# Assembly of Primary (Hetero)Arylamines via CuI/Oxalic Diamide-Catalyzed Coupling of Aryl Chlorides and Ammonia

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S *Supporting Information*

ABSTRACT: A general and practical catalytic system for aryl amination of aryl chlorides with aqueous or gaseous ammonia has been developed, with CuI as the catalyst and bisaryl oxalic diamides as the ligands. The reaction proceeds at 105−120 °C to provide a diverse set of primary (hetero)aryl amines in high yields with various functional groups.
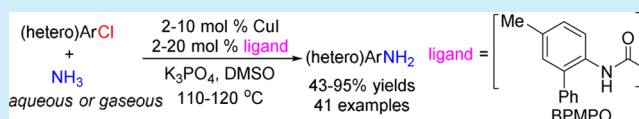
Primary (hetero)arylamines represent one of the most important feedstocks in organic chemistry that have been extensively employed in the manufacturing of pharmaceuticals, agrochemicals, dyes, and electronic materials.[1] To date, more than 6 million tons of primary (hetero)arylamines are produced every year, and the most common method for preparing them is nitration of arenes followed by hydrogenation (pathway I in Scheme 1).[2,3] Because of the serious waste issue caused by

Scheme 1. Two Pathways for Conversion of (Hetero)Arenes into Primary (Hetero)Arylamines
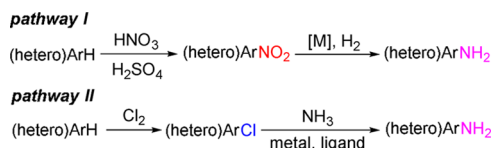
employment of a large excess of mixed HNO_3 and H_2SO_4, this process has already generated significant environmental problems.[4] In addition, the method is also limited by the imperfect regioselectivity and poor functional group tolerance of the nitration step, and the chemoselectivity issue in the hydrogenation step.[2a−d] On the other hand, chlorination of arenes is another inexpensive process for industry and in certain aspects has advantages over nitration. Consequently, a combination of this reaction and a subsequent aryl amination with ammonia may serve as an alternative approach for manufacturing primary (hetero)arylamines (pathway II).[4,5] However, the key to making the secondary pathway useful in industry is the development of a cost-effective catalytic system for the aryl amination step.

In the area of Pd-catalyzed amination of aryl halides, the groups of Hartwig,[6] Buchwald,[7] Beller,[8] and Stradiotto[9] have revealed that the combination of Pd complexes and some electron-rich and sterically demanding arylphosphine ligands could catalyze the coupling reaction of (hetero)aryl chlorides with ammonia to afford primary (hetero)arylamines. Quite recently, Stradiotto[10] and Hartwig[11] and their co-workers have

independently reported that a $Ni(COD)_2$/JosiPhos catalytic system enabled the first examples of ammonia monoarylation with aryl chlorides utilizing less expensive nickel catalysts. Although the recent achievements in the coupling of aryl chlorides with ammonia are remarkable, the high cost of either metal catalysts or phosphine ligands remains the limiting factor of these aryl amination reactions, particularly for large scale production.

Copper-catalyzed coupling of ammonia with aryl halides has a long history.[12] However, the previously developed methods all required unfavorable, harsh conditions and provided unsatisfactory yields.[12,13] This situation has been changed with the development of ligand-promoted Ullmann-type reactions.[13] In 2001, Merck chemists reported that Cu_2O-catalyzed direct amination of bromopyridines and other electron-poor aryl halides with ammonia took place at 80−100 °C in ethylene glycol,[14a] in which ethylene glycol might serve as both solvent and ligand.[14] Since then, several other ligands have been discovered to be effective for copper-catalyzed coupling reactions of aryl iodides and bromides with ammonia or its equivalents, which include L-proline,[15] L-*trans*-4-hydroxyproline,[16] 1,3-diketones,[17] 2-pyridinyl ketones,[18] ascorbic acid,[19] D-glucosamine,[20] *N,N*-dimethylethylenediamine (DMEDA),[21] and $N^2,N^{2'}$-diisopropyloxalohydrazide.[22] But none of them was effective in the case of aryl chlorides as the substrates.[5,23] Recently, we described that some bisaryl substituted oxalic diamides are effective ligands for CuI-catalyzed coupling of (hetero)aryl chlorides and aliphatic amines, allowing the reaction to proceed at 120 °C.[24] As an extension of this work, in this paper, we explore the CuI-catalyzed coupling of (hetero)aryl chlorides and ammonia by using oxalic diamides as the ligands.

