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CuI/DMPAO-Catalyzed *N*-Arylation of Acyclic Secondary Amines

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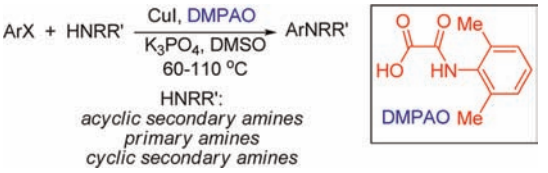
ABSTRACT



DMPAO has been found to be a powerful ligand to enable copper-catalyzed coupling of aryl halides with aliphatic acyclic secondary amines take place under relatively mild conditions, and coupling of aryl halides with primary amines and cyclic secondary amines proceeds at low catalyst loading.

In the past years, we have witnessed great progress in the discovery of mild conditions for copper-catalyzed coupling reaction of aryl halides with amines.[1] This progress is highly dependent on using some bidentate ligands such as amino acids,[2] diols,[3] amino alcohols,[4] β-diketones,[5] β-keto esters,[5] 2-pyridinyl β-ketones,[6] and 8-hydroxyquinoline *N*-oxide.[7] Although these ligands have been proven to be powerful for accelerating copper-catalyzed coupling of aryl halides with primary amines and cyclic secondary amines, none of them have displayed general efficiency for promoting copper-catalyzed *N*-arylation of aliphatic acyclic secondary amines.[2c,3a,7] This problem was presumably due to the relative bulkiness of acyclic secondary amines compared with primary amines and cyclic secondary amines and has become a major drawback of the copper-catalyzed aryl amination in contrast to the palladium-catalyzed *N*-arylation.[8] Because aryl tertiary amines also play an essential role in pharmaceutical and material sciences, and the advantage of copper catalysts over palladium catalysts for large-scale synthesis is obvious, it is highly desirable to develop more effective copper catalytic systems for *N*-arylation of acyclic secondary amines.[9] Recently, we discovered that 2-(2,6-dimethylphenylamino)-2-oxoacetic acid (DMPAO) is a powerful and inexpensive ligand for copper-catalyzed aryl amination, which not only effectively prompts *N*-arylation of a wide range of acyclic secondary amines but also works well for *N*-arylation of primary amines and cyclic secondary amines even at low catalytic loadings. Herein, we disclose our results.

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(7) Yang, K.; Qiu, Y.; Li, Z.; Wang, Z.; Jiang, S. *J. Org. Chem.* **2011**, *76*, 3151.

(8) For Pd-catalyzed N-arylation of acyclic secondary amines, see: (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (b) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586. (c) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766. (d) Henderson, J. L.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 4442.

(9) For synthesis of hindered anilines via copper-catalyzed electrophilic amination of aryl boronic esters, see: Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953.

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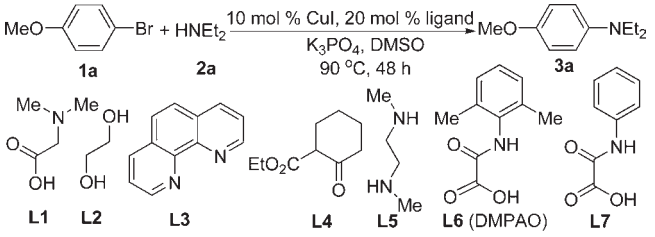
As indicated in Table 1, we ran a CuI-catalyzed coupling reaction of 4-bromoanisole with diethylamine as a model reaction to search for suitable ligands. It was found that at 90 °C a known ligand such as *N*,*N*-dimethylglycine, ethane-1,2-diol, 1,10-phenanthroline, ethyl 2-oxocyclohexanecarboxylate, or *N*,*N*′-dimethylethane-1,2-diamine gave either poor or no conversion. However, when DMPAO (**L6**)[10] was employed, the coupling yield jumped to 95%. The dimethyl groups in **L6** seemed to be important for this conversion because only 22% yield was observed in the case of 2-oxo-2-(phenylamino)acetic acid (**L7**) as a ligand.

