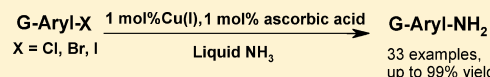


Copper(I)-Catalyzed Amination of Aryl Halides in Liquid Ammonia

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ABSTRACT: The amination of aryl halides in liquid ammonia (LNH₃) is catalyzed by a copper(I) salt/ascorbate system to yield primary aromatic amines in good to excellent yields. The low concentrations of catalyst required and the ease of product isolation suggest that this process has potential industrial applications. Commonly used ligands for analogous metal-catalyzed reactions are not effective. The rate of amination of iodobenzene in liquid ammonia is first order in copper(I) catalyst concentration. The small Hammett $\rho = 0.49$ for the amination of 4-substituted iodobenzenes in liquid ammonia at 25 °C indicates that the C–I bond is not significantly broken in the transition state structure and that there is a small generation of negative charge in the aryl ring, which is compatible with the oxidative addition of the copper ion being rate limiting.



INTRODUCTION

Primary aromatic amines are widely used in the manufacture of pharmaceuticals, agrochemicals, dyes, and polymers and thus are very important intermediates in the chemical industry.¹ Transition-metal-catalyzed C–N bond formation has become a powerful and reliable method for the synthesis of a variety of aromatic amines under mild and convenient conditions.² However, these metal-catalyzed reactions are rarely carried out directly with ammonia due to (i) the difficulty of forming the metal complexes without ammonia displacing the chelating ligands and thus causing the deactivation of the catalyst³ and (ii) the amination products potentially further reacting with the starting aryl halides, especially when the amination reactions are catalyzed by palladium complexes, to form di- and triarylamines as undesired byproduct in conventionally used solvents.⁴ Despite these disadvantages, as ammonia is one of the cheapest chemicals,⁵ extensive investigation of the metal-catalyzed direct amination of aryl halides using ammonia itself rather than ammonia surrogates^{2a,b,d,6} has been undertaken.⁷ Recent results have shown that using palladium or copper as metal catalysts with auxiliary chelating ligands for the amination of aryl halides with ammonia in conventional solvents is promising. However, the use of expensive palladium catalysts and toxic ligands, the formation of di- and triaryl amines as byproduct, the need to incorporate a deprotection step in the overall transformation for those reactions involving ammonia surrogates, which is not an atom economic process, and the relatively high loading of copper catalyst, etc. are all barriers yet to be overcome.^{4b,8}

We have been trying to combine the unique solvent properties of liquid ammonia⁹ and the potential benefit of using ammonia as an environmentally friendly direct nitrogen source to realize a number of amination reactions in liquid ammonia. Ideally, this would be under catalytic conditions and would be applicable to a range of reactions, such as the reductive amination of ketones and the direct amination of aryl halides; herein we report on the latter.

RESULTS AND DISCUSSION

Copper(I)-Catalyzed Amination of Aryl Iodides. Aryl iodides are stable in liquid ammonia at room temperature for days; however, in the presence of a catalytic amount copper(I) salt, iodobenzenes react with ammonia smoothly to give the corresponding anilines with good to excellent yields (Scheme 1,

Scheme 1

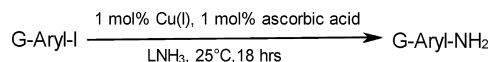


































Table 1). No further coupling reactions between starting iodobenzenes and product anilines are observed. Presumably, the product anilines are unable to compete with ammonia in forming the necessary complexes with copper ion due to the high effective concentration (ca. 35.5 M at 25 °C) and nucleophilic properties of liquid ammonia. Upon optimization of the reaction conditions, it was found that the copper(I)-catalyzed amination of iodobenzene in liquid ammonia at room temperature requires only 1 mol % copper catalyst, which is lower than that generally reported.¹⁰ Also the reaction does not require the presence of a strong base, such as *tert*-butoxide, which is widely used in similar reactions in conventional solvents. Furthermore, the product separation is much easier with liquid ammonia as reaction medium, as the product can be simply collected after the evaporation of ammonia.

