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Ligandless Copper-Catalyzed Coupling of Heteroaryl Bromides with Gaseous Ammonia

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Abstract: A range of different N- and S-containing heterocyclic bromides can be efficiently coupled with gaseous ammonia in the presence of copper(II) acetylacetonate [Cu(acac)$_2$] as catalyst and in the absence of additional ligands. Unstable aminothiophenes and aminobenzothiophenes can be further reacted *in situ* to afford functionalized derivatives.

Keywords: amination; catalysis; copper; cross-coupling; heterocycles

Ammonia represents one of the cheapest and most abundant sources of nitrogen available, with current worldwide production being estimated at 10^8 ton/year.[1] Although ammonia is massively employed in the chemical industry for the production of fertilizers and basic chemicals, the harsh reaction conditions entailing the requirement of special handling apparatus have precluded its use in fine chemical synthesis.[2]

In this respect, cross-coupling chemistry constitutes a field of major challenge.[3] Despite notable achievements in the area of palladium-catalyzed coupling of aryl halides with amines[4] that granted this methodology the limelight in both academy and industry,[5] its translation to ammonia has long remained out of reach. It was only in 2006 that Hartwig and co-workers reported the first efficient catalytic system tackling this challenging reaction,[6] followed by only few other reports.[7]

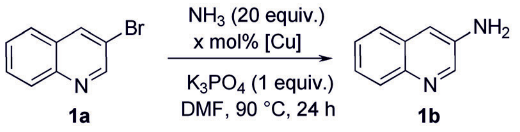
On the other hand, the ability of copper in promoting reactions of ammonia with aryl halides has been known since the beginning of the last century.[8] Remarkably, the introduction of supporting ligands has recently allowed the copper-catalyzed coupling of ammonia with aryl iodides[9] and bromides[10] to be accomplished under mild conditions.[11] However, the need of high amounts of ligand (up to 40 mol%) brings noticeable disadvantages in terms of cost, purification and waste production, important aspects especially in industrial settings. Not surprisingly, the development of ligandless systems has proved even more problematic.[12]

Another major issue is represented by the reactivity of heterocyclic substrates, essential building blocks in pharmaceuticals, agrochemicals and optoelectronics.[5b,13] Heteroaromatic halides are notoriously challenging coupling partners; coordination of the heteroarenes to the metal center through the heteroatom has been suggested to be at the origin of their sluggish reactivity.[14] Lang and co-workers reported a system for the coupling of various bromo- and chloropyridines and of 2-bromothiazole employing only 0.5 mol% of Cu_2O in ethylene glycol.[12c] Unfortunately, yields and selectivities were hampered by the competing ethylene glycol attack on the aryl halides, a side reaction that gave rise to up to 25% of by-product. Fischmeister et al. described the amination of 2-bromopyridines in the presence of 5 mol% Cu_2O and 10 mol% of dimethylethylenediamine (DMEDA) as ligand.[10d] Besides these two reports, only scattered examples of heteroaromatic substrates can be found in the literature; a general catalytic system able to couple ammonia with different types of heteroaryl halides is still lacking. In this report, we start filling this gap and describe an efficient ligandless copper-based catalytic system for the coupling of a wide range of heteroaryl bromides.

Aqueous solutions of ammonia, thanks to their user friendliness, have become the reagent of choice in copper-catalyzed coupling reactions. Nevertheless, it has been shown that, under basic aqueous conditions, formation of possibly insoluble copper hydroxo-complexes takes place.[15] Moreover, scrambling between water and ammonia in the metal coordination sphere may give rise to the various $[Cu(H_2O)_n(NH_3)_{x-n}]^{+/++}$ species.[16] Despite the fact that, due to the lack of specific studies, nothing can be inferred on the catalytic activity/inactivity of these copper compounds, it is clear that the presence of several species at equilibrium can increase the chances of unproductive reaction pathways.[17] In this view, gaseous ammonia seemed to us a better suited reagent for the challenging coupling with heterocyclic partners. We speculated that in the absence of any ancillary ligand an excess of ammonia would be beneficial to both stabilize the copper and disfavour the coordination of the substrate through its heteroatom.

