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Discovery of *N*-(Naphthalen-1-yl)-*N*′-alkyl Oxalamide Ligands Enables Cu-Catalyzed Aryl Amination with High Turnovers

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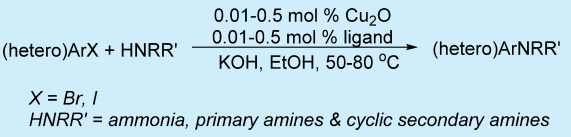
Supporting Information

ABSTRACT: A class of *N*-(naphthalen-1-yl)-*N*′-alkyl oxalamides have been proven to be powerful ligands, making a coupling reaction of (hetero)aryl iodides with primary amines proceed at 50 °C with only 0.01 mol % of Cu_2O and ligand as well as a coupling reaction of (hetero)aryl bromides with primary amines and ammonia at 80 °C with only 0.1 mol % of Cu_2O and ligand. A wide range of coupling partners work well under these conditions, thereby providing an easy to operate method for preparing (hetero)aryl amines.



Aryl amines are one of the most important classes of chemicals for both academics and industry. Their motifs are quite frequent in bioactive natural products and artificial compounds such as pharmaceuticals, agrochemicals, and material molecules. Additionally, they often serve as valuable building blocks in organic synthesis. Among the existing methods for preparing aryl amines, metal-catalyzed coupling reactions of (hetero)aryl halides with amines have become more and more attractive, mainly because they use very diverse, abundant, and cost-effective coupling partners as the starting materials, proceed under mild conditions with great scope, and allow late-stage transformations.[1] Although a great number of Pd- and Cu-based catalytic systems have been developed for arylation of amines during the past two decades,[1,2] an obvious problem is how to achieve high turnovers.[2] This is a challenging task because of the strong coordination affinities of amines to transition metals.[2] For Pd-catalyzed aryl amination reactions, in most cases 0.1−1 mol % catalytic loadings are necessary to ensure complete conversion. By using concisely designed phosphine ligands or precatalysts based on N-heterocyclic carbine ligands, the Buchwald,[3] Hartwig,[4] and Nolan[5] groups have demonstrated that some Pd-catalyzed aryl amination reactions could be carried out with only 0.01−0.001 mol % of catalysts and ligands. For Cu-catalyzed aryl amination reactions, relatively high catalytic loadings (>5 mol % copper salts and ligands) were used in most cases,[6] and little progress has been made toward carrying out the coupling reactions with low catalytic loadings of both copper catalysts and ligands. In 2007, the Buchwald group described that coupling of iodobenzene and imidazole proceeded smoothly under the catalysis of 0.025 mol % of Cu_2O and 0.075 mol % of 4,7-dimethoxy-1,10-phenanthroline at 110 °C,[7] but only one example was demonstrated, implying that this low catalytic loading was only suitable for a special case. Two years later, Bolm and co-workers reported that Cu-catalyzed coupling of iodobenzene with *N*-nucleophiles took place with part-per-million copper salt loadings, but very limited coupling partners gave satisfactory conversions, and over 20 mol % DMEDA ligand was required and the reaction temperature was rather high (135 °C).[8]

Recently, we revealed that a class of oxalic diamides are effective ligands for promoting Cu-catalyzed arylation with aryl chlorides, the difficult substrates for previous Cu-based catalytic systems.[9] Interestingly, for different coupling reactions, the optimized ligands are different, which indicated that subtle change in the electronic nature of ligands could greatly alter the coupling reaction process. Under the action of these ligands, CuI-catalyzed coupling reaction of (hetero)aryl chlorides with aliphatic primary amines and ammonia could be conducted at 110−120 °C with reasonable catalytic loadings (2−10 mol % CuI and ligands). Considering that (hetero)aryl iodides and bromides are more reactive toward Cu-catalyzed coupling reactions than corresponding (hetero)aryl chlorides, we envisioned that our newly developed ligands may have more superior activity for promoting Cu-catalyzed aryl amination with aryl bromides and iodides, thereby allowing the coupling reaction achieve high turnovers. After screening a series of oxalic diamide ligands, we identified some *N*-(naphthalen-1-yl)-*N*′-alkyl oxalic diamides as powerful ligands, which made the coupling reactions of aryl bromides with primary amines and ammonia complete with only 0.1 mol % of Cu_2O and ligand, and achieved 10000 turnovers in the case of coupling of aryl iodides with primary amines. More importantly, the reaction scope is rather satisfactory as evident from the finding that a broad range of (hetero)aryl halides (I, Br) and amines are compatible with these conditions. Herein, we disclose our results.