Given the high yields and fixed reaction time, this data is not a clear indicator of the effect of substituents although the yields appear to be independent of the position of the substituent relative to the iodo group, for example, 3-nitro- and 4-nitroiodobenzene give similar yields under same reaction conditions (Table 1, entries 4 and 5). Some heterocyclic iodides can also be converted to corresponding amines with excellent yields (Table 1, entries 9 and 15), which are much

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Table 1. Amination of a Variety of Aryl Iodides with Copper(I) Iodide (1 mol %) and Ascorbic Acid (1 mol %) in Liquid Ammonia at Room Temperature^a

entry	substrate	product	yield(%)
1			97
2			95
3			97
4			99
5			98
6			98
7			91
8			98
9			97
10			97
11			96
12			99
13			77 (94 ^b)
14			57
15			99
16			98

^aGeneral conditions, except otherwise noted: 1 mmol of iodobenzene, 1 mol % of CuI, 1 mol % of ascorbic acid, and 1 mL of liquid ammonia at room temperature for 18 h. ^b36 h.

higher than those previously reported for similar reactions in aqueous ammonia solution.^{7c,10c} Amination occurs preferentially with iodide as the leaving group compared with other halogen substituents (Table 1, entries 3, 12, and 16), but a lower yield is observed when the other ring substituent is hydroxyl (Table 1, entry 14) or amino, although the latter gives an excellent yield after a longer reaction time (Table 1, entry 13). The palladium-catalyzed amination of aryl halides that contain free NH or OH groups is also problematic.¹¹ A yield of 62% has been reported for the copper(I)-catalyzed (5 mol %) amination of 4-iodoaniline by benzylamine in 2-propanol, after 38 h at 90 °C.¹² To our knowledge, there has been no previous report of the metal-catalyzed direct amination of iodophenols.¹³

Different copper(I) salts can be used to catalyze the amination of iodobenzene in liquid ammonia, and the yields appear to be independent of the source of copper(I) (Table 2, entries 1–4). However, copper(II) salts show no catalytic activity in liquid ammonia, but they can be active in the presence of 2 equiv of ascorbic acid (Table 2, entries 5 and 6). Presumably, copper(II) is reduced to an active copper(I) species by the ascorbic acid.¹⁴ The stability of Cu(I) relative to Cu(II) is very dependent on the solvent, so for example, Cu(I) is more stable than Cu(II) in acetonitrile and the tetrahedral ion [Cu(MeCN)₄]⁺ is well-established (Table 2, entry 4). Under similar conditions, copper(0) shows reasonable catalytic ability, even though the reaction conditions are apparently heterogeneous in liquid ammonia (Table 2, entry 7).

Table 2. Amination of Iodobenzene with Various Copper Salts As Catalyst in Liquid Ammonia at Room Temperature^a

entry	copper(I) salt	yield (%) ^b
1	CuI (99.999%)	97
2	CuCl (99%)	97
3	CuOAc (97%)	98
4	Cu(CH ₃ CN) ₄ BF ₄ (97%)	99
entry	copper(II) salt	yield (%)
5	Cu(OAc) ₂ (98%) ^c	trace
6	Cu(OAc) ₂ (98%) ^d	95
entry	copper(0)	yield (%)
7	copper powder	88.4

^aReaction conditions: 1 mmol of iodobenzene, 1 mol % of copper catalyst, 1 mol % of ascorbic acid, and 1 mL of liquid ammonia at room temperature for 18 h. ^bGC yields. ^cIn the absence of ascorbic acid. ^d2 equiv of ascorbic acid (2 mol %) to the copper(II) catalyst.

In these types of reactions, copper-catalyzed C–N bond formation often involves ancillary ligands,¹⁵ such as 1,2-diamines,¹⁶ 1,2-diols,^{7e,12,17} amino acids,¹⁸ 2,2'-bipyridine,¹⁹ or 1,10-phenanthroline,^{2c,20} which can effectively reduce the amount of copper(I) catalyst required and achieve benign reaction conditions in some solvents. Consequently, the kinetics of the copper(I)-catalyzed amination of iodobenzene were measured in liquid ammonia at 25 °C, with and without some of these ancillary ligands (Table 3). However, except for

