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Copper-catalyzed arene amination in pure aqueous ammonia†

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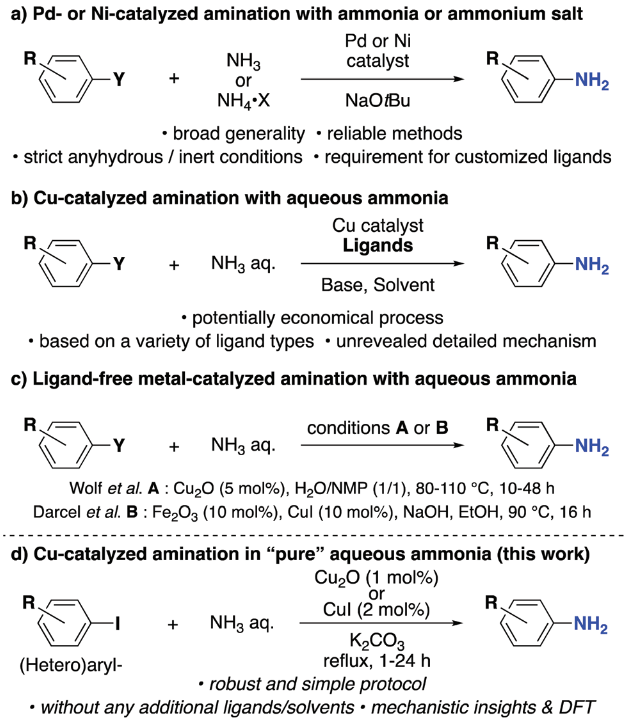
A simple protocol for copper-catalyzed arene amination using aqueous ammonia without any additional ligands and organic coordinating solvents has been developed. The reaction pathway *via* a Cu(I)/Cu(III) mechanism is proposed based on the results of control experiments as well as DFT calculations.

Ammonia is among the most abundant nitrogen sources, based on the established Haber–Bosch process. However, the direct use of ammonia in arene amination or Buchwald–Hartwig amination to afford primary arylamines has been rather limited.[1,2] This is mostly because the coordination of ammonia to transition-metals often forms inactive complexes due to the strong Lewis basicity. Its small size enables multiple coordination by filling the vacant sites. The strong N–H bonds of ammonia make the "N–H activation" difficult.[3] Moreover, the resultant monoarylamine is more reactive than ammonia to evoke unselective di- or triarylamine formation. Recently, Pd- or Ni-catalyzed amination reactions with ammonia or ammonium salts have been reported (Scheme 1a).[1,4] The key is the employment of customized ligands such as bulky phosphines and NHCs under anhydrous conditions.

Aqueous ammonia solution is a cost-effective reagent and easy to handle in the laboratory, even compared with ammonia gas, anhydrous ammonia solution, or its surrogates. While its use as a nitrogen source would make the process economical and user-friendly, the requirement of anhydrous and inert conditions in many transition-metal catalyses would not be suitable. In contrast, several Cu-catalyzed amination reactions of aryl halides using aqueous ammonia have been developed very recently (Scheme 1b).[1,5–7] The optimization of supporting ligands and the employment of coordinating solvents were important for the catalytic reactivity, since the stabilization of the copper center in the active species was crucial. For example, while high catalyst loadings were generally required in the copper system, Ma *et al.* reported that an optimized oxalamide ligand facilitates aryl amination with a low catalyst loading (0.01–0.5 mol% of Cu_2O).[6a] The ligand-free conditions were also reported using a coordinating solvent (NMP) or a bimetallic system (Scheme 1c).[6l,m] Herein, we describe arene amination using a catalytic amount of Cu_2O or CuI in "pure" aqueous ammonium solution without any


a) Pd- or Ni-catalyzed amination with ammonia or ammonium salt

• broad generality • reliable methods
• strict anyhydrous / inert conditions • requirement for customized ligands

b) Cu-catalyzed amination with aqueous ammonia

• potentially economical process
• based on a variety of ligand types • unrevealed detailed mechanism

c) Ligand-free metal-catalyzed amination with aqueous ammonia

Wolf *et al.* **A** : Cu_2O (5 mol%), H_2O/NMP (1/1), 80-110 °C, 10-48 h
Darcel *et al.* **B** : Fe_2O_3 (10 mol%), CuI (10 mol%), NaOH, EtOH, 90 °C, 16 h

d) Cu-catalyzed amination in "pure" aqueous ammonia (this work)

• *robust and simple protocol*
• *without any additional ligands/solvents* • *mechanistic insights & DFT*

Scheme 1 Metal-catalyzed arene amination using ammonia as a nitrogen source.