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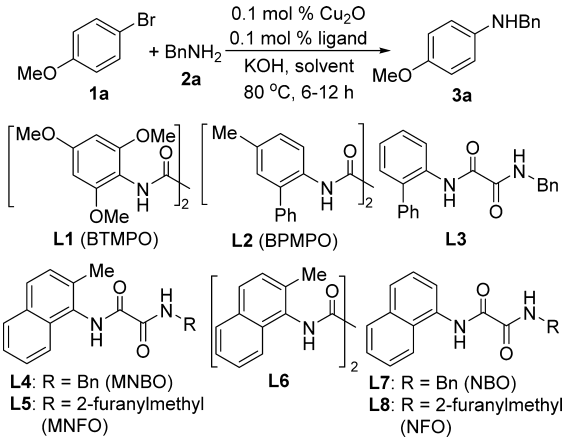
As indicated in Table 1, we started our exploration by conducting a coupling reaction of 4-bromoanisole and benzylamine under the catalysis of 0.1 mol % of Cu_2O and 0.1 mol % of ligand. Initially, BTMPO (**L1**),[9a] the best ligand for Cu-catalyzed coupling of aryl chlorides and primary amines, was tested. It was found that in *tert*-butyl alcohol at 80 °C after 6 h only 1% conversion was obtained (entry 1). A similar result was observed by using BPMPO (**L2**) that performed well in Cu-catalyzed coupling of aryl chloride and ammonia (entry 2). Therefore, we thought of modifying the ligands to observe the effect on the present reaction. Interestingly, a significant improvement was gained by using *N*-aryl-*N*′-alkyl-substituted oxalamide **L3** as a ligand (entry 3). Further structure−activity relationship studies based on **L3** revealed that *N*-(2-methylnaphthalen-1-yl)-*N*′-benzyl oxalamide (MNBO, **L4**) gave the best result (entry 4). In this case, prolonging the reaction time to 12 h gave a complete conversion (entry 5). Changing the benzyl group in **L4** to 2-furanylmethyl (MNFO, **L5**) did not affect the yield (entry 6). However, decreased yields were observed once the benzyl- and 2-methylnaphthalen-1-yl groups in **L4** were switched to 2-methylnaphthalen-1-yl (**L6**, entry 7) and naphthalen-1-yl (**L7**, entry 8), respectively. A similar result was obtained when **L8** (NFO), a simplified analogue of **L5**, was used (entry 9). Additionally, changing the solvent to ethanol did not affect the conversion (entry 8), and therefore, we used ethanol as the solvent in the subsequent investigations.

The established optimal reaction conditions were then tested with a variety of (hetero)aryl bromides and primary amines, and the results are summarized in Scheme 1. Several substituted aryl bromides have been demonstrated in 75−98% yields under the optimized conditions (**3b−i**). The successful formation of **3g** and **3i** showed good tolerance toward hydroxyl and carbamate functional groups. Some functionalized primary amines like 2-methyl-2-propen-1-amine (**3g**), (*R*)-2-phenylglycinol (**3k**), and 2-furanyl-methyl (**3l**) also worked well to afford the corresponding products in good yields. No *O*-arylated products were observed when an amino alcohol (**3k** and **3m**) were used, indicating that good chemoselectivity was achieved. Additionally, heteroaryl bromides such as pyridine (**3m**), *N*-benzyl-protected indole (**3n**), and quinoline (**3o**) could smoothly couple with some aliphatic primary amines under the present conditions, illustrating that the additional heterocycle did not alter the catalytic efficiency. When less nucleophilic primary aryl amines (**3p,q**) were used as the coupling partners, the reaction turned sluggish, and decreased yields were observed due to incomplete conversion under the same conditions. Indeed, excellent chemoselectivity between aryl amine and aliphatic amine moieties was achieved when 4-aminobenzenemethanamine was coupled with 2-bromonaphthalene (**3r**).