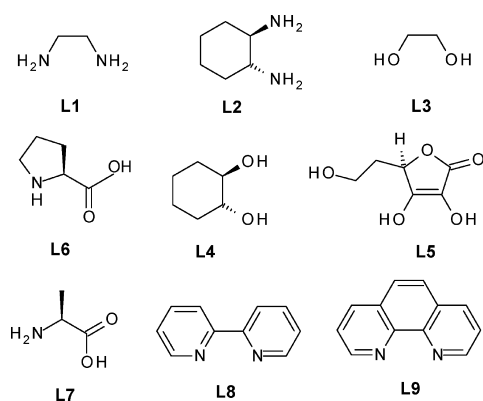
Table 3. Pseudo-First-Order Rate Constants for the Copper(I)-Catalyzed Amination of Iodobenzene with Various Ligands in Liquid Ammonia at 25 °C^a

entry	Cu(I) source	ligand	10 ⁵ k _{obs} /s ⁻¹
1	CuI	—	3.26
2	Cu(CH ₃ CN) ₄ BF ₄	—	3.63
3	CuI	L1	4.32
4	CuI	L2	3.95
5	CuI	L3	4.00
6	CuI	L4	4.92
7	CuI	L5	19.6
8	CuI	L6	0.037
9	CuI	L7	0.025
10	CuI	L8	5.23
11	CuI	L9	4.91

^aKinetics studied using 50 mM iodobenzene, 10 mM Cu(I) salt, 10 mM ligand, 40 mg of biphenyl as internal standard, and 10 mL of LNH₃ at 25 °C.

ascorbic acid (L5, Table 3, entry 7), there is no significant rate enhancement by any of the ligands (L1–L9) in the copper(I)-catalyzed reaction of iodobenzene in liquid ammonia at room temperature. Furthermore, the addition of nucleophiles, such as morpholine and phenoxide ion, give no substitution products other than aniline. The reaction rates are significantly hampered by added amino acids (L6 and L7) as ligands (Table 3, entries 8 and 9), in contrast to that observed in conventional solvents.¹⁸

The amino acids proline (L6) and alanine (L7) inhibit the reaction rate (Table 3, entries 8 and 9); there was no sign of precipitation, but the reaction solutions turned blue, indicative of the oxidation of Cu(I) to Cu(II). The inhibitory effect of the amino acids may simply be due to stabilization of Cu(II) by the ligands and reduction of the electrode potential (*E*₀) in liquid



ammonia. Presumably, the increase in reaction rate in the presence of ascorbic acid is due to its ability to maintain copper(I) in its reduced state and its use as an additive in copper-catalyzed organic reactions is known.²¹

In an attempt to distinguish between the role of ascorbic acid as a ligand and as a reductant, the kinetics of the reaction were determined as a function of the concentration of ascorbic acid. With a constant copper(I) catalyst concentration, the rate of the amination of iodobenzene significantly increases with added ascorbic acid in liquid ammonia, but when the concentration of ascorbic acid reaches about twice that of the catalyst, the rate levels out and becomes independent of further added ascorbic acid (L5) (Table 4, Figure 1). This rate saturation

Table 4. Effect of Ascorbic Acid Concentration (L5) on the Rate of the Copper(I) (CuI) Catalysed Amination of Iodobenzene in Liquid Ammonia at 25 °C

[iodobenzene]/mM	[CuI]/mM	[L5]/mM	$10^4 k_{\text{obs}}/s^{-1}$
50	10	0	0.326
50	10	10	1.96
50	10	20	2.15
50	10	40	2.22
50	10	50	2.23

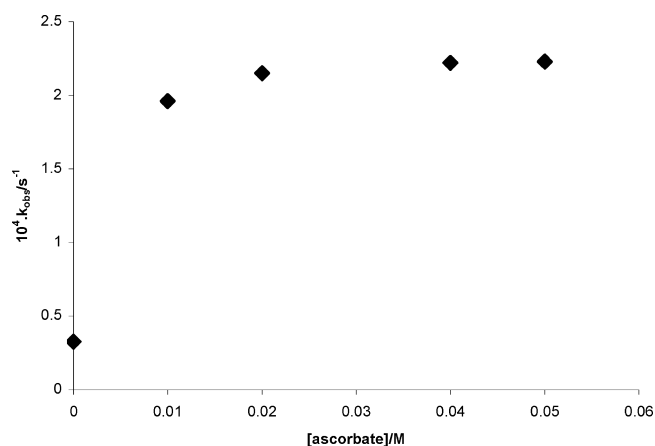


Figure 1. The effect of ascorbic acid (L5) concentration on the rate of the copper(I) (CuI, 10 mM) catalyzed amination of iodobenzene in liquid ammonia at 25 °C.

phenomenon could indicate association between copper(I) and ascorbic acid in liquid ammonia rather than simply indicating the optimum ratio of ascorbic acid to copper(I). However, the rate enhancement is not great (ca. 7-fold) and

another function of ascorbic acid may simply be to reduce any copper(II) formed back to active copper(I).