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† Electronic supplementary information (ESI) available: Experimental details, ^1H NMR spectra of known compounds, and computational details. See DOI: 10.1039/c8ob02708k

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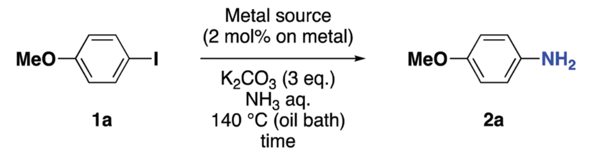
additional ligands and co-solvents (Scheme 1d). A variety of arylamines and heteroarylamines can be efficiently prepared using aqueous ammonia as a nitrogen source and K_2CO_3 as a base by a robust and simple protocol. The obtained mechanistic insights and results of DFT calculations are also presented.

In an aqueous ammonia solution, the multiple coordination of ammonia to the copper center[8] could be potentially beneficial at least in terms of stabilization, increased electron density for oxidative addition, and structural requirements of the amide complex for reductive elimination, even without supporting ligands and strongly coordinating organic solvents. Thus, we commenced our studies with the reaction of 4-iodoanisole (**1a**) using metal sources as a catalyst (2 mol% on a metal), K_2CO_3 as a base in aqueous ammonia solution (*ca.* 28%) after purging with N_2 (Table 1).[9] Using copper(I) iodide or copper(I) oxide as the copper source, the desired 4-methoxyaniline (**2a**) was obtained in 81 or 84% NMR yield (entries 1 and 2). While the use of copper(I) acetate gave similar results (77%, entry 3), the yield was drastically diminished (11%) when copper(II) acetate was used (entry 4). Other metal sources including $Pd(OAc)_2$, $CoCl_2$, $NiCl_2$, and $Mn(OAc)_3$ were ineffective (entries 5–8). The absence of a metal catalyst did not afford product **2a** (entry 9). Some ligand effects were examined (entries 10–12); PPh_3 and 1,10-phenanthroline did not show positive effects, and the use of **L1**[6b] gave similar reactivity. The chemical yield of **2a** was decreased under air (entry 13), and the reaction was retarded in the absence of K_2CO_3 (entry 14) and did not proceed at room temperature (entry 15). Using either copper(I) iodide or copper(I) oxide as a catalyst without any additional ligands, the reaction of **1a** was completed within 3 hours to afford the desired monoarylamine **2a** in an excellent yield (entries 16 and 17). The side reactions to afford the corresponding di- or triarylamine were not observed under these conditions.

With the optimized conditions in hand, the substrate scope of this reaction was investigated, as summarized in Table 2. **2a** was isolated in 89% yield. While copper catalysis is generally ineffective for sterically-hindered structures, *meta*- and *ortho*-substituted anisole derivatives **1b** and **1c** showed good reactivity. Not only electron-rich but also electron-deficient iodoarenes (**1e** and **1f**) were aminated well in good yield (>80%). The use of phenol and benzyl alcohol derivatives (**1g** and **1h**), both of which have free OH groups, was not a problem to give the desired anilines in 80 and 85% yields, respectively. The allyloxy group was tolerated, which may not be used in Pd-catalysis, and **2i** was obtained in 93% in 1 hour. Further, heteroaromatic

Table 1 Metal-catalyzed arene amination using aqueous ammonia as a nitrogen source



Entry	Metal source	Ligand	Time (h)	Yield[a] (%)
1	CuI	—	1	81
2	Cu_2O	—	1	84
3	CuOAc	—	1	77
4	$Cu(OAc)_2$	—	1	11
5	$Pd(OAc)_2$	—	1	0
6	$CoCl_2$	—	1	0
7	$NiCl_2$	—	1	0
8	$Mn(OAc)_3$	—	1	0
9	—	—	1	0
10	Cu_2O	PPh_3[b]	1	68
11	Cu_2O	1,10-Phen[b]	1	54
12	Cu_2O	**L1**[b]	1	84
13[c]	Cu_2O	—	1	45
14[d]	Cu_2O	—	1	14
15[e]	Cu_2O	—	23	0
16	CuI	—	3	Quant.
17	Cu_2O	—	3	96

[a] ^1H NMR yields using dimethylsulfone as an internal standard were noted. [b] 4 mol% of ligand was used. The structure of **L1** is shown. [c] The reaction was performed under air. [d] The reaction was performed in the absence of K_2CO_3. [e] The reaction was performed at room temperature.

