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Copper-Catalyzed Synthesis of α-Amino Imides from Tertiary Amines: Ugi-Type Three-Component Assemblies Involving Direct Functionalization of sp^3 C−Hs Adjacent to Nitrogen Atoms

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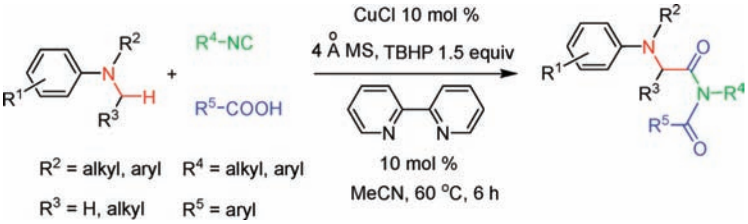
ABSTRACT



α-Amino imides can be accessed straightforwardly from tertiary amines through copper-catalyzed three-component reactions involving the direct functionalization of sp^3 C−Hs adjacent to nitrogen atoms. This reaction has demonstrated a tolerance to a wide range of functionalizations and can be performed under very mild conditions. A plausible mechanism has been proposed in which an Ugi-type cascade assembly has been included.

α-Amino amides have been constantly found in many natural products and pharmaceuticals.[1] They have also been intensively used as intermediates for the synthesis of many heterocycles.[2] Moreover, the utilization of them as organocatalysts and catalyst ligands has attracted much attention.[3,4] Traditionally, these motifs could be prepared straightforwardly by the Ugi reaction involving the imines generated in situ from the amines and aldehydes.[5,6] However, due to the involvement of acyl migration as the key step (the Mumm rearrangement), the classic Ugi reaction usually required primary amines and therefore showed limited success in the preparation of α-nonacylamino amides.[7] To address this limitation, Suginome et al. developed the acid-free Ugi-type three-component reaction which had proven to be applicable to secondary amines.[8] Nevertheless, these reactions mechanistically had to be performed under the promotion of aminoborane, which needed to be presynthesized and used in a stoichiometric amount. Hence, the development of novel access to α-amino amides, especially the α-nonacylamino amides, from readily available materials is still of much significance.

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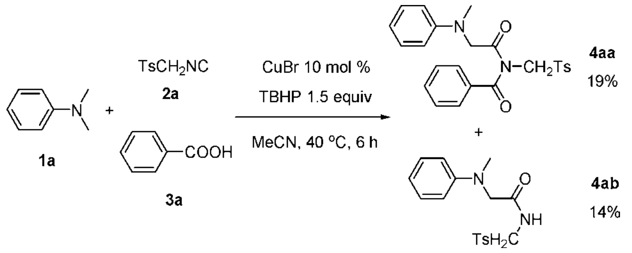
In recent years, oxidative isocyanide-based multicomponent reactions have become a challenge since isocyanides are known to be sensitive toward a variety of oxidants.[9] Synthesis of α-amino amides by IBX (2-iodoxybenzoic acid) mediated oxidative Ugi-type three-component reaction has already been achieved by Zhu and his co-workers.[10] On the other hand, transition-metal-catalyzed direct functionalization of unactivated sp^3 C−Hs has attracted wide attention mainly for its atom-economical significance.[11,12] Among the various methods that have been developed,[13−18] copper-catalyzed strategies for the activation of sp^3 C−Hs α to nitrogens under the promotion of peroxides have been well documented.[19] A variety of nucleophiles such as terminal alkynes,[20] nitromethanes and malonates,[21] indoles,[22] naphthols,[23] amides,[24] phosphonates,[25] as well as silyl enol ethers[26] have been successfully used for the direct functionalization of saturated C−Hs in amines. Considering that the iminiums can be readily accessed from the activation of the sp^3 C−Hs α to nitrogens in amines by coppers as described by Li and his co-workers,[19] we assumed that the α-amino amide frameworks were able to be synthesized conveniently by the three-component assemblies of saturated amines with isocyanides and carboxylic acids under the promotion of copper and peroxides.

As an initial study of our investigations, we performed the reaction of *N*,*N*-dimethylbenzenamine **1a** with 1-(isocyanomethylsulfonyl)-4-methylbenzene **2a** and benzoic acid **3a** under the promotion of 10 mol % CuBr and 150 mol % TBHP (*tert*-butyl hydroperoxide in decane) in MeCN at 40 °C for 6 h. To our delight, the reaction indeed occurred, affording the isolable α-amino imide product **4aa** and α-amino amide **4ab** in 19% and 14% yields (Scheme 1). To achieve a better performance, we next conducted an optimization on the reaction conditions, and the results are summarized in Table 1.

