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Homogeneous Catalysis (2)

A Very Simple Copper-Catalyzed Synthesis of Anilines by Employing Aqueous Ammonia**

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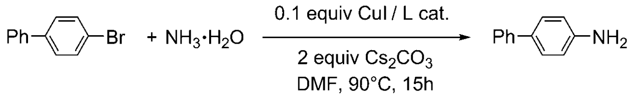
Ammonia is one of the most abundant and least expensive synthetic inorganic chemicals.[1] It is made industrially from dinitrogen and dihydrogen under harsh conditions (up to 550 °C and 350 atm) by the catalytic Haber–Bosch process.[2] Production, which requires 1 % of the energy consumed annually by humans, reaches 10^8 tons per annum.[3,4b] This scale is equivalent to that of the biological reduction of dinitrogen to ammonia by nitrogenase enzymes, which represents the main source of nitrogen for living organisms.[4] Ammonia is also the common nitrogen source for the industrial production of fertilizers and organic amino compounds.[1] It is therefore evident that the development of new processes that use NH_3 as a feedstock constitutes a very important research target. Activation of N–H bonds by transition metals or singlet carbenes has attracted increasing attention, but remains difficult.[5,6] The other way to activate NH_3 involves the well-known formation of Lewis acid/base adducts between transition metals and ammonia (Werner-type complexes). However, catalytic reactions that consume NH_3 are extremely rare.[7] One such reported example of copper-catalyzed amination of aryl halides suffers from several drawbacks: reactions are performed under pressure (3–4 bars) using liquid ammonia and activated aromatic or heteroaromatic bromides; moreover, the method encounters problems with selectivity because of competitive C–O arylation of the ethylene glycol solvent.[8] Recently, the palladium-catalyzed amination of non-activated aryl halides with ammonia has been reported by Shen and Hartwig[7] as well as by Surry and Buchwald[9] in which bulky ferrocene or electron-rich phosphine ligands were used.[10] These methods provide an interesting route to anilines, which are key intermediates in aromatic processes[1,11] and can be carried out without the ammonia surrogates traditionally required with palladium catalysts.[12] Here too there are drawbacks: the necessary use of ammonia pressure in one of the two methods (5–6 bars),[7] as well as the use of strong bases, a toxic and expensive metal, and sophisticated supporting ligands. During the submission process, a copper–L-proline catalyzed arylation of NH_4Cl or aqueous NH_3 was reported. The system is very efficient for aryl iodides, but the only example involving more challenging non-activated aryl bromides shows low reactivity even in the presence of 20 % of CuI at 80 °C.[13]

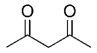
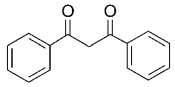
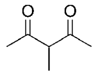
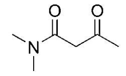
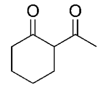
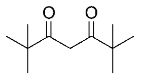
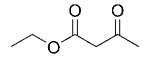
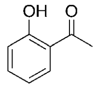
As part of our studies on the copper-catalyzed arylation of nucleophiles,[14] we now report that the amination of both activated and unactivated aryl and heteroaryl bromides and iodides can be achieved under very mild conditions by using aqueous ammonia (a convenient and cheap source of NH_3) in a catalytic system in which the less toxic and inexpensive metal copper is used together with simple diketone ligands.[15]

We initially selected 4-bromobiphenyl as a model substrate for optimization of the reaction conditions. In our preliminary studies we were pleased to find that, with DMF as the solvent, this aryl bromide can be successfully coupled with $NH_3{\cdot}H_2O$ at 90 °C in the presence of catalytic amounts of CuI and the ligand 2,4-pentadione (**1**) to afford 4-aminobiphenyl in a yield of 76 % (Table 1, entry 1).

It is worth noting that the reaction is carried out at approximately atmospheric pressure (1.3 bars), which permits

Table 1: Amination of 4-bromobiphenyl using diketone ligands L.[a]



	Ligands L		Yield [%][b]	Selectivity [%][c]
1		**1**	76	92
2		**2**	24	92
3		**3**	7	–
4		**4**	29	91
5		**5**	35	99
6		**6**	79	99
7		**7**	7	–
8		**8**	0	–

[a] L (0.6 equiv) and commercial 28 % aqueous NH_3 (5 equiv) were used. [b] GC yield determined with 1,3-dimethoxybenzene as an internal standard. [c] Selectivity/C–C coupling between L and 4-bromobiphenyl.

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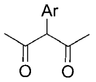
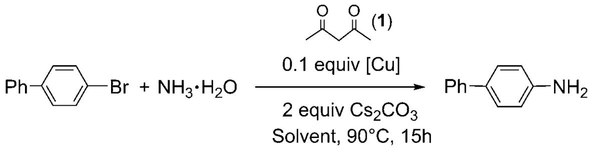
Supporting information for this article (general procedures for the isolation and full characterization of all the aniline derivatives) is available on the WWW under http://dx.doi.org/10.1002/anie.200802569.

the use of common glass reactors. Concerning the selectivity, no trace of di- or triarylamines—by-products frequently formed with palladium catalysis—was observed. However, small amounts of the C–C coupling product (ca. 5 %), resulting from arylation of the diketone, was detected (see above structure).



