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A new ligand for copper-catalyzed amination of aryl halides to primary (hetero)aryl amines

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ABSTRACT

N,*N*′-Bis(3,5-dimethoxyphenyl)cyclopentane-1,1-dicarboxamide was found as a new ligand for copper-catalyzed amination of aryl iodides, bromides and chlorides to afford various primary (hetero)aryl amines. These reactions proceeded efficiently under mild conditions when inexpensive aqueous ammonia (28% NH_3 in H_2O) was used as the amino source.

Introduction

Primary (hetero)aryl amines are present in a number of biologically active natural products and privileged building blocks in pharmaceuticals, agrochemicals, and material molecules [1]. Although transition-metal catalyzed cross-coupling reactions are among the most common methods to prepare substituted arylamines [2–4], the direct synthesis of primary (hetero)aryl amines are rare until recently [5,6].

Buchwald [7] and Hartwig [8] independently reported palladium-catalyzed cross-coupling reaction of aryl halides with ammonia. These methods demonstrate the effectiveness of palladium catalysts to access primary arylamines. However, the development of less expensive copper catalysts with readily available ligands for such transformation is desirable.

Earlier copper-catalyzed examples that converted aryl halides into primary arylamines often suffer from high reaction temperature, limited substrate scope, or the use of ammonia gas/liquid ammonia as nitrogen source [9–28].

The first room-temperature method for the coupling of aryl iodides with ammonia has been developed by Chang and co-workers [29]. In this methodology, cheap ammonium chloride (NH_4Cl) was utilized as an ammonia surrogate. L-Proline has been found as the effective ligand. However, 20% mol copper and 40 mol% ligand were needed to proceed this amination reaction at room temperature. Other ligands such as 2-pyridinyl-β-ketones [30] and pyridydiketone derivatives [31] were identified as efficient ligands for copper-catalyzed amination reaction of aryl iodides at room temperature.

In 2011, CuI nanoparticles-nBu_4NOH system was used for the amination of aryl iodides at room temperature [32]. No additional ligand is required. Page and co-worker disclosed the use of 1 mol% ascorbic acid as the ligand to achieve the cross-coupling of aryl iodides and ammonia [33]. However, liquid ammonia should be the ammonia source.

Herein we describe a mild copper catalyst system for the direct amination of aryl iodides at room temperature, and of aryl bromides and aryl chlorides at higher temperatures by utilizing *N*,*N*′-bis(3,5-dimethoxyphenyl)cyclopentane-1,1-dicarboxamide as the new ligand (Fig. 1).

Results and discussion

We initially selected 4-methyliodobenzene as a model substrate for optimization of the reaction conditions. With the newly-prepared ligand **L1** employed, the desired coupling product 4-methylaniline was obtained in 44% yield at room temperature (Table 1, entry 1). The replacement of base K_3PO_4 with CsOH led to decreased yield, while Cs_2CO_3 improved the reaction efficiency (Table 1, entry 2–3). Among the ligands screened, *N*,*N*′-bis(3,5-dimethoxyphenyl)cyclopentane-1,1-dicarboxamide **L2** turned out to be the best, affording the product in 87% yield (Table 1, entry 4). This suggests the importance of the electronic effect of ligand

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0040-4039/

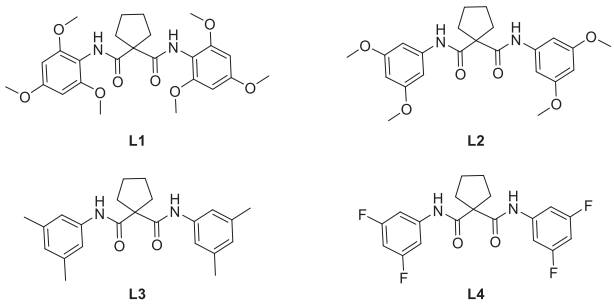
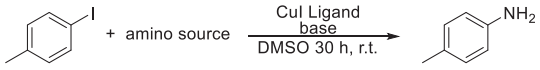


Fig. 1.