Scheme 1. Initial Experiment



In view of the structural difference between **4aa** and **4ab**, we deduced that **4ab** might be produced by the reaction of **1a** and **2a** with H_2O which was formed in situ under the above reaction conditions. So we next added 4 Å MS (molecular sieves) into the reaction mixture and found that the formation of **4ab** was successfully inhibited (Table 1, entry 1). To improve the reaction efficiency further, we next introduced the *N*^{1},*N*^{2}-dimethylethane-1,2-diamine and 2-(pyridin-2-yl)pyridine as bidentate ligands and discovered that the latter was superior, with a 32% yield of **4aa** being delivered (Table 1, entries 2 and 3). Screening of the copper catalysts had revealed that CuCl worked best (Table 1, entries 4−7). On the other hand, other peroxides such as benzoyl peroxide, *tert*-butyl perbenzoate, and 2-(*tert*-butylperoxy)-2-methylpropane had proven to be less effective oxidants (Table 1, entries 8−10). When employing *tert*-butyl perbenzoate and 2-(*tert*-butylperoxyl)-2-methylpropane as the reaction promoters, only a trace amount of the desired product **4aa** was provided. Optimization of the reaction temperature

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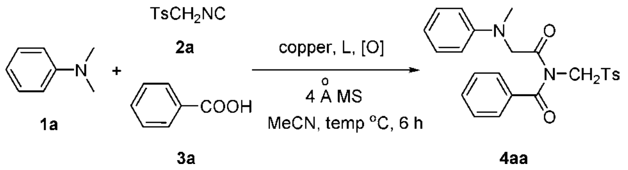
Table 1. Optimization[a]



entry	conditions	yield %[b]
1	CuBr, TBHP, 40 °C	18
2	CuBr, TBHP, N^1,N^2-dimethylethane-1,2-diamine, 40 °C	10
3	CuBr, TBHP, 2-(pyridin-2-yl)pyridine, 40 °C	32
4	CuI, TBHP, 2-(pyridin-2-yl)pyridine, 40 °C	67
5	CuBr$_2$, TBHP, 2-(pyridin-2-yl)pyridine, 40 °C	43
6	CuCl$_2$, TBHP, 2-(pyridin-2-yl)pyridine, 40 °C	50
7	CuCl, TBHP, 2-(pyridin-2-yl)pyridine, 40 °C	68
8	CuCl, (PhCO$_2$)$_2$, 2-(pyridin-2-yl)pyridine, 40 °C	54
9	CuCl, PhCO$_3$-*t*-Bu, 2-(pyridin-2-yl)pyridine, 40 °C	trace
10	CuCl, (*t*-BuO)$_2$, 2-(pyridin-2-yl)pyridine, 40 °C	trace
11	CuCl, TBHP, 2-(pyridin-2-yl)pyridine, 60 °C	84
12	CuCl, TBHP, 2-(pyridin-2-yl)pyridine, 80 °C	78

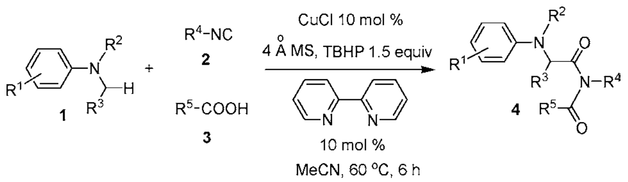
[a] Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), **3a** (1.5 mmol), copper catalysts (0.1 mmol), ligands (0.1 mmol), peroxides (1.5 mmol), MeCN (5.0 mL). [b] Isolated yields based on **2a**.

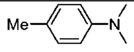
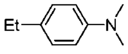
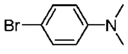
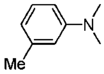
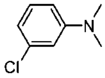
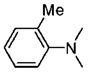
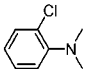
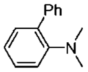
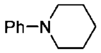
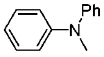
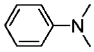
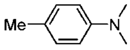
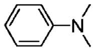
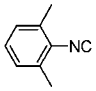
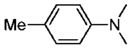
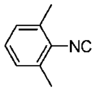
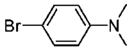
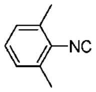
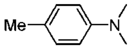
had revealed that elevating the temperature was beneficial for the reaction, and a higher yield (84%) could be obtained when the reaction was performed at 60 °C (Table 1, entry 11). However, further increasing the temperature seemed to be disadvantageous, and just a 78% yield of **4aa** was afforded while the reaction was carried out at 80 °C (Table 1, entry 12).

With the optimal conditions in hand, we next studied the scope of the three-component reaction, and the results are illustrated in Table 2. Various *N*,*N*-dimethylanilines bearing both electron-donating substituents (Table 2, entries 1 and 2) and an electron-withdrawing substituent (Table 2, entry 3) at the 4-positions had proven to be reliable substrates for the three-componnet reaction, leading to the synthesis of α-arylamino imides in good yields. It was noteworthy that Br could be well tolerated in the copper-catalyzed reaction since it had been proven to be rather reactive for copper catalysis[27] and therefore making the further modification of the as-synthesized α-arylamino imide convenient.

Moreover, *N*,*N*-dimethylanilines bearing both electron-donating and electron-withdrawing groups at both 3- and 2-postions had also been used as reaction partners with isocyanide **2a** and carboxylic acid **3a**, yielding various α-arylamino imides in moderate to good yields (Table 2, entries 4−8). Similarly, the halogen atom Cl had proven to be compatible in the reaction and would allow further functionalization of the products.

