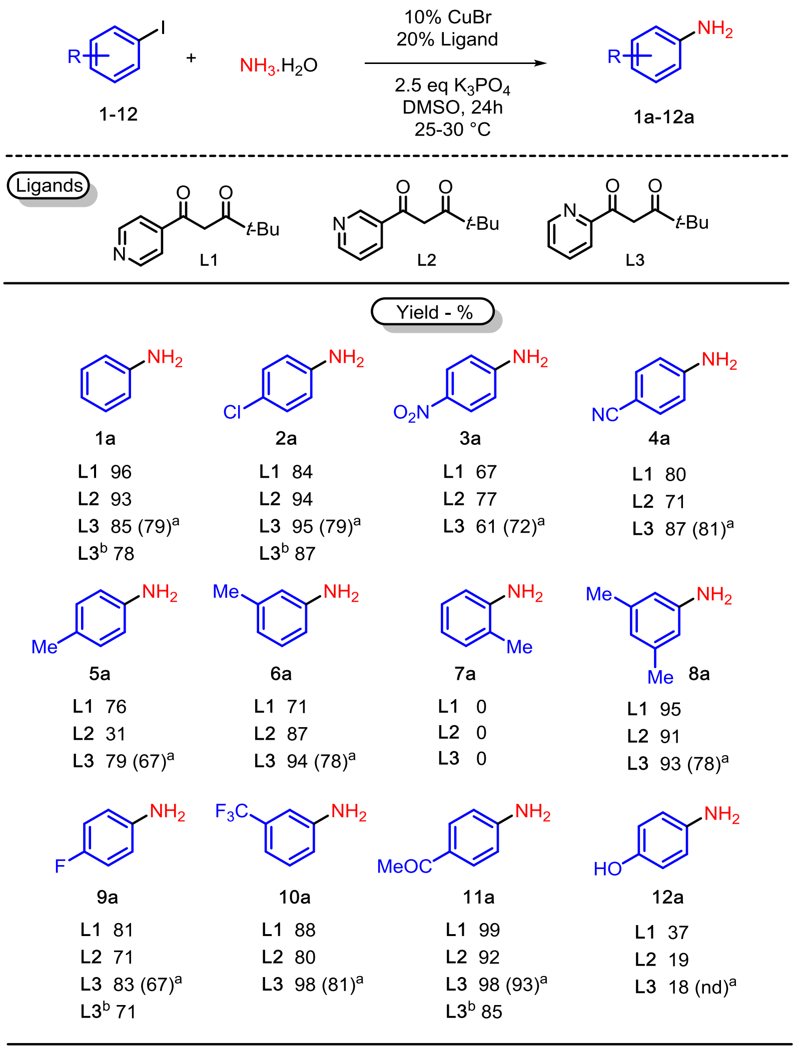


entry	Ligand	Base	Solvent	Yield[b]
1	L1	Cs_2CO_3	DMF	65
2	L2	Cs_2CO_3	DMF	66
3	L3	Cs_2CO_3	DMF	64
4	L1	Cs_2CO_3	DMSO	68
5	L2	Cs_2CO_3	DMSO	75
6	L3	Cs_2CO_3	DMSO	75
7	L1	K_3PO_4	DMF	22
8	L2	K_3PO_4	DMF	68
9	L3	K_3PO_4	DMF	71
10	L1	K_3PO_4	DMSO	84
11	L2	K_3PO_4	DMSO	94
12	**L3**	**K_3PO_4**	**DMSO**	**95 (87)[c]**

[a] Reaction conditions: **2** (0.5 mmol), $NH_3 \cdot H_2O$ (2.5 mmol), base (1.25 mmol), 10 % mol CuBr, 20 % mol ligand were placed in a screw tube under argon in solvent for 24 h at 30 °C. [b] NMR yields using 1,3,5-

trimethoxybenzene as internal standard. [c] Reaction performed at 25°C.