We then tested other diketone ligands, and observed that **1** gives yields almost as high as the electron-rich, but more expensive 2,2,6,6-tetramethyl-3,5-heptanedione (**6**). All other ligands tested (Table 1, entries 2–5, 7, and 8) gave only poor yields. The relationship between the structure of the ligand and reactivity is still not clear. We presume that there is a compromise between the solubility of the ligand in the water phase and its electron-donating ability, which may explain the similar yields observed in the presence of ligands **1** and **6** (the former is more soluble in water but less electron-donating than the latter). We presume that the low reactivity observed with ligands **3** and **5** results from the presence of a substituent in the middle position of the diketone. Several copper sources were screened using the same model substrate and supporting ligand **1**.[16] The presence of copper, ligand, and base are all necessary in this protocol (Table 2, entries 1–3). Different forms of Cu (oxidation state 0, I, or II) gave quite similar results (63 to 79 % yield of product) in the presence of 0.6 equivalents of **1** (Table 2, entries 4–8), or with 0.4 equivalents of **1** in the case of $[Cu(acac)_2]$ (Table 2, entry 10). By a systematic variation of the reaction parameters we were able to establish a protocol that permitted the amination of 4-bromobiphenyl with ammonia in excellent yield. Of the solvents, bases, additives, and copper sources tested (Table 2), DMF, caesium carbonate, $[Cu(acac)_2]$ (10 %), and ligand **1** (0.4 equiv) were found to be the best combination (93 % yield of 4-aminobiphenyl; Table 2, entry 18). It is noteworthy that the key factor for the success of our system is its biphasic character.[17] On heating, two phases are present and this seems necessary, as attested to by the absence of reactivity in either neat water (Table 2, entry 14) or neat DMF saturated with NH_3 (Table 2, entry 15). We can reasonably assume that the reaction takes place in the organic phase and that the aqueous phase plays the role of a reservoir for NH_3 (which is only sparingly soluble in DMF) and copper complexes such as $[Cu(NH_3)_4]^{2+}$. These observations are very preliminary, but work is currently in progress to better understand how this biphasic catalytic system functions.

Table 2: Amination of 4-bromobiphenyl using various copper sources (0.1 equiv) in the presence of supporting ligand 2,4-pentadione (**1**).[a]



	[Cu]	Ligand **1** (equiv)	Solvent	Yield [%][a]
1	–	0.6	DMF	0
2	CuI	–	DMF	0[b]
3	CuI	0.6	DMF	2[c]
4	CuI	0.6	DMF	76
5	Cu	0.6	DMF	68
6	CuO	0.6	DMF	79
7	$Cu(OAc)_2$	0.6	DMF	73
8	Cu_2O	0.6	DMF	63
9	$[Cu(acac)_2]$	–	DMF	23
10	$[Cu(acac)_2]$	0.4	DMF	76
11	$[Cu(acac)_2]$	0.4	DMSO	18
12	$[Cu(acac)_2]$	0.4	CH_3CN	34
13	$[Cu(acac)_2]$	0.4	NMP	50
14	$[Cu(acac)_2]$	0.4	H_2O	0
15	$[Cu(acac)_2]$	0.4	DMF	6[d]
16	$[Cu(acac)_2]$	0.4	DMF	45[e]
17	$[Cu(acac)_2]$	0.4	DMF	45[f]
18	$[Cu(acac)_2]$	0.4	DMF	93,[g] 20[h]

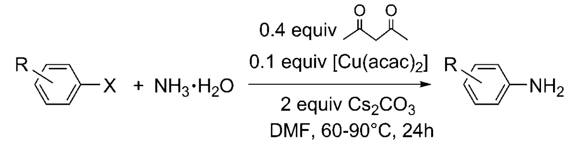
[a] GC yield determined using 1,3-dimethoxybenzene as an internal standard. [b] Same result at 140 °C. [c] Without base. [d] DMF presaturated with gaseous ammonia. [e] Addition of 0.5 equiv NBu_4Br. [f] K_2CO_3 was used instead of Cs_2CO_3. [g] Reaction time 24 h. [h] Reaction time 24 h, 3 % of $[Cu(acac)_2]$was used. acac = acetylacetanoate.