Further investigations of the kinetics of the amination of iodobenzene in liquid ammonia show, as expected,²² that the rate of the reaction shows a first-order dependence on the concentration of the copper(I) salt, even at different substrate to catalyst ratios (Table 5, Figure 2).

Table 5. Dependence of the Pseudo-First-Order Rate Constants (k_{obs}) for the Amination of Iodobenzene on the Copper(I) Catalyst Concentration in Liquid Ammonia at 25 °C

$^a[\text{Cu}^{\text{I}}]/\text{mM}$	$10^4 k_{\text{obs}}/s^{-1}$	$^b[\text{Cu}^{\text{I}}]/\text{mM}$	$10^4 k_{\text{obs}}/s^{-1}$
5	1.25	25	5.50
10	2.23	40	8.64
20	3.82	50	10.7
40	9.60	70	13.1

^a50 mM iodobenzene, 50 mM ascorbic acid (L5), and various CuI concentrations. ^b10 mM iodobenzene, 50 mM ascorbic acid (L5), and various CuI concentrations.

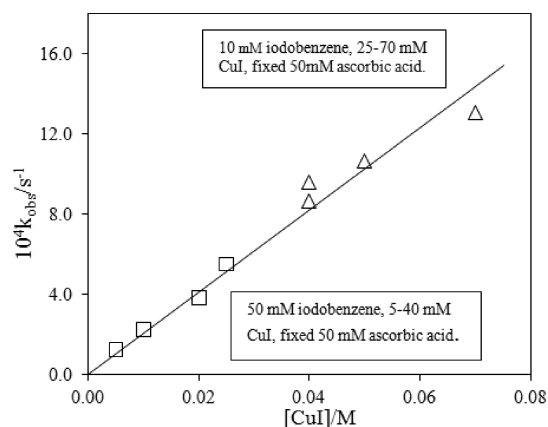


Figure 2. The first-order dependence of k_{obs} for the amination of 50 mM iodobenzene (\square) and 10 mM iodobenzene (Δ) at different copper(I) concentrations in liquid ammonia at 25 °C.

The first-order rate constants for the copper(I)-catalyzed amination of 4-substituted phenyl iodides in liquid ammonia increase with electron-withdrawing substituents (Table 6) and generate a Hammett ρ value of 0.49 (Figure 3). This small positive value of $\rho = 0.49$ indicates an increase in electron density in the aryl ring in the transition state of the reaction and is similar to that found for the Cu(I)-catalyzed N-arylation of

Table 6. Dependence of the Observed Pseudo-First-Order Rate Constants on Substituents for the Copper(I)-Catalyzed Amination of 4-Substituted Iodobenzenes in Liquid Ammonia at 25 °C^a

substituent	σ_p	$10^4 k_{\text{obs}}/s^{-1}$
4-MeO	-0.27	0.83
4-Me	-0.17	1.12
4-H	0	1.25
4-Cl	0.23	1.55
4-NO ₂	0.78	2.95

^aReaction conditions: 50 mM 4-substituted phenyl iodide, 5 mM CuI, and 5 mM ascorbic acid (L5) in 10 mL of liquid ammonia.

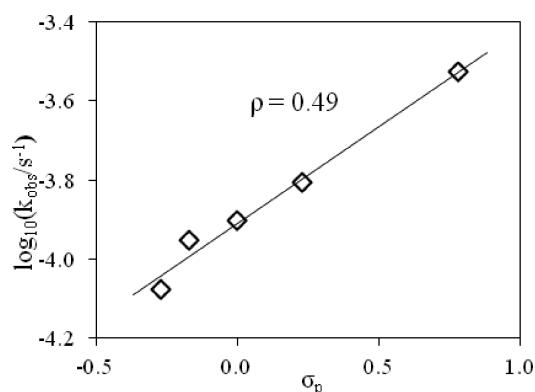


Figure 3. Hammett plot for the copper(I)-catalyzed amination of iodobenzene in liquid ammonia at 25 °C.

aryl iodides in toluene using 1,2-diamine ligands.^{22b} It suggests that the C–I bond is not significantly broken in the transition-state structure for the copper(I)-catalyzed amination of 4-substituted phenyl iodides in both liquid ammonia and toluene. It contrasts with the much larger $\rho = 2.3$ for analogous reactions catalyzed by palladium(0) with phosphine ligands in toluene.²³