Using the coupling of 4-(hydroxymethyl)phenyl chloride **1a** with aqueous ammonia as a model reaction, we investigated the influence of different oxalic diamides. As shown in Table 1, we

Table 1. CuI-Catalyzed Coupling of 4-(Hydroxymethyl)phenyl Chloride with Aqueous Ammonia under the Assistance of Different Ligands[a]

entry	ligand	solvent	temp (°C)	time (h)	yield (%)[b]
1	L1	DMSO	115	24	90
2	L2	DMSO	115	24	80
3	L1	DMSO	105	10	58
4	L3	DMSO	105	10	69
5	L4	DMSO	105	10	75
6	L5	DMSO	105	10	87
7	L6	DMSO	105	10	84
8[c]	L5	DMSO	110	24	90
9	L7	DMSO	110	12	68
10	L8	DMSO	115	24	80
11	L9	DMSO	115	24	61
12	L10	DMSO	110	12	79
13	L11	DMSO	110	12	0
14	L12	DMSO	110	12	0
15	L13	DMSO	110	12	0
16	L14	DMSO	110	12	0
17	L15	DMSO	110	12	10
18[c]	L5	DMF	110	24	61
19[c]	L5	DMA	110	24	63
20[c]	L5	MeCN	110	24	21
21[c]	L5	dioxane	110	24	<10

[a]General conditions: **1a** (0.5 mmol), aqueous ammonia (1 mmol), CuI (0.05 mmol), ligand (0.05 mmol), base (0.5 mmol), solvent (1.0 mL). [b]The yield was determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c]The reaction was conducted with 5 mol % CuI and 5 mol % L5.

initially tried N,N′-bis(2,4,6-trimethoxyphenyl)oxalamide (BTMPO, **L1**) as the ligand, which has shown excellent ability in our previous studies.[24] The reaction proceeded well at 115 °C, affording 4-(hydroxymethyl)-phenylamine **2a** in 90% yield (entry 1). When N,N′-bis(2,4,6-trimethylphenyl)oxalamide (**L2**) was used, the reaction yield was decreased slightly (entry 2).
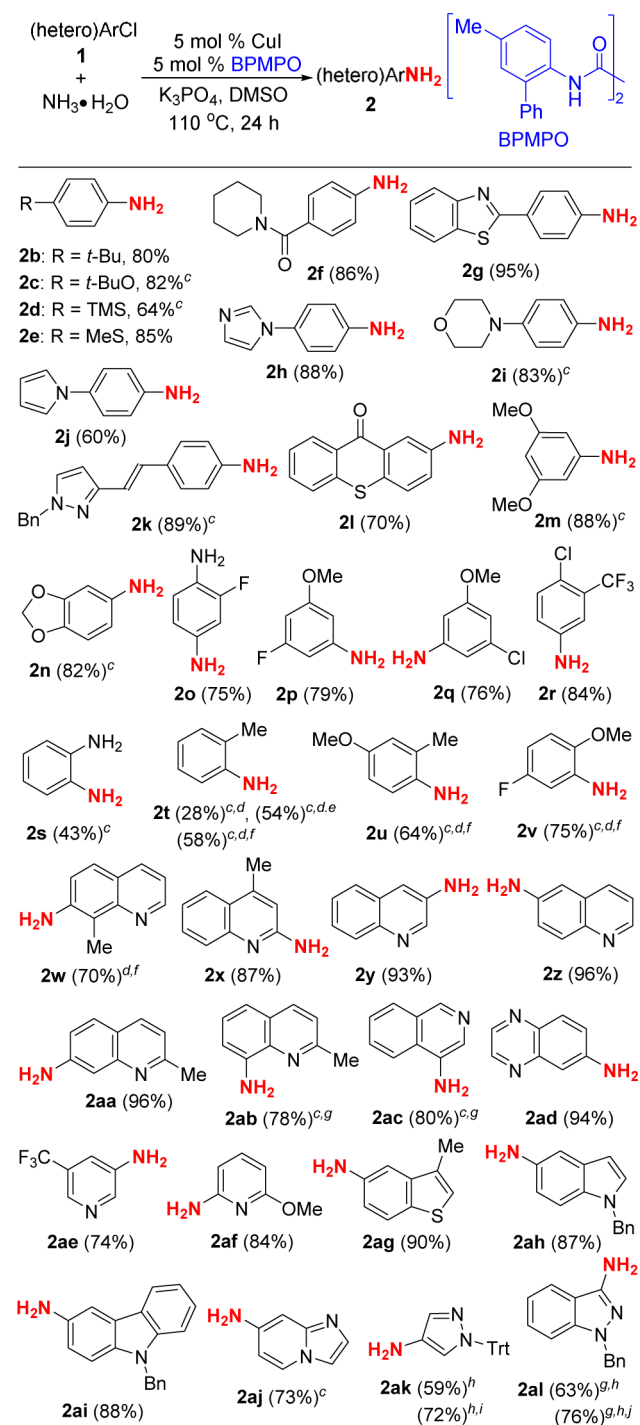
To confirm if **L1** was the best ligand for this transformation, we compared it with other ligands by lowing the reaction temperature and shortening the reaction time. Once the reaction was carried out at 105 °C for 10 h, **L1** gave **2a** in only 58% yield (entry 3). Surprisingly, improved yields were observed when two less electron-rich ligands **L3** [N,N′-bis(4-methoxy-2,6-dimethylphenyl)oxalamide, BMDMPO] and **L4** were utilized (entries 4 and 5), while much higher yields were