Table 1
Copper-catalyzed amination of 4-methyliodobenzene with aqueous ammonia at room temperature.[a]



Entry	Ligand	Amino source	Base	Yield (%)[b]
1	**L1**	$NH_3{\cdot}H_2O$	K_3PO_4	44
2	**L1**	$NH_3{\cdot}H_2O$	CsOH	10
3	**L1**	$NH_3{\cdot}H_2O$	Cs_2CO_3	56
4	**L2**	$NH_3{\cdot}H_2O$	Cs_2CO_3	87
5	**L3**	$NH_3{\cdot}H_2O$	Cs_2CO_3	71
6	**L4**	$NH_3{\cdot}H_2O$	Cs_2CO_3	43
7	**L2**	NH_4Cl[c]	Cs_2CO_3	46
8	**L2**	$(NH_4)_2CO_3$[c]	Cs_2CO_3	35
9	**L2**	NH_4OAc[c]	Cs_2CO_3	27
10	**L2**	$NH_3{\cdot}H_2O$[d]	Cs_2CO_3	93
11	–	$NH_3{\cdot}H_2O$	Cs_2CO_3	0[e]

[a] Reaction condition: 4-methyliodobenzene (1 mmol), $NH_3{\cdot}H_2O$ (4 mmol), CuI (10 mol%), ligand (20 mol%), and base (2 mmol) in DMSO (1 mL) under Ar.
[b] HPLC yield.
[c] H_2O (300 μL) was added to dissolve the ammonium salt.
[d] 12 mmol $NH_3{\cdot}H_2O$ was used.
[e] 4-Bromotoluene was used as the substrate.

on catalyst efficiency. Other ammonia surrogates were tested on this conversion to provide the desired product, albeit in lower yields (Table 1, entries 7–9). When 12 equivalent of $NH_3{\cdot}H_2O$ was used, the yield was further improved to 93%.

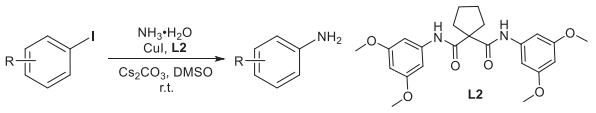
With the optimized condition on hand, the substrate scope for the amination of aryl iodides with aqueous ammonia was explored (Table 2). To our delight, all of these aryl iodides yielded the corresponding aryl amines in good to excellent yield.

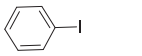
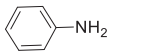
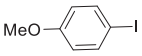
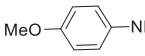
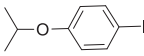
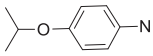
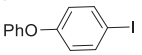
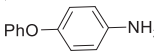
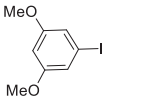
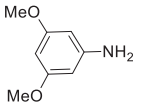
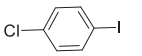
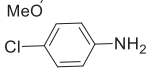
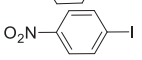
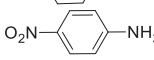
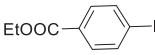
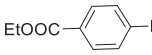
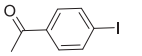
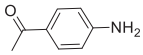
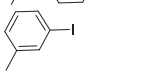
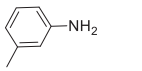
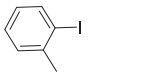
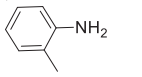
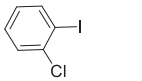
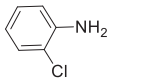
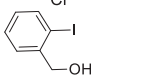
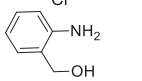
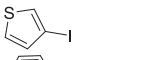
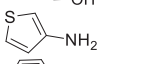
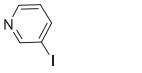
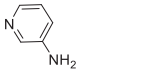
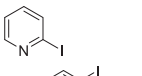
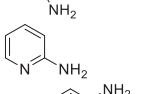
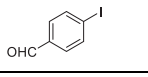
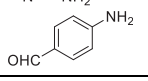
In general, the reaction with electron-deficient aryl iodides (Table 2, entries 6–9) resulted in better yields than that of electron-rich aryl iodides.

This catalyst system displayed a great tolerance to functional groups such as nitro, ketone, carboxylic ester and hydroxyl groups (Table 2, entries 7–9 and 13). In consistent with those of results reported by Ding [29] and Chang [28], sterically-hinder aryl iodides with an *ortho* substituent had a great influence on this transformation, and only less than 10% isolated yields of the desired coupling product were obtained for 2-methyl iodide (Table 2, entry 11) and 2-chloride iodide (Table 2, entry 12), respectively, at room temperature. However, these reactions could proceed at higher temperature (90 °C) and with more catalyst used.