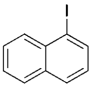
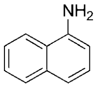
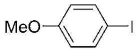
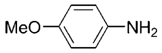
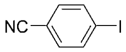
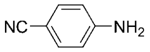
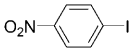
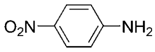
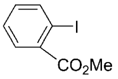
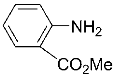
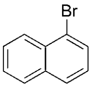
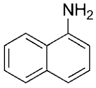
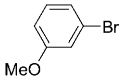
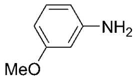
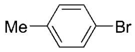
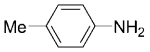
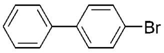
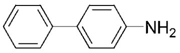
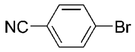
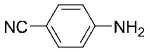
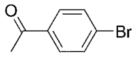
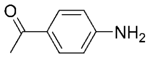
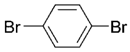
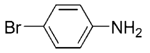
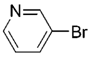
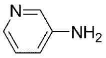
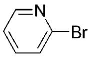
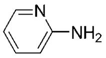
Next we explored the scope of this new method. Our catalytic system efficiently promotes cross-coupling reactions between aqueous ammonia and aryl iodides with either electron-donating or electron-withdrawing substituents (Table 3, entries 1–4) at 90 °C. The reaction is even possible at lower temperatures (60 °C) with activated substrates such as *p*-iodocyanobenzene (Table 3, entry 3).[18] A poor yield is obtained with 2-iodobenzoic ester because of partial hydrolysis of the ester group (Table 3, entry 5). Furthermore, the yield of the aniline derivative from the highly activated 4-nitroiodobenzene (63 %; Table 3, entry 4) was slightly lowered because of disubstitution at the nitrogen atom.

Although the aryl iodides are interesting substrates, we focused our attention on arylation with aryl bromides, which are less reactive electrophiles but of much greater interest for industrial applications. Our procedure is in this case also compatible with a wide range of substituents. Various aniline derivatives were obtained with both unreactive and reactive aryl bromides including PhBr, bromonaphthyl, 3-bromoanisole, 4-bromotoluene, 4-bromobiphenyl, 4-bromocyanobenzene, and 4-acetobromobenzene. In most cases, good to excellent yields of the isolated products were obtained when the reactions were carried out at 90 °C and, as in the case of the corresponding iodides, excellent yields were obtained even at 60 °C with activated aryl bromides (Table 3, entries 11 and 12). The reaction with the electron-rich 4-bromotoluene was slower, but the product could be isolated in good yield by extending the reaction time to 36 h (Table 3, entry 9). In the case of 1,4-dibromobenzene, 4-bromoaniline was isolated in only 41 % yield because of the formation of disubstituted product (Table 3, entry 13). We were successful in extending the procedure to include heterocyclic aromatic bromides (2- or 3-bromopyridines; Table 3, entries 14 and 15), which are important pharmaceutical intermediates.[19]

In conclusion, we have discovered a general, practical, economical, and efficient method for transforming aryl iodides and bromides into aniline derivatives in one step. This biphasic catalytic procedure is unusual, and work is currently in progress to elucidate exactly how it functions. The very low operational pressure allows this reaction to be performed without autoclaves, which are required for working with liquid ammonia, and this should be an enormous

Table 3: Copper/ligand-catalyzed amination of aryl halides.



	ArX	ArNH$_2$	Yield [%][a]
1			90
2			80
3			94,93[b] 99[c]
4			63
5			23
6	PhBr	PhNH$_2$	78
7			88
8			85
9			65, 79[d]
10			90,98[c]
11			92, 82[b]
12			92, 84[b]
13			41
14			84
15			82

[a] At 90°C (general case). [b] At 60°C. [c] At 90°C with ligand **6**. [d] Reaction time, 36 h.

advantage in terms of both cost and safety for scaling-up the process. The convenience of aqueous ammonia and low cost of the catalytic copper system make this method readily adaptable to production on an industrial scale, where safety and environmental factors are of particular concern. We believe that the simple procedure outlined here is extremely competitive with existing palladium-based catalysts and that it will be rapidly adopted in custom synthesis and industrial processes.[15]

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Keywords: amination · ammonia · anilines · copper · homogeneous catalysis

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[15] Our results, published in patent form in 2007, appear only now in the literature due to the time required for patent protection: Procédé de Synthèse d'arylamines, M. Taillefer, N. Xia, Fr 2007 06827 and PCT 2008 051701.

[16] Although slightly less selective than **6**, 2,4-pentadione (**1**) was chosen because it is about 200-times less expensive, an important factor from an industrial perspective.

[17] Under the conditions of Table 2, entry 18, the optimized ratio of DMF and aqueous ammonia is 20:3 by volume.

[18] Note that at 90°C the reaction is fully selective (99%) in the presence of supporting ligand **6** (Table 3, entries 3 and 10).

[19] An additional finding of our general study is that the demanding iron-mediated arylation of ammonia with aryl iodides can also be achieved. Preliminary results show that in a biphasic/[Fe(acac)$_3$] (0.2 equiv)/diketone **6** (0.8 equiv) system, the amination of iodobenzene with NH$_3$ is possible, although low yields of the aniline derivatives (20–30%) were obtained.[15]