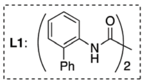
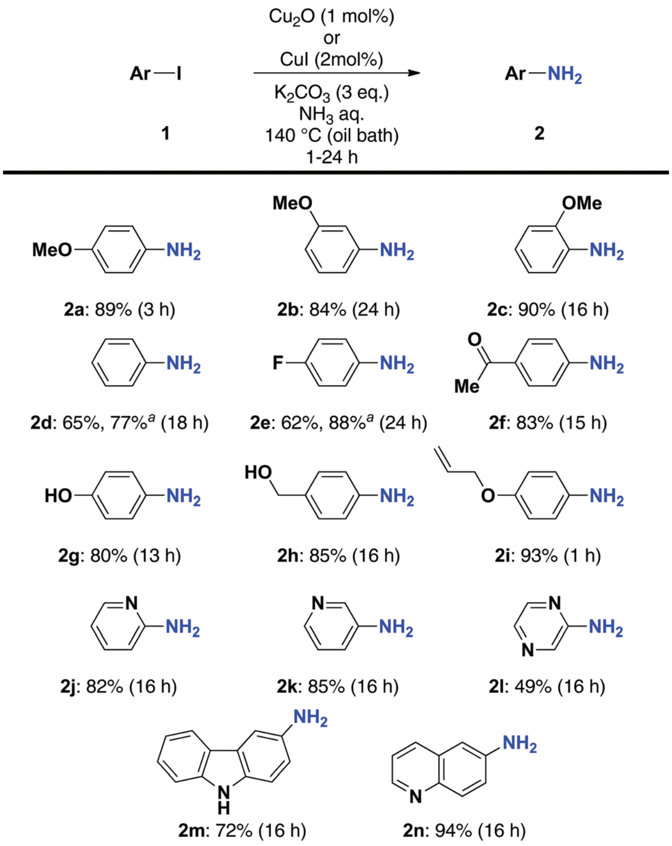


Table 2 Copper-catalyzed arene amination in pure aqueous ammonia as a nitrogen source



[a] ^1H NMR yields using dimethylsulfone as an internal standard were noted. These compounds are volatile.

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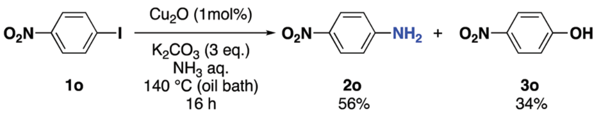
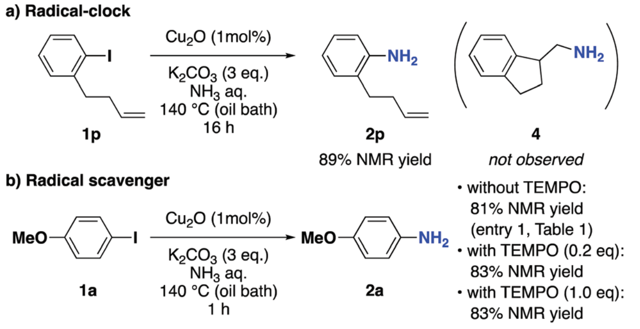
substrates can also be utilized, and mono-pyridyl and -pyrazinyl amines (**2j**, **2k**, and **2l**) were efficiently produced under identical conditions. Unprotected iodocarbazole with a free NH group was directly converted to the corresponding aniline **2m** in 72% yield. 6-Aminoquinoline (**2n**) was also obtained in 94% yield.

Regarding the side reactions, while the formation of di- or triarylamine was not observed, tiny amounts of corresponding phenol derivatives were generated, in particular with electron-deficient substrates. Thus, we examined the reaction of 1-iodo-4-nitrobenzene (**1o**) (eqn (1)), a highly electron-deficient substrate. Under the reaction conditions, the corresponding phenol **3o** was formed in 34% NMR yield, concomitant with the aniline **2o** in 56%. Given the substrate dependency, the decreased aniline formation using **1o** implied that the nucleophilic aromatic substitution (S_NAr) mechanism should not be operative in the present copper-catalyzed amination reaction.



(1)

Further mechanistic insights were obtained through control experiments. Given the results in Table 1, copper(I) species, rather than copper(II) complexes, should be involved in the catalysis. The involvement of a radical mechanism is unlikely, based on the radical-clock[10] and radical scavenger (TEMPO) experiments shown in Scheme 2. The cyclized product (*i.e.* **4**) was not observed in the reaction of **1p**,[6b] and the corresponding monoarylamine **2p** was generated in 89% NMR yield (Scheme 2a). The presence of a catalytic or stoichiometric amount of TEMPO did not affect the reaction outcome (Scheme 2b). From these results, the oxidative addition/reductive elimination mechanism *via* a Cu(I)/Cu(III) cycle[5b,11] can be reasonably proposed.