obtained in the case of **L5** [N,N′-bis(2-phenyl-4-methylphenyl)-oxalamide, BPMPO] and **L6**, two simple analogues of **L4** with the additional methoxy or methyl group (entries 6 and 7). These results illustrated that the suitable electronic property of the aromatic rings in oxalic diamides is the key for exhibiting their efficiency. After reducing the loadings of CuI and **L5** to 5 mol %, we found that an excellent yield could still be obtained when the reaction was conducted at 110 °C (entry 8). These optimized conditions were chosen for all subsequent work.

Interestingly, N,N′-bis(2-benzoxyphenyl)oxalamide (BBPO, **L7**) was less effective than **L4** (compare entry 5 and 9), which is inconsistent with that observed in our previous studies.[24] To check if the steric effect has an influence on the ligands, we synthesized **L8** and **L9** and found that **L8** was as effective as **L2**, but **L9** gave a decreased yield (entries 10 and 11). In addition, **L6** was superior to **L10** (entries 7 and 12), indicating that N-aryl-N′-alkyl substituted oxalic diamides were less effective than N,N′-bisaryl oxalic amides. We also examined some known ligands (**L11**−**L14**) and found none of them had an effect on this reaction (entries 13−16). Only a salt of 2-(2,6-dimethyl-phenylamino)-2-oxoacetic acid (**L15**)[25] gave **2a** in less than 10% yield. An evaluation of solvents showed that DMSO was still the best choice, and use of DMF, DMA, MeCN, and dioxane significantly decreased the yields (entries 18−21).
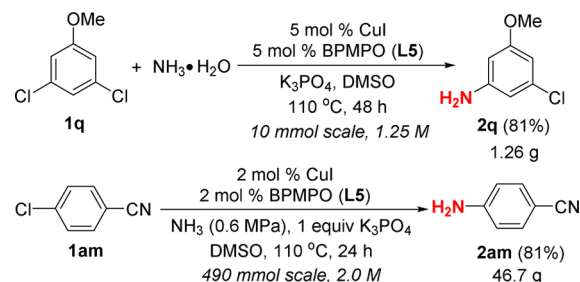
The established optimized conditions were then examined with a variety of substituted (hetero)aryl chlorides, and the results are summarized in Scheme 2. Gratifyingly, we were able to couple aqueous ammonia with a range of aryl chlorides that contain functionalized groups at the para-position, including alkyl (**2b**), alkoxyl (**2c**), trimethylsilyl (**2d**), thioether (**2e**), amide (**2f**), heterocycles (**2g**, **2h**, **2j**), amine (**2i**, **2o**), and olefin (**2k**). In general, electron-poor aryl chlorides are more reactive than electron-rich ones (compare **2b**−**2i**). For some electron-rich substrates, the ligand loading at 10 mol % was required to achieve satisfactory yields. A similar phenomenon was seen in couplings with meta-substituted aryl chlorides (**2l**−**2r**). When 2,5-dichloroanisole was used, monoamination product **2q** was isolated in 76% yield, presumably because coupling of the more electron-rich **2q** with ammonia was slower than that of 2,5-dichloroanisole. Another remarkable influence on reactivity was the steric hindrance of aryl chlorides. For example, coupling with 2,4-dichlorotrifluoromethylbenzene occurred solely at its less hindered 4-position to provide **2r** in 84% yield. Indeed, coupling of 2-chloroaniline was found to be rather sluggish even at 120 °C, and diamine **2s** was obtained in only 47% yield. For formation of 2-methylaniline **2t**, a low yield was also observed initially. This problem could be solved by changing the ligand to **L10** or **L1** and prolonging the reaction time. Under these conditions, four sterically hindered substrates gave **2t**−**2w** in moderate to good yields.