Table 1. Ligand Effect on CuI-Catalyzed Coupling of 4-Bromoanisole and Diethylamine[a]



ligand	L1	L2[c]	L3	L4	L5	L6	L7
yield[b] (%)	20	23	0	0	0	95	22

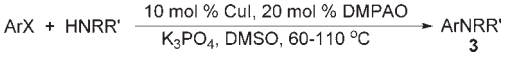
[a] Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), CuI (0.1 mmol), ligand (0.2 mmol), K_3PO_4 (2 mmol), DMSO (1 mL), 90 °C. [b] Isolated yield. [c] 200 mol % of ligand was used.

In view of the encouraging result, we next explored the scope and limitations of CuI/DMPAO catalyzed arylation of aliphatic acyclic secondary amines. As summarized in Table 2, coupling between diethylamine and a series of aryl halides was examined. To our delight, both electron-rich and electron-deficient aryl halides worked well under these conditions, providing the corresponding *N*-arylation products with good to excellent yields. The exception came from *ortho*-substituted aryl halides, which led to no or poor conversions (entries 4 and 12). This result indicated that steric hindrance of aryl halides could greatly decrease the coupling rate. Electron-deficient aryl halides seemed to be more reactive than electron-rich ones, as shorter reaction times were required when aryl halides bearing an electron-withdrawing group were employed (compare entries 3 and 6, 11 and 14). This phenomenon is consistent with that observed in previous studies on ligand-promoted Ullmann-type aryl amination.[2−5] In the case of 1-(4-bromophenyl)ethanone as a substrate, the coupling reaction could be completed even at 60 °C (entry 15). As usual, aryl iodides showed higher reactivity than aryl bromides.

(10) The crystal structure of a complex generated from Cu(II) salts has been reported. See: Ferrando-Soria, J.; Pardo, E.; Ruiz-García, R.; Cano, J.; Lloret, F.; Julve, M.; Journaux, Y.; Pasán, J.; Ruiz-Pérez, C. *Chem.—Eur. J.* **2011**, *17*, 2176.

For example, coupling with 1-naphthyl bromide gave no product (entry 8), while 1-naphthyl iodide delivered tertiary amine **3i** in 72% yields under the same conditions (entry 9).

Table 2. CuI/DMPAO-Catalyzed Coupling Reaction of Aryl Halides with Diethylamine[a]



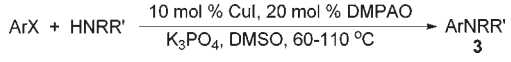
entry	Ar	X	time (h)	product (yield, %)[b]
1	2-naphthyl	Br	36	**3b** (76)
2	4-MeC_6H_4	Br	48	**3c** (91)
3	3-MeC_6H_4	Br	48	**3d** (89)
4	2-MeC_6H_4	Br	48	**3e** (0)
5	4-$MeSC_6H_4$	Br	60	**3f** (80)
6	3-AcC_6H_4	Br	24	**3g** (82)
7	4-$NO_2C_6H_4$	Br	20	**3h** (94)
8	1-naphthyl	Br	36	**3i** (0)
9	1-naphthyl	I	40	**3i** (72)
10	3-$MeOC_6H_4$	I	24	**3j** (95)
11	4-$MeOC_6H_4$	I	48	**3a** (94)
12	2-$MeOC_6H_4$	I	48	**3k** (26)
13	3-MeC_6H_4	I	36	**3d** (91)
14	4-AcC_6H_4	I	16	**3l** (78)
15	4-AcC_6H_4	I	40	**3b** (100)[c]
16	3-$NO_2C_6H_4$	I	16	**3m** (100)
17	4-PhC_6H_4	I	40	**3n** (97)