When more reactive (hetero)aryl iodides were employed, we were pleased to find that 0.01 mol % of Cu_2O and MNBO were enough to catalyze the aryl amination. The reaction proceeded smoothly at 50 °C in ethanol to give the coupling products in 88−95% yields (Scheme 2, **3a,s−v**). To exactly weigh both Cu_2O and MNBO, we had to carry out the reaction at 200

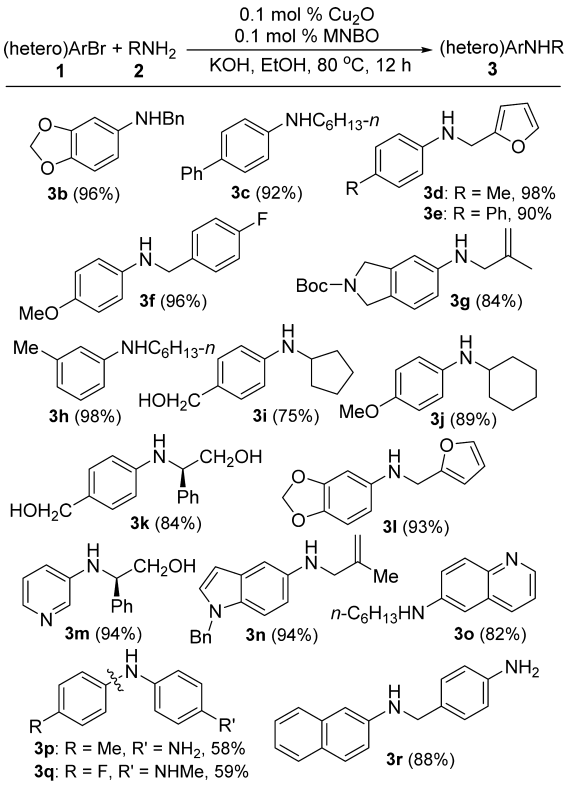
Table 1. Cu_2O-Catalyzed Coupling of 4-Bromoanisole with Benzylamine under the Assistance of Different Ligands[a,b]



entry	ligand	solvent	time (h)	yield[b] (%)
1	**L1**	*t*-BuOH	6	1
2	**L2**	*t*-BuOH	6	5
3	**L3**	*t*-BuOH	6	42
4	**L4**	*t*-BuOH	6	60
5	**L4**	*t*-BuOH	12	98
6	**L5**	*t*-BuOH	12	98
7	**L6**	*t*-BuOH	12	60
8	**L7**	*t*-BuOH	12	52
9	**L8**	*t*-BuOH	12	59
10	**L4**	EtOH	12	95

[a]Reaction conditions: **1a** (20 mmol), **2a** (30 mmol), Cu_2O (0.02 mmol), ligand (0.02 mmol), KOH (26 mmol), solvent (2 mL), 80 °C, 6−12 h. [b]Isolated yield.

Scheme 1. Cu_2O/MNBO-Catalyzed Coupling of (Hetero)aryl Bromides with Primary Amines[a]



[a]General conditions: **1** (20 mmol), **2** (30 mmol), Cu_2O (0.02 mmol), ligand (0.02 mmol), KOH (26 mmol), solvent (2 mL), 80 °C, 12 h. [b]Isolated yield.