We started our investigation by determining the optimal copper source for the coupling of 3-bromoquinoline **1a** with 3 mol% catalyst loading (Table 1). The reactions were set up in an autoclave to which ammonia was transferred from a gas tank (9 bar pressure), the loaded mass being determined by weight difference of the autoclave itself. Among the various copper salts tested we found that $Cu(acac)_2$ (acac = acetylacetonate)[18] gives the best result (entry 6). Full conversion is achieved by increasing the amount of $Cu(acac)_2$ to 5 mol%, thus leading to 86% yield of **1b** (entry 8). No conversion is observed in the absence of a copper source (entry 7).

Table 1. Reactivity of various copper sources in the coupling of 3-bromoquinoline with ammonia.[a]

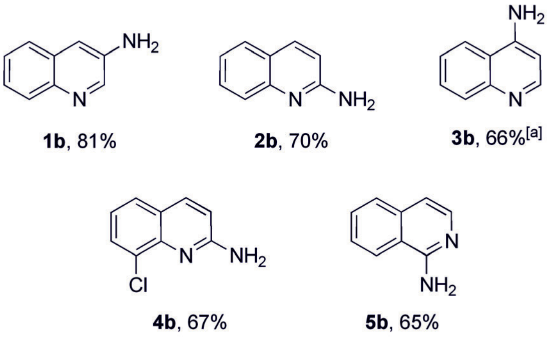


Entry	Cu source	x mol%	Conv. [%][b]	Yield [%][b]
1	$Cu(OAc)_2$	3	1	1
2	$CuBr_2$	3	32	n.o.
3	CuBr	3	76	73
4	CuI	3	72	70
5	Cu_2O	3	40	37
6	$Cu(acac)_2$	3	82	79
7	–	–	<1	n.o.
8	**$Cu(acac)_2$**	**5**	**>99**	**86**

[a] Table [**1a**] = 1 M in DMF.

[b] GC values based on naphthalene as internal standard.

Under the same reaction conditions various bromoquinolines can be coupled with ammonia (Figure 1). The presence of an additional chlorine substituent[19] in 2-bromo-8-chloro-quinoline **4a** does not affect the outcome of the reaction, allowing the isolation of **4b** in 67% yield. Aminoisoquinoline **5b** can be also synthesized in satisfactory yields.



[a] 10 mol% $Cu(acac)_2$.

Figure 1. Scope of the copper-catalyzed coupling of ammonia with bromoquinolines and -isoquinolines. *Reaction conditions:* 5 mol% $Cu(acac)_2$, K_3PO_4 (1 equiv.), NH_3 (20 equiv.), [substrate] = 1 M in DMF, 90 °C, 24 h. Conversion: ≥95% with all substrates. Yields are of isolated material.

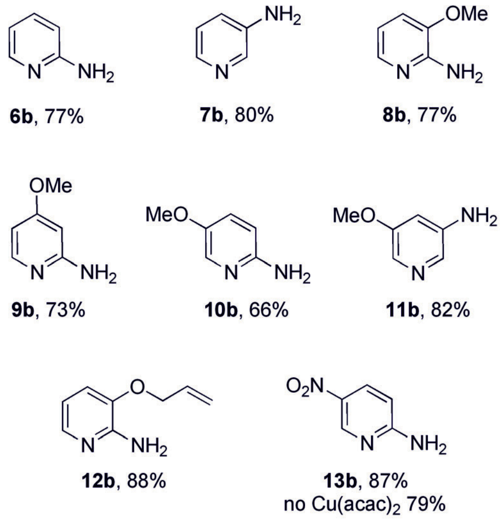
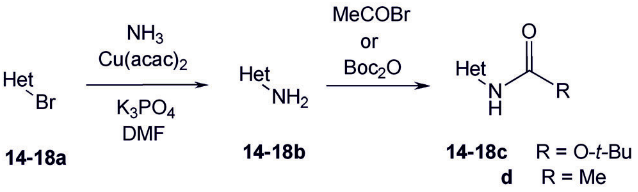
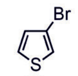
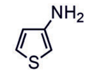
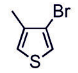
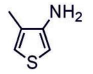
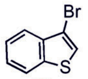
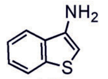
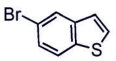
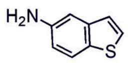
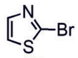
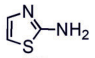