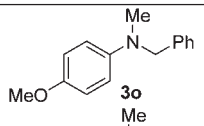
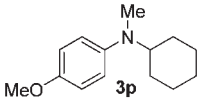
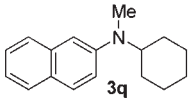
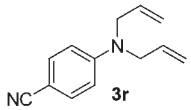
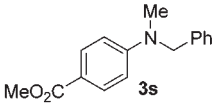
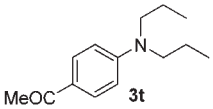
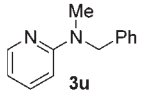
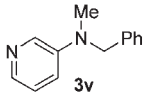
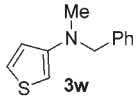
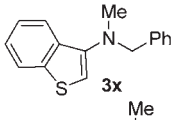
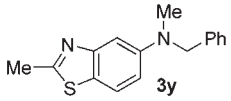
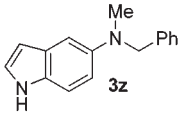
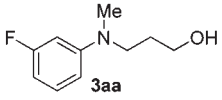
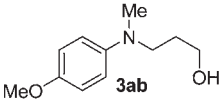
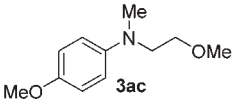
[a] Reaction conditions: aryl halide (1 mmol), diethylamine (1.5 mmol), CuI (0.1 mmol), DMPAO (0.2 mmol), K_3PO_4 (2 mmol), DMSO (1 mL), 90 °C. [b] Isolated yield. [c] Reaction was carried out at 60 °C.

We next moved our attention to employing other aliphatic acyclic secondary amines to couple with aryl and heteroaryl halides, and the results are summarized in Table 3. Coupling of 4-bromoanisole with *N*-methyl-*N*-benzylamine gave **3o** in 86% yield (entry 1). When bulkier *N*-methylcyclohexanamine was used, the reaction became sluggish and an incomplete conversion was observed at 110 °C (entries 2 and 3). This problem could be solved by changing the coupling partners to aryl iodides (compare entries 3 and 4). Like the coupling of diethylamine with 1-(4-iodophenyl)ethanone, reactions of three other secondary amines and electron-deficient aryl iodides proceeded well even at 60−75 °C to provide **3r**−**t** in 83−97% yields (entries 6−8). This result represents the lowest temperatures for copper-catalyzed *N*-arylation of acyclic secondary amines.

Further attempts revealed that coupling of *N*-methyl-*N*-benzylamine with three heteroaryl bromides could reach completion at 90 °C in 20 h (entries 9−11). However, prolonged reaction time was required to ensure complete conversion in the case of 3-bromobenzothiophene and 5-bromo-2-methylbenzo[*d*]thiazole as the coupling partners (entries 12 and 13). When 5-bromoindole was utilized, the coupling reaction in DMSO gave a complicated mixture (entry 14), which implied that homocoupling of

Table 3. Assembly of Tertiary Anilines via CuI/DMPAO-Catalyzed N-Arylation of Acyclic Scondary Amines[a]



entry	X	temp (°C)/ time (h)	product	yield (%)[b]
1	Br	90/24	 **3o**	86
2	Br	110/48	 **3p**	62
3	Br	110/48	 **3q**	64
4	I	90/48		81
5	Br	90/24	 **3r**	70
6	I	60/40		91
7	I	60/40	 **3s**	97
8	I	75/48	 **3t**	83
9	Br	90/20	 **3u**	91
10	Br	90/20	 **3v**	85
11	Br	90/20	 **3w**	90
12	Br	90/36	 **3x**	73
13	Br	90/36	 **3y**	71
14	Br	110/24		-
15	Br	110/20[c]	 **3z**	64
16	Br	110/15[c]	 **3aa**	87
17	Br	110/15[c]	 **3ab**	85
18	Br	110/20[c]	 **3ac**	75

[a] Reaction conditions: aryl halide (1 mmol), amine (1.5 mmol), CuI (0.1 mmol), DMPAO (0.2 mmol), K_3PO_4 (2 mmol), DMSO (1 mL). [b] Isolated yield. [c] Reaction was carried out in *n*-BuOH.