We then moved our attention to coupling with more challenging heteroaryl chlorides. A number of heteroaryl amines could be prepared in good to excellent yields, which include aminoquinolines (**2w**−**2ab**), 4-aminoisoquinoline (**2ac**), 3-aminoquinoxaline (**2ad**), aminopyridines (**2ae**, **2af**), 5-amino-3-methylbenzothiophene (**2ag**), 5-amino-1-benzyl-indole (**2ah**), 4-amino-1-benzylcarbazole (**2ai**), aminoimidazo-pyridine (**2aj**), 4-amino-1-tritylpyrazole (**2ak**), and 3-amino-1-benzylindazole (**2al**). In the case of **2ak** and **2al**, using **L5** as the ligand gave unsatisfactory yields initially. A quick screening of several ligands revealed that **L6** and **L3** were more suitable for formation of **2ag** and **2ah**, respectively.

Scheme 2. Scope of CuI/BPMPO Catalyzed Coupling Reaction of (Hetero)Aryl Chlorides with Amines[a,b]

Scheme 3. Scaling up the Coupling Reactions of 1q and 1am

presence of 5 mol % CuI and 5 mol % **L5** on a 10 mmol scale, **2q** was obtained in 81% yield, together with a deamination product in 10% yield. In the coupling of 4-chlorobenzonitrile with gaseous ammonia to produce 4-aminobenzonitrile **2am**, the reaction could be scaled to over 50 g without loss of efficiency, and the loadings for CuI and ligand **L5** could be dropped to as low as 2 mol %.

To explore the possible mechanism, we conducted a coupling reaction of aqueous ammonia with olefin **1an** (Scheme 4), a

Scheme 4. Possible Reaction Mechanism
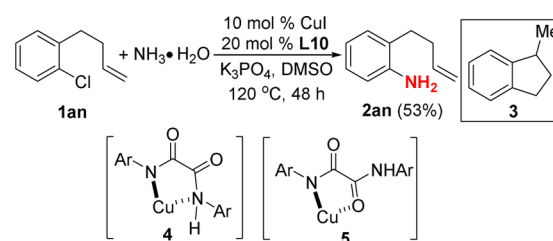
similar substrate employed by Hartwig and Green to probe the possible aryl radical intermediate in their Ni-catalyzed coupling reaction.[11] If this radical was produced during the coupling reaction, it would quickly undergo an intramolecular cyclization to afford **3**. In our hands, amination product **2an** was isolated in 53% yield, while no cyclization product **3** was determined according to GC-MS analysis. Thus, we ruled out the radical mechanism, and the present coupling is likely to go through a commonly proposed Cu(I)/Cu(III) catalytic cycle via an oxidative addition/reductive elimination process[13,26] with oxamido bridged copper(I) complex **4** or **5** as the active catalytic species.[27]

In conclusion, we have demonstrated a general and practical CuI-catalyzed coupling reaction of aryl chlorides and aqueous (or gaseous) ammonia with bisaryl oxalic diamides as the ligands. This newly developed transformation proceeded under mild conditions (105−120 °C) and provided an easy access to a wide range of densely substituted primary (hetero)arylamines. This approach would complement many of the other existing methods for assembling primary (hetero)arylamines from (hetero)aryl chlorides and in many cases would have definite advantages in terms of cost (catalyst, ligand, and base), scope, and the conditions of reaction.[6−11] Thus, it may find applications in organic synthesis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03230.

[a]General conditions: **1** (1 mmol), aqueous ammonia (2 mmol), CuI (0.05 mmol), BPMPO (0.05 mmol), K₃PO₄ (1.1 mmol), DMSO (1.0 mL), 110 °C, 24 h. [b]Isolated yield. [c]10 mol % ligand was used. [d]The reaction was conducted at 120 °C for 48 h. [e]Using **L10** as the ligand. [f]Using **L1** as the ligand. [g]The reaction was conducted at 120 °C. [h]20 mol % ligand was used. [i]Using **L6** as the ligand. [j]Using **L3** as the ligand.

It is notable that the present coupling reaction could be easily scaled up, and the catalytic loading could be further reduced. As depicted in Scheme 3, when the coupling reaction of 2,5-dichloroanisole with aqueous ammonia was carried out in the

Experimental procedures, spectral data, and copies of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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