The activation parameters provide a further characterization of the copper(I)-catalyzed amination of aryl iodides in liquid ammonia. A linear Arrhenius plot using the second-order rate constants (Table 7, Figure 4) gives $\Delta H^\ddagger = 65.6 \text{ kJ mol}^{-1}$, ΔS^\ddagger

Table 7. Dependence of the Observed Pseudo-First-Order and Corresponding Second-Order Rate Constants for the Copper(I)-Catalyzed Amination of Iodobenzene in Liquid Ammonia on Temperature^a

temp/K	$10^4 k_{\text{obs}}/\text{s}^{-1}$	$k_{\text{Cu}}/\text{M}^{-1} \text{s}^{-1}$
318.2	6.11	1.22×10^{-1}
308.2	2.35	4.7×10^{-2}
298.2	1.25	2.50×10^{-2}
288.2	0.39	7.80×10^{-3}

^a50 mM iodobenzene, 5 mM CuI, and 5 mM ascorbic acid (LS) in 10 mL of liquid ammonia.

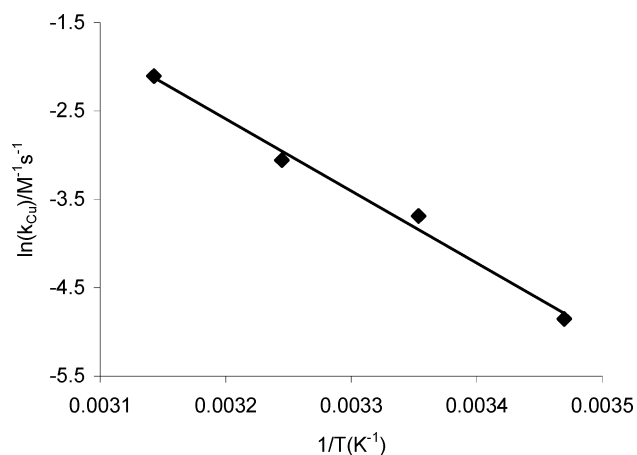


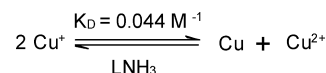
Figure 4. Arrhenius type plot for the copper(I)-catalyzed amination of iodobenzene in liquid ammonia.

$= -58.0 \text{ J K}^{-1} \text{ mol}^{-1}$ (if correcting for a standard state of 1 M for ammonia $\Delta S^\ddagger = -87.7 \text{ J K}^{-1} \text{ mol}^{-1}$). The entropy of activation is compatible with a bimolecular reaction but not one

generating a charged transition state requiring significant changes in solvation. The overall reaction requires the expulsion of iodide anion, which is better solvated by liquid ammonia than the other halide ions, as shown by its relative small positive Gibbs transfer energy from water to ammonia, compared with the larger values for chloride and bromide anions.²⁴ Therefore, it is less likely that the expulsion of iodide anion from the active complex would be the rate-limiting step as occurs with the nucleophilic substitution of nitrofluorobenzenes by phenoxide anions in liquid ammonia.^{9c}

To understand the mechanism of these catalyzed reactions, it is important to know the active coordination state of copper(I) under our reaction conditions. The rate of the reaction appears generally insensitive toward several potential copper(I) ligands, except for the small inhibitory effects of amino acids and the small rate enhancement brought about by ascorbic acid (Table 3). With the large and effectively constant concentration of ammonia (35.5 M, 298 K), copper(I) ion is presumably coordinated to ammonia, and perhaps with the exception of ascorbic acid, the added ligands do not compete with ammonia to form complexes with the metal. On the basis of EXAFS and ⁶³Cu NMR spectroscopy, it is claimed that copper(I) ion is three-coordinated in liquid ammonia, $[\text{Cu}(\text{NH}_3)_3]^+$, possibly with a coplanar trigonal geometry.²⁷ In contrast, in aqueous ammonia solution, the linear diaminecopper(I) complex, $[\text{Cu}(\text{NH}_3)_2]^+$, is the dominant species relative to $[\text{Cu}(\text{NH}_3)_3]^+$,²⁵ and even in highly concentrated aqueous ammonia solution, only 27% of copper(I) ion adopts three-coordinated coplanar structure.^{26,27} Copper(I) ion is in equilibrium with copper(0) and -(II) (Scheme 2) in liquid ammonia but with a