5-bromoindole might occur. Fortunately, when this reaction was carried out in *n*-butanol, the desired cross-coupling product **3z** was isolated in 64% yield (entry 15), indicating that changing solvent could influence the chemical selectivity between the secondary amine and indole NH groups.

Some functionalized acyclic secondary amines were also applicable for this reaction (entries 16−18). In the case of 3-(methylamino)propan-1-ol, only a trace of *O*-arylation products were determined, which illustrated that aryl amination exclusively occurred. This selectivity is similar to that observed in CuI/1,3-diketone-catalyzed reaction of aryl iodide with amino alcohols.[5c] Taken together, we concluded that the present catalytic system could be applied for preparing tertiary *N*-arylamines from a wide range of functionalized aryl halides and aliphatic secondary amines.

The excellent promoting ability displayed by DMPAO prompted us to develop a more efficient catalytic system for *N*-arylation of primary amines and cyclic secondary amines. The previous catalytic systems normally required at least 5 mol % of copper salts to maintain satisfactory conversions.[2−6] Very few examples employed ≤1% [Cu] mol catalyst loading, and in these studies substrates were limited to primary amines.[7] Gratifyingly, use of 1 mol % of CuI and 2 mol % of DMPAO as the catalysts provided complete conversions for a wide range of aryl bromides, primary amines, and cyclic secondary amines (Table 4). It is noteworthy that under similar catalytic loading and reaction conditions, other ligands such as L-proline, 1,10-phenanthroline, 2,2,6,6-tetramethylheptane-3,5-dione, and ethyl 2-oxocyclohexanecarboxylate gave very poor conversions. These results demonstrated that DMPAO is probably one of the most powerful ligands for copper-catalyzed aryl amination to date.

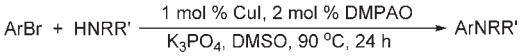
Interestingly, under the same conditions, coupling of 4-bromoanisole with *N*-methylaniline did not give *N*-arylation product, while *N*-methylcyclohexanamine produced the desired product **3p** in 48% yield (Scheme 1). This result demonstrated that the electronic nature of amines plays an essential role for the present coupling reaction, although the steric hindrance of amines has a remarkable influence on their reactivity.

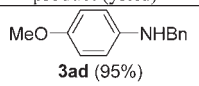
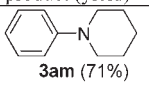
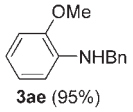
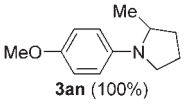
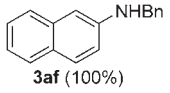
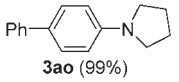
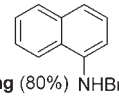
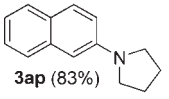
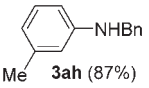
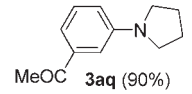
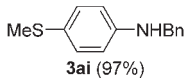
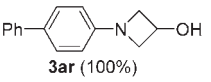
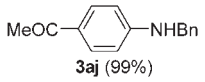
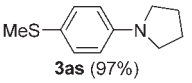
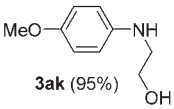
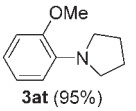
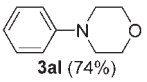
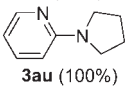
In Lloret's X-ray crystal structure,[10] DMPAO was shown to coordinate with Cu(II) as a dianion form, where both the amidate nitrogen and the carboxylate oxygen atoms participate in the coordination. In our case, we realized that a *O*,*O*-coordination complex **A** (Scheme 2) might exist from CuI and DMPAO. Similar complexes resulted from Cu(I) salts, and anionic 1,3-diketone ligands have been discussed.[11] Indeed, the present catalytic system has similar behavior with the combination of CuI and 1,3-diketone in terms of

(11) Yu, H.-Z.; Jiang, Y.-Y.; Fu, Y.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 18078.