Table 2. Scope of the Three-Component Reaction[a]



entry	1	R^4	R^5	yield %[b]
1	 **1b**	TsCH$_2$ **2a**	Ph **3a**	66
2	 **1c**	TsCH$_2$ **2a**	Ph **3a**	62
3	 **1d**	TsCH$_2$ **2a**	Ph **3a**	70
4	 **1e**	TsCH$_2$ **2a**	Ph **3a**	46
5	 **1f**	TsCH$_2$ **2a**	Ph **3a**	59
6	 **1g**	TsCH$_2$ **2a**	Ph **3a**	50
7	 **1h**	TsCH$_2$ **2a**	Ph **3a**	44
8	 **1i**	TsCH$_2$ **2a**	Ph **3a**	70
9	 **1j**	TsCH$_2$ **2a**	Ph **3a**	24
10	 **1k**	TsCH$_2$ **2a**	Ph **3a**	37[c]
11	 **1a**	Bn **2b**	Ph **3a**	68
12	 **1b**	*t*-Bu **2c**	Ph **3a**	51
13	 **1a**	 **2d**	Ph **3a**	77
14	 **1b**	 **2d**	Ph **3a**	54
15	 **1d**	 **2d**	Ph **3a**	78
16	 **1b**	TsCH$_2$ **2a**	4-Me-C$_6$H$_4$ **3b**	42

[a] Reaction conditions: amines (2.0 mmol), isocyanides (1.0 mmol), acids (1.5 mmol), CuCl (0.1 mmol), 2,2′-bipyridyl (0.1 mmol), TBHP (1.5 mmol), MeCN (5.0 mL), 60 °C, 6 h. [b] Isolated yields based on isocyanides. [c] The reaction time was 24 h.

In addition, *N*-phenyl piperidine **1j**, which had both α C−H bonds and *β* C−H bonds, was also able to proceed with the three-component reaction, affording the α C−H bond transformation product, albeit with a relatively lower

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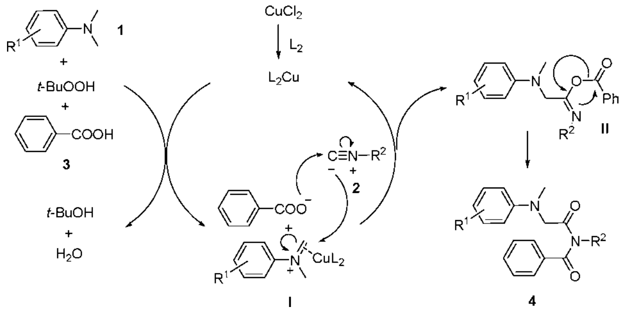
yield (24%, Table 2, entry 9). Besides these, *N*,*N*-diaryl alkylamines such as *N*-methyl-*N*-phenylbenzenamine **1k** were likewise found able to undergo the reaction, producing the α-diphenylamino imide in a 37% yield (Table 2, entry 10).

On the other hand, various isocyanides including alkyl isocyanide **2b** and **2c** as well as aryl isocyanide **2d** had also been subjected to the three-component reaction and proved to be reliable reaction partners with tertiary amines and carboxylic acid **3a** with moderate to good yields delivered (Table 2, entries 11−15). Substituted benzoic acids such as 4-methylbenzoic acid **3b** could also work with tertiary amine **1b** and isocyanide **2a** and provided a moderate yield (42%, Table 2, entry 16).

On the basis of the above results, a plausible mechanism has been proposed as depicted in Scheme 2. As an initial step of the cascade events, the *N*,*N*-dialkyl amines **1** were converted into copper−iminium complexes **I** under the promotion of copper and peroxides. Then the tandem nucleophilic additions of isocyanides **2** and the formed carboxylates generated the imino anhydride intermediates **II** and liberated the copper species. Lastly, owing to the fact that the nitrogens of the amines had been blocked, the migration of the acyls to the nitrogens of the isonitrile would occur,[28] producing the α-amino imide products **4**. However, in the absence of molecular sieves, the water which was generated in the first step would competitively react with **I** and **2**, affording the byproduct **4ab**.

Scheme 2. Proposed Mechanism



In conclusion, we have reported a novel three-component assembly involving the copper-catalyzed activations of sp^3 C−Hs adjacent to nitrogens. Notably, the reaction could be conducted under mild conditions and demonstrated a tolerance to a broad range of functional groups, leading to the synthesis of α-amino imides from tertiary amines in a concise manner. On the basis of the results, a possible reaction mechanism has been proposed. Further research on the asymmetric synthesis of the α-amino amides and detailed mechanistic explanation, as well as applications of this assembly in organic synthesis, are now ongoing in our laboratory.

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Supporting Information Available: General experimental procedures and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Similar transfer of acyls to the nitrogens of isonitriles had already been reported in ref 7b and the following reference: Ugi, I.; Steinbruckner, C. *Chem. Ber.* **1961**, *94*, 2802.