Figure 2. Scope of the copper-catalyzed coupling of ammonia with bromopyridines. *Reaction conditions:* 5 mol% $Cu(acac)_2$, K_3PO_4 (1 equiv.), NH_3 (20 equiv.), [substrate] = 1 M in DMF, 90 °C, 24 h. Conversion: ≥95% with all substrates. Yields are of isolated material.

Likewise, bromopyridines undergo the amination reaction smoothly (Figure 2). Remarkably, substrates containing a methoxy group – which is considered as deactivating – are effectively coupled without complication regardless of the position of the substituent. Moreover, the present catalytic system is compatible with a rather sensitive group such as an allylic ether: 3-allyloxy-2-aminopyridine **12b** can be synthesized in 88% yield. It is worth mentioning that the so far only reported approach to **12b** – the allylation of the corresponding aminohydroxypyridine – suffers from low yields, very likely as the result of the competing formation of *N*-allyl by-products.[20] Not surprisingly, the presence of the strong electron-withdrawing nitro group triggers the formation of 2-amino-5-nitropyridine **13b** also in absence of $Cu(acac)_2$ (79% *vs.* 87% yield). Notably, the reactions of 2-bromo-4-nitropyridine and 5-bromo-2-nitropyridine show very low se-

Table 2. Copper-catalyzed coupling of ammonia with S-containing heterocycles.[a]



Entry	Substrate a	T [°C]	Product b	Yield[b] b	Yield[c] c/d
1	 14a	90	 14b	78%	59% **14c**
2	 15a	90[d,e]	 15b	64%	48% **15c**
3	 16a	70[e]	 16b	75%[f]	70% **16d**
4	 17a	90	 17b	74%[g] 87%[h]	57% **17c** 67% **17d**
5	 18a	25[e]	 18b	82%	77% **18c**

[a] *Reaction conditions:* 10 mol% Cu(acac)$_2$, K$_3$PO$_4$ (1 equiv.), NH$_3$ (20 equiv), [substrate] = 1 M in DMF, 24 h. Conversion: ≥95% with all substrates.
[b] GC yield based on naphthalene as internal standard.
[c] Yields of isolated materials.
[d] 20 mol% Cu(acac)$_2$.
[e] 48 h.
[f] NMR yield, toluene as internal standard.
[g] 85% conversion.
[h] 30 equiv. NH$_3$, 99% conversion.

lectivity towards the desired amino products both in the presence and in the absence of Cu(acac)$_2$.[21]

Next, we examined the reactivity of sulfur-containing heterocycles (Table 2). Aminothiophenes and aminobenzothiophenes are important scaffolds in medicinal chemistry[22] and have recently gained attention also in material science.[23] Despite the straightforward availability of 2-amino derivatives prepared by the Gewald reaction,[22c] access to the 3-amino analogues is more problematic. Indeed, the established synthetic approaches are often hampered by the cost and availability of the required starting materials, or by the overall low yields obtained as the consequence of multi-step routes.[22a,b] In this respect, bromo-heterocycle precursors are usually inexpensive and available in kg quantity such that their direct amination would represent a straightforward approach to the target amino compounds.

