

The Synthesis of *N*-Arylated Amides *via* Copper(II) Triflate-Catalyzed Direct Oxygenation and *N*-Arylation of Benzylamines with Aryl Iodides

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Abstract: An efficient approach for the synthesis of *N*-arylated amides by copper(II) triflate-catalyzed direct oxygenation and *N*-arylation reaction of benzylamines with aryl iodides is reported. Various benzylamines and aryl iodides can participate in the reaction, providing a series of *N*-arylated amides in moderate to good yields.

Keywords: aryl iodides; *N*-arylated amides; benzylamines; copper(II) triflate catalysis; oxygenation and *N*-arylation

Amide derivatives are an important class of organic compounds that are present in many natural products and medicinal intermediates.^[1] Many amides are found to exhibit a wide range of biological activities, including antifungal,^[2] antitumor,^[3] antimicrobial,^[4] anticancer^[5] and anti-inflammatory activities.^[6] Owing to their great utility, great interest has been directed to construction of the amide scaffold for many years.^[7]

Generally, the traditional syntheses of amides are the reactions of carboxylic acid derivatives, such as acid chlorides, anhydrides and esters, with amines at high temperatures or with the help of Lewis acids,^[8] which are not atom economical and usually generate stoichiometric amounts of by-product.^[9] Alternative methods, such as the Beckmann rearrangement,^[10] hydration of the nitrile,^[11] amidations of aldehydes with amines^[12] and metal-mediated aminocarbonylations of aryl halides^[13] have appeared to improve the procedures for amide synthesis. Recently, more effort is being paid to develop other facile, highly efficient and economical methods by introduction of new starting

materials or new catalysts. For example, the Cu- or Pd-catalyzed *N*-arylations of amides have been demonstrated by Buchwald,^[14] Hartwig^[15] and Ma,^[16] respectively. Notably, the metal-catalyzed oxidations of alcohols with amines^[17] or ammonia^[18] into amide derivatives have been developed by many groups: Madsen's^[19] or Williams',^[20] for instance. However, the metal-catalyzed direct oxygenation of a primary amine to the amide is very difficult, and there are relatively few reports about this conversion. Mizuno^[21] and Kaneda^[22] reported the successful metal-catalyzed oxygenation of primary amines to primary amides respectively. Recently, Fu and co-workers^[23] demonstrated the copper-catalyzed aerobic oxidative synthesis of primary amides from (aryl)methanamines. These excellent works urged us to postulate that the *N*-arylated amides could be synthesized from benzylamines and aryl iodides by the simultaneous oxygenation and *N*-arylation of benzylamines with the aid of O₂. To the best of our knowledge, this is the first strategy utilizing Cu(OTf)₂-catalyzed oxygenation and arylation reaction of benzylamines with aryl iodides for the formation of *N*-arylated amides. Here, we report the results in detail.

The reaction between benzylamine (**1a**) and iodo-benzene (**2a**) to afford *N*-phenylbenzamide (**3**) was chosen to screen the optimal conditions (Table 1). Initially, a series of nitrogen ligands, including 2,2-bipyridine (L1), 1,10-phenanthroline (L2), 4,7-dimethyl-1,10-phenanthroline (L3), 2,9-dimethyl-1,10-phenanthroline (L4), L-proline (L5), were tested for the reaction of substrate **1a** when using 10 mol% Cu(OTf)₂ as the catalyst, 2.5 equiv. K₂CO₃ as base and toluene as solvent at 110°C (entries 1–5). It can be seen that the ligands affected the yields slightly and 1,10-phenanthroline (L2) gave the best result. Next, K₂CO₃ was replaced with different bases, such as Na₂CO₃,

Table 1. Optimization of the reaction conditions.^[a]