Scheme 2

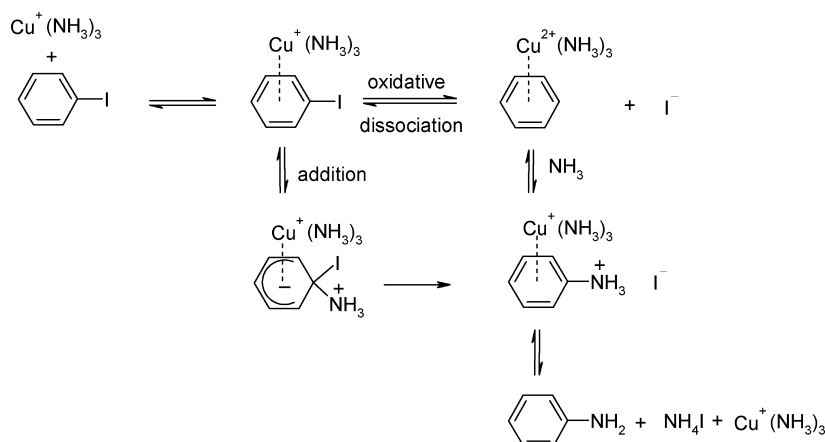


small disproportion constant $K_D = 0.044 \text{ M}^{-1}$; the copper(I)–ammonia complex is the dominant species (>99%) at low concentration of copper(I) liquid ammonia solution (<0.1 M).²⁷

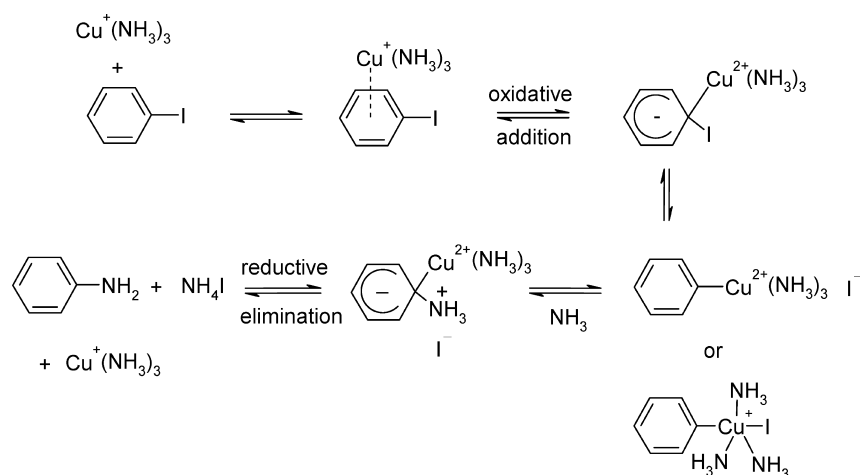
The copper(I)-catalyzed amination of iodobenzene in concentrated aqueous ammonia (30% w/w) is much slower than that in liquid ammonia at 25 °C. The pseudo-first-order rate constant, $k_{\text{obs}} = 5.0 \times 10^{-6} \text{ s}^{-1}$, for the copper(I)-catalyzed amination of iodobenzene in 30% w/w aqueous ammonia at 25 °C is 40-fold smaller than the analogous reaction under similar conditions in liquid ammonia (Table 3, entry 7). The triamminecopper(I) is the dominant species in liquid ammonia and is apparently a better catalyst than the diamminecopper(I), which is the major complex in aqueous ammonia.^{25,27,28}

In principle, Cu^+ can act as either an electron donor or acceptor, but on the basis of the small rate enhancement by the reductant ascorbic acid, it seems likely that in liquid ammonia, Cu^+ is acting as a reducing agent. The Cu(I) catalyst is present at only 1 mol % and any adventitious oxidation to Cu(II) will terminate the reaction, so the function of the ascorbic acid is probably to reduce any such Cu(II) to its catalytically active form. Theoretical studies on the cation– π interactions of Cu^+ and benzene indicate that, in the gas phase, Cu^+ forms a η^2 complex with benzene, especially if a counterion is present.²⁹ Other theoretical studies^{22,23,30} on the copper(I)-catalyzed amination of aryl halides have suggested a mechanism involving rate-limiting oxidative addition through a penta-coordinated

Scheme 3



Scheme 4



copper(III) intermediate and a single electron transfer (SET) mechanism depending on the electron-donating abilities of the ligand and the nucleophile.³¹ The small rate enhancement brought about by ascorbic acid (Table 4, Figure 1), given its ability to act as a radical trap, does not suggest that a SET mechanism is operative in liquid ammonia.