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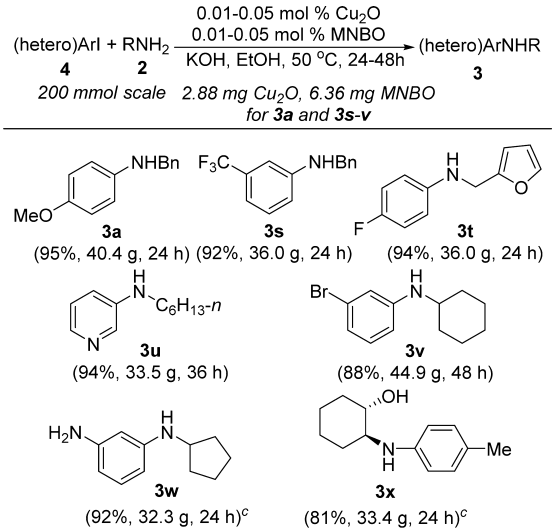
Scheme 2. Cu_2O/MNBO-Catalyzed Coupling of (Hetero)aryl Iodides with Primary Amines.[a,b]



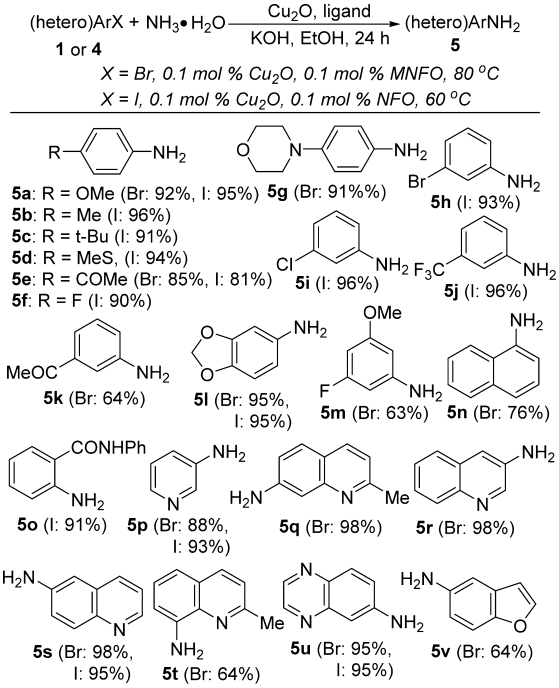
[a]General conditions: **4** (200 mmol), **2** (300 mmol), Cu_2O (0.02 mmol), MNBO (0.02 mmol), KOH (250 mmol), solvent (20 mL), 50 °C, 24 h. [b]Isolated yield. [c]Cu_2O (0.1 mmol) and ligand (0.1 mmol) were used.

mmol scale, and thus, 33.5−44.9 g of **3a** and **3s−v** were obtained by using only 2.88 mg of Cu_2O and 6.36 mg of MNBO. When substrates with another polar group were used, increasing the catalytic loading to 0.05 mol % was needed to get complete conversion (**3w** and **3x**). Because the reaction scale was so large, we only examined these seven examples. However, they have already demonstrated the robustness of our newly designed ligand, as evident from the fact that some functional groups in both coupling partners showed no or slight influence from high catalytic efficiency. The formation of **3v** and **3w** in 88−92% yields indicated that the excellent chemoselectivity between iodide and bromide, as well as aliphatic amine and aryl amine, could be obtained. To the best of our knowledge, no Cu/ligand catalytic system has been reported to have 10000 turnovers for both copper catalyst and ligand.

Later, we turned our attention to testing the efficiency of the method toward the synthesis of primary arylamines through coupling with ammonia (Scheme 3). In this regard, coupling of various electron-rich and electron-deficient aryl halides with ammonia−water under the catalysis of 0.1 mol % of Cu_2O and MNFO (or NFO for aryl iodides) were conducted, and they delivered the desired amination products **5a−o** in 63−96% yields. Not surprisingly, coupling of all the aryl iodides have been carried out at lower temperature than corresponding bromides with similar efficacy. Subsequently, a number of heteroaryl halides were examined under these reaction conditions. To our delight, their reactions worked well to give synthetically important aminoheterocycles, which include 3-aminopyridine (**5p**), aminoquinolines (**5q−t**), 6-amino-quinoxaline (**5u**), and 5-aminobenzofuran (**5v**).