Entry	Cu source	Ligand	Base	Solvent	Temperature [°C]	Yield ^[b] [%]
1	Cu(OTf) ₂	L1	K ₂ CO ₃	toluene	110	37
2	Cu(OTf) ₂	L2	K ₂ CO ₃	toluene	110	49
3	Cu(OTf) ₂	L3	K ₂ CO ₃	toluene	110	42
4	Cu(OTf) ₂	L4	K ₂ CO ₃	toluene	110	33
5	Cu(OTf) ₂	L5	K ₂ CO ₃	toluene	110	43
6	Cu(OTf) ₂	L2	Na ₂ CO ₃	toluene	110	10 (50+6) ^[c]
7	Cu(OTf) ₂	L2	NaHCO ₃	toluene	110	< 5 (56+6) ^[c]
8	Cu(OTf) ₂	L2	Cs ₂ CO ₃	toluene	110	< 5 (60+7) ^[c]
9	Cu(OTf) ₂	L2	KOH	toluene	110	< 5 (62+9) ^[c]
10	Cu(OTf) ₂	L2	KO- <i>t</i> -Bu	toluene	110	< 5 (65+8) ^[c]
11	Cu(OTf) ₂	L2	K ₂ CO ₃	DMF	110	trace (70+9) ^[c]
12	Cu(OTf) ₂	L2	K ₂ CO ₃	MeCN	110	< 5 (65+6) ^[c]
13	Cu(OTf) ₂	L2	K ₂ CO ₃	DMSO	110	61
14	Cu(OTf) ₂	L2	K ₂ CO ₃	DMSO	140	73 (87 ^[d])
15 ^[e]	Cu(OTf) ₂	L2	K ₂ CO ₃	DMSO	140	—
16 ^[d]	Cu(OAc) ₂	L2	K ₂ CO ₃	DMSO	140	< 5 (72 ^[f])
17 ^[d]	CuO	L2	K ₂ CO ₃	DMSO	140	< 5 (65 ^[f])
18 ^[d]	CuBr ₂	L2	K ₂ CO ₃	DMSO	140	67
19 ^[d]	—	L2	K ₂ CO ₃	DMSO	140	—
20 ^[d]	Cu(OTf) ₂	—	K ₂ CO ₃	DMSO	140	—

^[a] Reaction conditions: **1a** (0.45 mmol), **2a** (0.3 mmol), [Cu] (10 mol%), base (2.5 equiv.), ligand (20 mol%) and solvent (3 mL) for 3 days.

^[b] Isolated yields.

^[c] The respective yields (**3a**+**3b**) derived from **1a** were determined by GC-MS analysis.

^[d] Using O₂ instead of air

^[e] Under N₂.

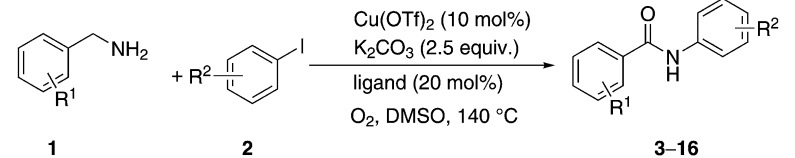
^[f] Isolated yields of the oxidative product of benzylamine (**3a**).

NaHCO₃, Cs₂CO₃, KOH and KO-*t*-Bu, the results indicated that the identity of base was critical to the success of the amination reaction (entries 6–10) and the by-product of benzylimine **3a**, resulting from the oxidation of benzylamine,^[21b,24] was found to be formed associated with a small quantity of **3b** as shown by GC-MS analysis. Examination of the effects of solvents and reaction temperatures showed that the reaction proceeded optimally in DMSO at 140 °C. The by-products of **3a** and **3b** were mainly generated when using DMF or MeCN as solvent (entries 11–14). In view of the important roles of O₂ as oxidant,^[25] by bubbling O₂ into the reaction mixture, the yield of **3** can be increased to 87%, whereas when the reaction was performed under N₂, no amide product **3** or benzylimine **3a** but only a trace of **3b** can be detected by GC-MS, which indicated that O₂ was beneficial to the oxygenation of benzylamines and the oxygen atom of

3 is derived from the molecular oxygen (entries 14 and 15). Under O₂, other Cu catalysts, such as Cu(OAc)₂, CuO or CuBr₂, were investigated and found to be inferior to Cu(OTf)₂ (entries 16–18). No amide product or benzylimine was observed from the reaction of substrate **1a** with **2a** in the absence of catalyst or ligand (entries 19 and 20).