(12) For other recent reports on mechanistic studies of Ullmann coupling reactions, see: (a) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613. (b) Tye, J. W.; Wang, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971. (c) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326.

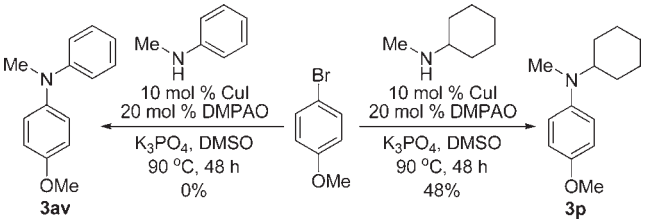
Table 4. CuI/DMPAO-Catalyzed Coupling of Aryl Bromide with Amines under Low Catalytic Loading[a]



entry	product (yield)[b]	entry	product (yield)[b]
1	 **3ad** (95%)	10	 **3am** (71%)
2[c]	 **3ae** (95%)	11	 **3an** (100%)
3	 **3af** (100%)	12	 **3ao** (99%)
4	 **3ag** (80%)	13	 **3ap** (83%)
5	 **3ah** (87%)	14	 **3aq** (90%)
6[c]	 **3ai** (97%)	15	 **3ar** (100%)
7	 **3aj** (99%)	16[c]	 **3as** (97%)
8	 **3ak** (95%)	17[c]	 **3at** (95%)
9	 **3al** (74%)	18	 **3au** (100%)

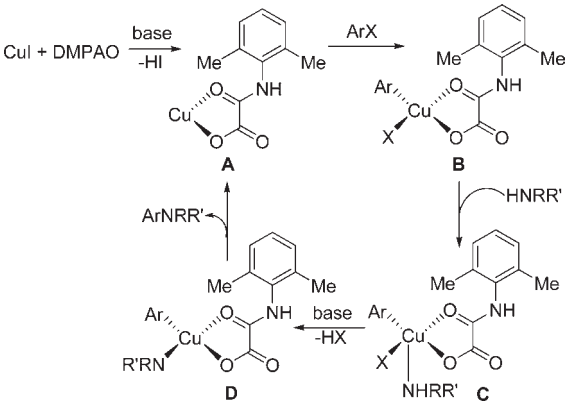
[a] Reaction conditions: aryl halide (1 mmol), amine (1.5 mmol), CuI (0.01 mmol), DMPAO (0.02 mmol), K_3PO_4 (2 mmol), DMSO (1 mL), 90 °C. [b] Isolated yield. [c] Reaction time: 40–48 h.

Scheme 1



selectivity for *N*-arylation and *O*-arylation as mentioned previously.[5c] For CuI/1,3-diketone-catalyzed *N*-arylation, a possible mechanism has been proposed on the basis of calculation studies.[11] Based on this study, we proposed a catalytic cycle as depicted in Scheme 2. Oxidative addition of **A** to an aryl halide produced Cu(III) complex **B**, which could undergo ligand exchange to afford Cu(III) complex **C**. Reductive elimination of **C** would deliver the aryl amination product and regenerate the complex **A**. The electronic nature of the present ligand might make the formation of the intermediate **C** easier, and therefore, the coupling reaction could proceed smoothly. More studies are needed to figure out the detailed reaction course.[12]

Scheme 2



In conclusion, we have revealed that the combination of CuI and DMPAO is a powerful catalytic system for *N*-arylation of aliphatic acyclic secondary amines. Our result gives an excellent solution to a long-lasting problem in ligand-promoted Ullmann-type aryl amination. Additionally, low catalytic loading employed here for *N*-arylation of primary amines and cyclic secondary amines is notable. Taking into consideration the inexpensive catalytic system and the generality for a wide range of amines, this combination can find numerous applications in organic synthesis. Applications of this ligand to other coupling reactions, together with detailed mechanistic studies, are being explored in our laboratory.

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Supporting Information Available. Experimental procedures and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.