Simple aminothiophenes and aminobenzothiophenes are known to be unstable compounds, being prone to oxidation and oligomerization. They are usually isolated as salts or, in multistep synthesis, subjected directly as crude product to the next reaction step.[24]

In order to further test the synthetic utility of the present methodology, we investigated the *in situ* conversion of the aminothiophene and aminobenzothiophene products into their *tert*-butoxycarbonyl (Boc) or acetyl compounds.[25] 3-Aminothiophenes **14b** and **15b** are isolated in satisfactory yields as their Boc derivatives (entries 1 and 2), although the presence of a methyl group in **15a** requires the catalyst loading to be increased to 20 mol% to entirely consume the starting material. Aminobenzothiophenes **16b** and **17b** can be isolated as the corresponding acetamides in 67% and 70% yields, respectively (entries 3 and 4), yet for substrate **17a** 30 equivalents of ammonia are needed to reach full conversion.[26] It is worth mentioning that 5-aminobenzothiophene **17b** is typically synthesized by reduction of the corresponding nitro derivative.[24f,27] However, concerns about the formation of possible genotoxic intermediates (nitroso, azoxy and hydroxylamine derivatives) that might contaminate the final product, have made this methodology less appealing to the pharmaceutical industry.[28] The present catalytic system represents thus a highly sought alternative to this class of reactions. Finally, 2-bromothiazole **18a** can be coupled at room temperature in 82% yield and can be isolated as Boc-protected amine **18c** in 77% yield (entry 5). Remarkably, since 2-bromothiazole is a heat-sensitive compound (storage temperature: 2–8 °C), the key to the high yielding coupling is the possibility to perform the reaction at room temperature.

In summary, we have developed an efficient, ligandless, copper-catalyzed coupling of ammonia with N- and S-containing bromo-heterocycles. A wide range of bromopyridines and bromoquinolines can be efficiently coupled regardless of the position of the reactive halogen in the aromatic ring. The unstable aminothiophenes and aminobenzothiophenes are formed with good chemoselectivities and can be further transformed *in situ* into their Boc or acetyl derivatives in good yields, supporting the synthetic usefulness of the present methodology. Lastly, we would like to point out that the apparatus required to perform the described coupling – an autoclave and a gas tank – are the same as those used for hydrogenation reactions, a standard technology by now in most academic and industrial laboratories.[29] We are thus confident that – simple and efficient catalytic systems becoming more and more available – the use of gaseous ammonia will no longer be hampered by technical issues.

Experimental Section

General Procedure for the Amination of Aryl Bromides 1a–13a

A 35-mL glass-lined stainless steel autoclave (Premex reactor AG) was charged with the aryl bromide (if solid, 5 mmol, 1 equiv.), K_3PO_4 (1.06 g, 5 mmol, 1 equiv.) and Cu(acac)$_2$ (65.5 mg, 0.25 mmol, 0.05 equiv.). The autoclave was introduced into a glovebox where dry and degassed DMF (5 mL) and the aryl bromide (if liquid) were added. After closing, the autoclave was charged out of the glovebox with ammonia (1.7 g, 20 mmol, 20 equiv.) and the reaction mixture was stirred for 24 h at 90 °C. The autoclave was allowed to cool down to room temperature, then the ammonia was released into the fume hood by opening the autoclave valve. The autoclave was then opened and the reaction mixture was filtered over celite. The conversion of the reaction was determined by the appropriate analytical method and the filtrate was concentrated under reduced pressure (20 mbar). The crude product was purified by chromatography. Specific procedures and characterization data are available in the Supporting Information.

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[25] Some publications on copper-catalyzed coupling of ammonia reported the isolation of 3-aminothiophene in high yields (refs.[9a,10h,10i]). Attempts to reproduce the described isolation and purification procedures failed in our hands.

[26] We have not been able to isolate the Boc-protected 3-aminobenzothiophene **16c** due to its decomposition during purification.

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