Scheme 2 Radical-clock and radical scavenger experiments of Cu-catalyzed amination in aqueous ammonia.

Then, we carried out preliminary DFT calculations on the reaction pathway at the ωB97X-D/SDD (for Cu and I) and 6-31+G* (for other atoms) levels of theory (Fig. 1). **INT_1** was used as the model starting complex for the oxidative addition based on the above-mentioned findings. The rather high activation energy for **TS_1** ($\Delta G^‡$ = +36.2 kcal mol^{-1}) is observed for the first oxidative addition, consistent with the requirement of a high reaction temperature (entry 15, Table 1). The stabilized amide complex **INT_4** was obtained after the deprotonation by K_2CO_3.[7] The reductive elimination to form a C–N bond under the present copper catalysis proceeded very efficiently *via* **TS_2** ($\Delta G^‡$ = +2.0 kcal mol^{-1}) to afford the aniline product in **INT_5**. In addition, the reductive elimination directly from the ammonia complex **INT_2** can also be postulated. The transition state **TS_{2b}** is located at a very high energy (+45.3 kcal mol^{-1} from **INT_1**), suggesting that the reaction should be retarded in

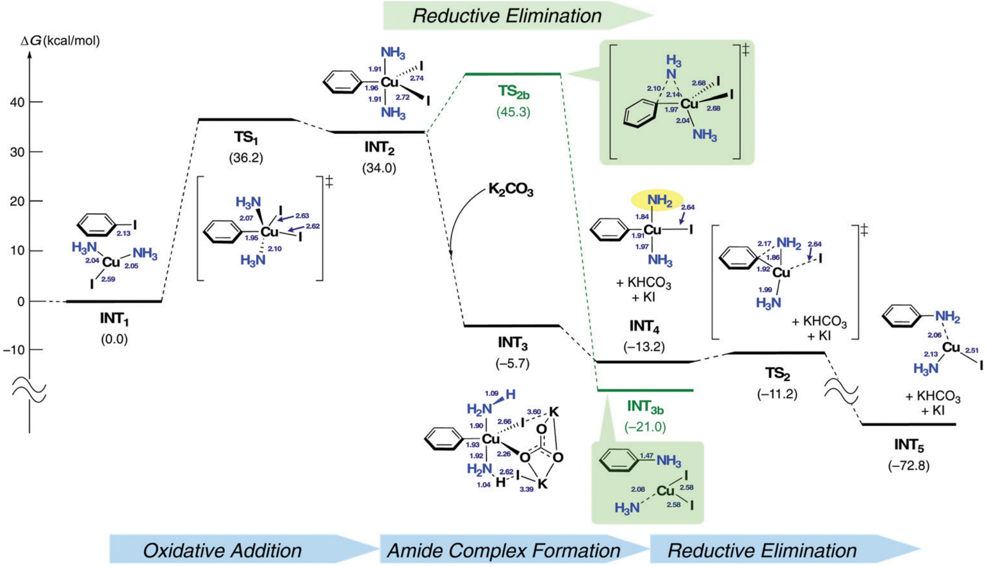


Fig. 1 DFT calculations for a model reaction with a Cu(I) complex. Energy changes and bond lengths at the ωB97X-D/SDD (for Cu and I) and 6-31+G* (for other atoms) levels of theory are shown in kcal mol^{-1} and Å, respectively. The green line represents a model reaction in the absence of a base.

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the absence of the base (entry 14, Table 1). While other possibilities (*i.e.* different mechanisms[5b,12] and numbers of ammonia ligands) are not completely excluded at this moment, the proposed mechanism should adequately represent the experimental results described above.

Conclusions

In summary, we have developed a simple protocol for copper-catalyzed amination reaction of aryl iodides using aqueous ammonia as a nitrogen source without any additional ligands and organic solvents. This catalytic system is composed of inexpensive reagents (Cu_2O or CuI, K_2CO_3, and aqueous ammonia), and applicable for various aromatic and heteroaromatic substrates. Some mechanistic insights were obtained and the reaction pathway *via* a Cu(I)/Cu(III) mechanism is proposed with the results of DFT calculations. We are conducting further investigations to expand the substrate scope, as well as to identify the precise reaction mechanisms by both theoretical and experimental ways.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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