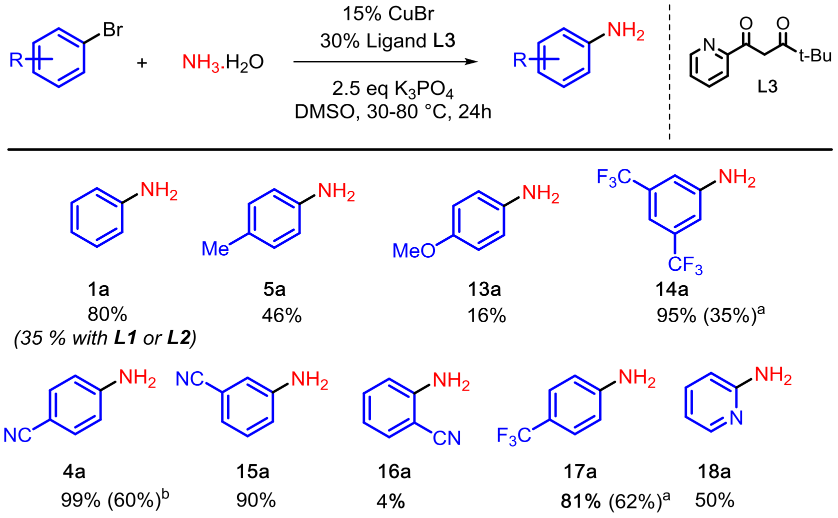
Aniline **1a** was obtained in excellent yields whatever the ligand used (respectively 96%, 93% and 85% with ligands **L1**, **L2** and **L3**). In many other cases, reactions in the presence of CuBr and ligand **L3** appeared to be the highest yielding with a large scope of substrates bearing electrodonating (ED) or electrowithdrawing (EW) groups. For instance, 4-chloroaniline **2a**, 4-cyanoaniline **4a**, 4- and 3-tolylaniline **5a** and **6a**, 4-fluoroaniline **9a**, 3-trifluoromethylaniline **10a** and 4-aminoacetophenone **11a** were obtained in good to excellent yields in the presence of this ligand. However, some limitations were observed when hindered 2-methyliodobenzene **7** and 4-iodophenol **12** were engaged.



Scheme 2: Copper-catalyzed amination of ArI at 30 °C. [a] Isolated yields. [b] Reaction performed at 25 °C.

It may be noted that some tests with **L3** conducted at 25 °C gave good but lower yields for **1a**, **2a**, **9a** and **11a** (ranging between 71 and 87% yields – Scheme 2), this reaction temperature constituting the limit below which the yields the yields are very low.

In a second part of this study we focused our attention on arylation of aqueous ammonia with more challenging aryl bromides. The latter are less reactive electrophiles but are more attractive in terms of availability and prize compared to their iodides homologs. To further this study, we tested the activity of ligands **L1**, **L2** and **L3** under different conditions. After optimization we observed that 15 mol % of CuBr and 30 mol % of **L3** represented the best combination to reach the best yield for **1a** at 80 °C. These conditions were kept to perform reaction with different aryl bromides (Scheme 3). Aryl bromides bearing electron-withdrawing groups afforded the corresponding anilines in high yields at 80 °C (**4a**, **14a**, **15a**, **17a**) and with lower yields at 30-40°C (up to 62 % - **4a**, **17a**). Aryl bromides substituted by donor groups gave the corresponding aminated product (**5a**, **13a**, **18a**) in moderate to poor yields (respectively in 46%, 16% and 50 %). It should be noted that whatever the reaction conditions tested with aryl bromides (copper loading, Cu/Ligand ratio, reaction temperature) the ligand **L3** was much more efficient than **L1** and **L2** (see Scheme 3 and Table S1 in supporting information). That was not the case from aryl iodides for which only a slightly higher efficiency was observed with **L3**.



Scheme 3: Copper-catalyzed amination of ArBr at 80 °C. [a] At 30 °C. [b] At 40 °C.

A mechanism involving the generation of an anionic copper(I) by reaction of an in situ formed Cu^I(pyridyldiketone) complex with the N-nucleophile in the presence of a base could be proposed.[14] The reaction of the latter with the aromatic halide would lead to a new copper (III) species (ligand)Cu^{III}(Ar)-Nu, from which the cross-coupling product would be formed via reductive elimination. The positive effect of ligand **L1-L3** might be linked to the presence of two distinct donor sites (*i.e.* anionic *β*-diketonate and neutral pyridine). The higher efficiency of ligand **L3**, particularly illustrated in the case of reactions performed with aryl bromides, could be connected to a possible simultaneous chelation of its two donor sites on the same metallic center.

In conclusion, we have developed a catalytic system based on copper and a set of ambidentate pyridyldiketone ligands for amination of aryl iodides and bromides with aqueous ammonia. The accessibility of the pyridyldiketones make this method easy to perform in one of the mildest temperature conditions described in the literature. At this stage it is difficult to understand the relationship between the structure of the ligand and the reactivity observed. Work is now in progress to better identify a potential correlation and to understand the mechanism.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgements

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