Interestingly, 2-hydroxymethylaniline was obtained in 47% yield at room temperature (Table 2, entry 13), presumably due to the coordination of the hydroxyl group into the copper center. In addition, heteroaryl iodides such as thiophene and pyridine derivatives reacted smoothly with aqueous ammonia at room temperature to furnish the corresponding coupling products in good yields (Table 2, entries 14–16).

Table 2
CuI/**L2**-catalyzed amination of aryl iodides with aqueous ammonia at room temperature.[a]



Entry	Aryl Iodide	Product	Yield(%)[b]
1			84
2			65[c]
3			64[c]
4			68[c]
5			75
6			86
7			78
8			78
9			73
10			75
11			55[d]
12			38[d]
13			47
14			68
15			78
16			59
17			33

[a] Reaction condition: aryl iodide (1 mmol), $NH_3{\cdot}H_2O$ (12 mmol), CuI (10 mol%), L2 (20 mol%), and Cs_2CO_3 (2 mmol) in DMSO (1 mL) under Ar for 24 h.
[b] Isolated yield.
[c] 20 mmol $NH_3{\cdot}H_2O$ was used.
[d] CuI (20 mol%) was used, 90 °C.

Next, we turned our attention to the amination reaction of aryl bromides and chlorides. Most aryl(hetero) bromide substrates could be completely consumed at 90 °C within 24 h, affording the corresponding aryl amines in moderate to good yields (Table 3 entries 1–10). For aryl chlorides, the electronic property on substrate significantly affected the efficiency of this amination reaction. Moderate yields could be obtained when aryl chlorides containing electron-drawing substituents such as cyano or nitro group (Table 3 entries 11–12).

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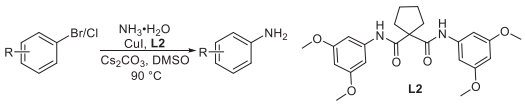
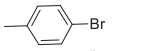
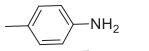
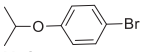
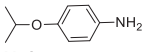
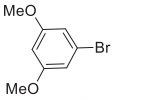
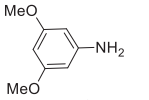
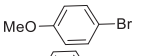
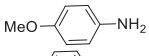
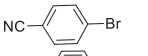
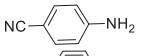
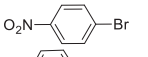
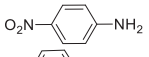
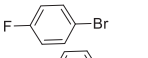
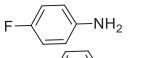
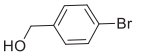
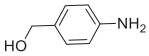
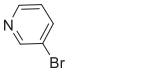
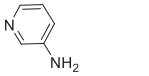
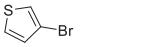
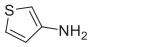
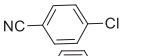
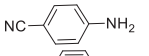
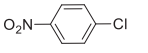
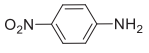
Table 3
Cu-catalyzed amination of aryl bromides and aryl chlorides with aqueous ammonia.[a]



Entry	Aryl Bromide/Chloride	Product	Yield (%)[b]
1			68
2			73
3			68
4			76
5			57
6			56
7			65
8			72
9			70
10			72
11			67[c]
12			42[c]

[a] Reaction condition: aryl bromide or aryl chloride (1 mmol), $NH_3{\cdot}H_2O$ (12 mmol), CuI (10 mol%), L2 (20 mol%), and Cs_2CO_3 (2 mmol) in DMSO (1 mL) under Ar.
[b] Isolated yield.
[c] At 120 °C.

Conclusions

In conclusion, we have disclosed an efficient catalytic system that could convert various aryl halides to the corresponding primary (hetero)aryl amines using the cheap aqueous ammonia as the amino source. The readily accessible *N,N'*-bis(3,5-dimethoxyphenyl)cyclopentane-1,1-dicarboxamide was found as an efficient ligand to promote such amination reaction with broad substrate scope under mild conditions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151683.

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