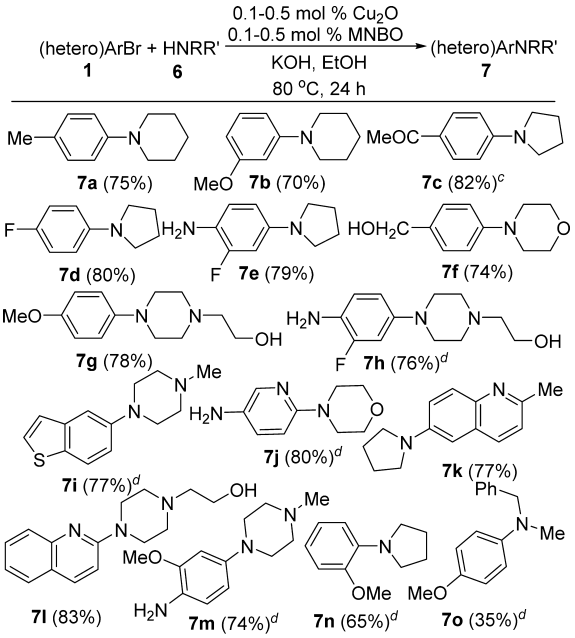
Cyclic secondary amines appended (hetero)aryl motifs are highly important in drug discovery. In this context, coupling reaction with cyclic secondary amines was checked using our new catalytic system (Scheme 4). We found that the combination of Cu_2O and MNBO is sensitive to steric hindrance of the amine coupling partners, so that increasing catalytic loadings was required for complete conversion in some

Scheme 3. Cu_2O/MNBO-Catalyzed Coupling of (Hetero)aryl Bromides and Iodides with Ammonia Water[a,b]



[a]General conditions: **1** or **4** (10 mmol), ammonia−water (2.5 mL), Cu_2O (0.01 mmol), MNFO (or NFO, 0.01 mmol), KOH (13 mmol), solvent (1 mL), 60 or 80 °C, 24 h. [b]Isolated yield.

Scheme 4. Scope of Cu_2O/MNBO-Catalyzed Coupling Reaction of (Hetero)aryl Bromides with Cyclic Secondary Amines[a,b]



[a]General conditions: **1** (20.0 mmol), **6** (30.0 mmol), Cu_2O (0.02 mmol), MNBO (0.02 mmol), KOH (26.0 mmol), EtOH (2 mL), 80 °C, 24 h. [b]Isolated yield. [c]75 °C. [d]Cu_2O (0.1 mmol) and MNBO (0.1 mmol) were used at 80 °C.

cases. In general, 0.1−0.5 mol % of Cu_2O and MNBO could effectively catalyze the coupling of (hetero)aryl bromides with

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simple and functionalized cyclic secondary amines to afford the tertiary amines **7a**−**m** in good yields. Our primary goal was to test our method by synthesizing some known building blocks that have been employed for assembling bioactive molecules. Toward this, the coupling products **7h** (a key intermediate for preparing protein kinase inhibitors),[10] **7j** (used for synthesizing KCNQ2/Q3 potassium channel opener[11a] and hedgehog pathway inhibitor[11b]), and **7m** (a building block for producing potent epidermal growth factor (EGFR) receptor inhibitor)[12] were successively obtained by using suitable coupling partners. Notably, the present coupling reaction is very sensitive to steric hindrance of both coupling partners because incomplete conversion is observed during the preparation of **7n** and **7o** even at a higher catalytic loading.

In summary, we have discovered that MNBO and related amides are superior ligands for promoting Cu-catalyzed coupling of aryl halides with amines. Over 10000 turnovers were observed in the case of the Cu_2O/MNBO-catalyzed coupling reaction of some aryl iodides with primary amines. Only 0.1−0.5 mol % Cu_2O and ligand were necessary for coupling reactions with a wide range of (hetero)aryl bromides and amines. The mild, environmentally friendly reaction conditions and high turnover numbers attributed the potentiality of the present method toward the preparation of aryl amines, particularly in large-scale production. Application of this catalytic system to other coupling reactions is being actively investigated in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00901.

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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