A traditional view of this aromatic nucleophilic substitution reaction would regard the likely mechanism to involve initial copper(I)- π complex formation, followed by dissociative or addition-elimination steps (Scheme 3).³² Although the former, by the elimination of iodide ion, effectively leaves what would normally be an unstable aromatic carbocation, in this case it could be stabilized by electron transfer from Cu(I) to form a Cu(II) complex. However, if either this step or formation of triammine copper(I)-aryl ring complex is rate-limiting, a negative Hammett ρ value would be expected, with electron-withdrawing groups decreasing the rate. The addition-elimination pathway is consistent with the Hammett $\rho = 0.49$ and observed activation parameters, but the weak Lewis acid character of Cu(I) seems insufficient to explain the rate enhancement.



































The differences between these mechanisms (Scheme 3) and the type proposed for Pd(0)-catalyzed reactions³³ are the timing and extent of bond making and breaking. If Cu(I) acts initially as a nucleophile, then catalysis could occur by its oxidative addition to generate a Meisenheimer type σ -complex

with negative charge distributed around the aromatic ring and with copper now in the +2 oxidation state (Scheme 4). Breakdown of this intermediate by expulsion of iodide ion could be followed by a repeat process involving nucleophilic displacement of the Cu^{2+} by reductive elimination and regeneration of the Cu(I) catalyst (Scheme 4). In liquid ammonia, the product of iodide expulsion from the Meisenheimer intermediate may be a very tight ion pair in which iodide is strongly bound to copper and may be represented as a possible trigonal bipyramidal intermediate. The relatively small Hammett $\rho = 0.49$ suggests that the C-I bond is not significantly broken in the transition-state structure and that there is a small generation of negative charge in the aryl ring, which is compatible with the oxidative addition of the copper ion being rate-limiting.

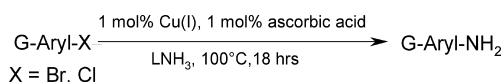
Copper(I)-Catalyzed Amination of Aryl Bromides and Chlorides. With 1 mol % CuI as catalyst in liquid ammonia at room temperature, less than 1% of bromobenzene is converted into aniline after 18 h; however, at 100 °C, the yield of aniline increases to 96% after 18 h (Table 8, entry 1). Under similar conditions, other substituted aryl bromides can also be smoothly converted to the corresponding anilines with good to excellent yields in liquid ammonia (Scheme 5, Table 8).

The amination of bromobenzene in aqueous ammonia using 5 mol % copper(0) powder as a catalyst at 100 °C for 24 h gives a lower yield of aniline (85%)³⁴ compared with that in

Table 8. Amination of Various Aryl Bromides and Chlorides with Copper(I) Iodide Catalyst at 100 °C for 18 h in Liquid Ammonia^a

entry	substrate	product	yield(%) ^b
1			96
2			95
3			97
4			94
5			86
6			91
7			80
8			96
9			97
10			85
11			99
12			96
13			92
14			<5
15			74 ^c
16			88 ^c
17			63 ^c

^aGeneral reaction conditions: 1 mmol of aryl halide, 1 mol % of CuI, 1 mol % of ascorbic acid, in 1.5 mL of liquid ammonia at 100 °C for 18 h. ^bGC yields unless otherwise noted. ^c36 h, isolated yields; the uncatalyzed reaction requires temperatures >200 °C.