With the optimal reaction conditions in hand, the electronic and steric effects of substituted benzylamines and aryl iodides were investigated (Table 2). Initially, a set of aryl iodides derivatives (**2a–2h**) was examined by reaction with benzylamine (**2a**) (entries 1–8). The result showed that the reaction seemed to be sensitive to the electronic effects on the aromatic ring of the aryl iodides. For example, aryl iodides with Cl and F moieties gave higher yields than their methyl and methoxy equivalents (entries 2–5). The substrate scope was extended to 3-methyl- and 2-me-

Table 2. The investigation of electronic and steric effects on the amination reaction.^[a]

					
Entry	Benzylamine		Aryl iodide		Product (yield [%] ^[b])
1		1a		2a	3 (87)
2		1a		2b	4 (40)
3		1a		2c	5 (45)
4		1a		2d	6 (60)
5		1a		2e	7 (66)
6		1a		2f	8 (55)
7		1a		2g	9 (50)
8		1a		2h	10 (32)
9		1b		2a	11 (55)
10		1c		2a	12 (58)
11		1d		2a	13 (62)
12		1e		2a	14 (65)
13		1f		2a	15 (35)
14		1g		2a	16 (41)

^[a] Reaction conditions: **1** (0.45 mmol), **2** (0.30 mmol), Cu(OTf)₂ (10 mol%), K₂CO₃ (2.5 equiv.), 1,10-phenanthroline (20 mol%) and DMSO (3 mL) at 140 °C for 3 days.

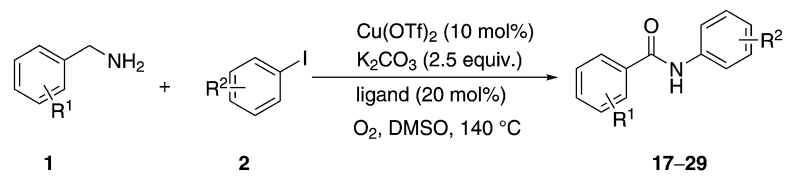
^[b] Isolated yield.

thoxyphenyl iodides, obtaining the *meta*- and *para*-arylated benzamides in moderate yields (entries 6 and 7). Gratifyingly, α -iodonaphthalene was also tolerated in this process, providing the corresponding benzamide in 32% yield (entry 8), demonstrating that the amination is possible even in cases where steric hindrance from the aryl iodide is increased. Nevertheless, when we attempted to react iodomethane or bromobenzene with benzylamine (**1a**) under the optimal

conditions, we obtained no target amide but only the by-products of benzylamine and benzamide.

Subsequently, the scope of the benzylamines for this reaction with iodobenzene was evaluated (entries 9–14), giving similar results with aryl iodides. Benzylamines bearing electron-withdrawing groups, such as F and Br, showed slightly higher reactivity than those with electron-donating groups, like methyl and methoxy moieties (entries 9–12). When the sub-

Table 3. The Cu(OTf)₂-catalyzed amidation of benzylamine (**1**) with aryl iodide derivatives (**2**).^[a]

					
Entry	Benzylamine		Aryl iodide		Product (yield%) ^[b]
1		1b		2b	trace
2		1b		2c	17 (57)
3		1b		2d	18 (65)
4		1b		2e	19 (70)
5		1b		2f	20 (48)
6		1b		2g	21 (36)
7		1b		2h	22 (39)
8		1e		2b	23 (69)
9		1e		2c	24 (75)
10		1e		2d	25 (85)
11		1e		2e	26 (89)
12		1e		2f	27 (73)
13		1e		2g	28 (38)
14		1e		2h	29 (43)

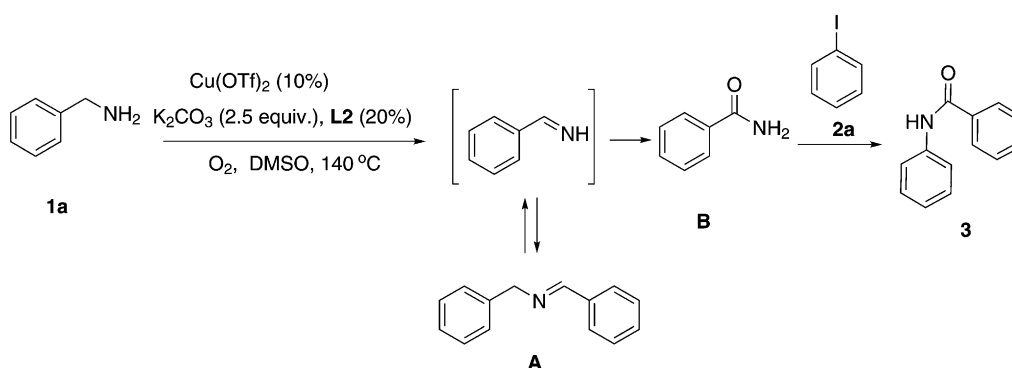
^[a] Reaction conditions: **1** (0.45 mmol), **2** (0.30 mmol), Cu(OTf)₂ (10 mol%), K₂CO₃ (2.5 equiv.), 1,10-phenanthroline (20 mol%) and DMSO (3 mL) at 140 °C for 3 days.

^[b] Isolated yield.

strate scope was extended to 3- or 2-fluorobenzylamine, the corresponding products were obtained in lower yields (entries 13 and 14). During our experiments, the direct dehalogenated by-products from benzylamines and aryl iodides can be detected by GC-MS, resulting in the relatively low yields.

Excited by the facile synthesis of amides from substituted benzylamines and aryl iodides, 4-methoxyben-

zylamine (**1b**) and 4-fluorobenzylamine (**1e**) were examined with respect to various aryl iodides to synthesize *N*-arylated amide derivatives (Table 3). As in previous studies, 4-fluorobenzylamine (**1e**) (entries 8–14) generated its corresponding amides in higher yields than 4-methoxybenzylamine (**1b**) (entries 1–7). Similarly, the aryl iodides having electron-withdrawing groups (entries 3, 4, 10, 11) favored the amination



Scheme 1. The reaction pathway.

more than those with electron-donating groups (entries 1, 2, 8, 9). When both the amine and aryl iodide possessed an electron-rich group, such as a methoxy moiety, only a trace of the desired product can be obtained (entry 1). On the contrary, 4-fluoro-*N*-(4-fluorophenyl)benzamide and 4-fluoro-*N*-(4-chlorophenyl)benzamide were produced with higher yields of 89% and 85%, respectively (entries 10 and 11). Moreover, 3-methyliodobenzene and 2-methoxyiodobenzene were also good substrates, giving the corresponding amides in moderate yields (entries 5, 6, 12, 13). Although the yields of 39% and 43% were not so good, α -iodonaphthalene was also applicable for this reaction (entries 7 and 14).

The reaction process was monitored by GC-MS and the reaction mixture was sampled every two hours. It was found that the benzylimine **A** was first produced by the Cu-catalyzed oxidative reaction of **1a** with the aid of O₂,^[24] then disappeared slowly to give the intermediate **B**,^[26] which was reacted with iodobenzene to give the amide product **3** by removing HI. The possible reaction pathway is proposed in Scheme 1. The interesting conversion of primary amine (**1a**) to intermediate **B** was also demonstrated by Mizuno through the sequence of oxidative dehydrogenation and successive hydration.^[21b] A controlled reaction of benzylamine (**1a**) was carried out in the absence of iodobenzene, giving **B** as a major product with a small quantity of **A** by GC-MS analysis.

In summary, we have developed an efficient approach for the synthesis of amides via Cu(OTf)₂-catalyzed oxygenation and *N*-arylation reaction of benzylamines with aryl iodides with the aid of O₂, which allows the reaction between various benzylamines and aryl iodides for the synthesis of *N*-arylated amides in moderate to good yields. Efforts to explore the detailed mechanism and extend the applications to different substrate, such as aliphatic amines (iodides) and aryl bromides, are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Cu(OTf)₂-Catalyzed Direct Oxygenation and *N*-Arylation of Benzylamines with Aryl Iodides

Iodide (0.3 mmol), amine (0.45 mmol), Cu(OTf)₂ (10 mol%), K₂CO₃ (2.5 equiv.), 1,10-phenanthroline (20 mol%) and DMSO (3 mL) were added to a Schlenk tube. The tube was then charged with O₂, and the reaction mixture stirred at 140 °C for 3 days. After the reaction was finished, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with brine. The combined organic extracts were dried over Na₂SO₄, concentrated under vacuum, and the resulting residue was purified by silica gel column chromatography to afford the desired product.

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