Scheme 5

liquid ammonia. Electron-donating groups significantly decrease the yields of amination of substituted bromobenzenes (Table 8, entries 5–8) but not that of bromopyridines which give excellent yields in liquid ammonia (Table 8, entries 12 and 13). The amination of 4-*tert*-butylphenyl bromide gives a slightly lower yield (Table 8, entry 10) but is still comparable with that using palladium(II) (Pd[P(*o*-tol)₃]₂) catalyzed amination with ammonia in 1,4-dioxane (65 °C, 15 h, 88% yield).^{7b}

No di- or triarylamine products, which can occur as a result of further reaction of the initial product aniline, are found, even under the elevated temperatures required for the copper(I)-catalyzed amination of aryl bromides in liquid ammonia. By contrast, the formation of di- and triarylamines byproduct is often unavoidable when strong bases are utilized for the palladium-catalyzed amination of aryl bromides or chloride in

other solvents, especially under high temperature.^{4c,7a} At a similar temperature, the yields of the copper(I)-catalyzed amination of aryl bromides in liquid ammonia are generally higher than those using aqueous ammonia solution or ammonia surrogates as nitrogen source.^{7c,e,h,35} Furthermore, the amination of aryl bromides in liquid ammonia requires only 1% copper(I) catalyst, which is much lower than those required with aqueous or organic ammonia solutions.⁸

As expected, unactivated chlorobenzenes are very inert under similar conditions to that used for the amination of aryl bromides in liquid ammonia (Table 8, entry 14). For example, even at 120 °C, with 10 mol % copper(I) catalyst, less than 5% chlorobenzene is converted into aniline after 12 h in liquid ammonia. However, electron-withdrawing groups are activating so that nitrochlorobenzenes can be smoothly converted into corresponding aniline with only 1 mol % copper(I) catalyst to give moderate yields in liquid ammonia (Table 8, entries 15–17).

CONCLUSION

We have developed a method for the amination of aryl halides in liquid ammonia using copper(I) catalysis which enables direct synthesis of a number of primary amines with good to excellent yields. This method does not require strong base and ligands as additives, which are often used for the similar metal-catalyzed amination of aryl halides in other solvents. The amination in liquid ammonia also has exclusive selectivity for the formation of primary amines, with no formation of di- or triaryl amine products, even at 100 °C. The amount of catalyst required for the reaction is lower than that generally used and the convenience of product separation with liquid ammonia as a reaction medium indicates its potential industrial application. The rate of amination shows a first-order dependence on the concentration of copper(I) catalyst and, due to strong coordination of solvent molecules to the copper(I) ion, the kinetics of the reaction are generally insensitive to the addition of other ligands in liquid ammonia. The small Hammett $\rho = 0.49$ suggests that the C–I bond is not significantly broken in the transition-state structure and that there is a small generation of negative charge in the aryl ring, which is compatible with oxidative addition of copper ion being rate-limiting.

EXPERIMENTAL SECTION

Materials. Liquid ammonia was 99.98% pure with moisture levels <200 ppm and other impurities <5 ppm. It was used directly as reaction medium without further purification. The organic chemicals were purchased from commercial source with at least 98% purity; the inorganic salts were either analytical or laboratory grade and both used without further purification unless otherwise noted.

Pressure Equipment. The glassware pressure equipment has been described previously.⁹ In order to investigate the amination of aryl halides in liquid ammonia under high temperature, several pressure tube reactors were made from standard 1/4 in. o.d. Swagelok stainless steel tubing (316 L seamless, ammonia resistant), and the length of these tube reactors was varied from 10 to 20 cm. Both ends of these reactors had standard Swagelok fittings that could be sealed with Swagelok caps. These tube reactors were tested to withstand pressures up to 1200 bar by the provider. The working temperature for these reactors was from 50 to 110 °C. Liquid ammonia has a very high coefficient of expansion with temperature and great caution must be taken to avoid overfilling these pressure tube reactors. Ammonia expands by 20% on heating from 25 to 100 °C (volumetric coefficient of expansion for liquid ammonia is $2.45 \times 10^{-3} \text{ K}^{-1}$).³⁶

General Procedures. The amination of aryl iodides was conducted in several 3 mL thick-wall GC vials. The GC vial was

precharged with substrate and copper catalyst and then cooled with dry ice or liquid nitrogen. With the dry ice as cooling bath, the amount of liquid ammonia required was injected by a pressure syringe, and then the vial was quickly sealed with a GC cap. After the required amount of time, the vial was cooled with dry ice and the cap removed; after the evaporation of ammonia, the products were collected and analyzed by GC or HPLC. The structures of the products were confirmed by GC–MS or LC–MS analysis. The amination of aryl bromides and chlorides was conducted in several pressure tube reactors as described above. The pressure tube reactor filled with liquid ammonia solution was then placed in a GC oven to accurately control the temperature of the reaction. The kinetics methods for the amination of iodobenzene in liquid ammonia were similar to those described previously.⁹

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Notes

The authors declare no competing financial interest.

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