Synthetic Methods

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Efficient Copper(II)-Catalyzed Transamidation of Non-Activated Primary Carboxamides and Ureas with Amines**

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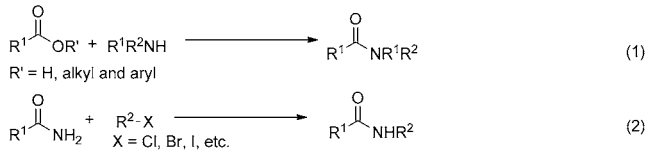
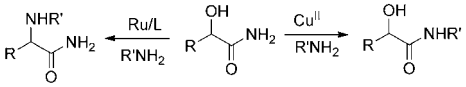
Carboxamides represent an important class of compounds found in numerous bioactive products,[1] such as top-sold medicines (i.e., Lipitor, Lidoderm, Vyvanse),[2] as well as in biological and synthetic polymers (i.e., proteins and nylons).[3] In addition, amides serve as versatile building blocks for the preparation of pharmaceuticals, agrochemicals, polymers, etc.[4] In general, substituted amides are prepared by substitution reactions of carboxylic acid derivatives with amines[14] [Scheme 1, Eq. (1)], or by the coupling of aryl/alkyl halides with primary amides[15] [Scheme 1, Eq. (2)]. Alternatively, well-established name reactions (i.e., Ritter,[5] Schmidt,[6] Beckmann,[7] Ugi,[8] Wolff,[9] etc.) and more recently established approaches[10–15] are applied for their synthesis.



Scheme 1. General approaches for the synthesis of amides.

In spite of these significant developments, the so-called transamidation process in which amides are reacted with a second, but different amine represents an interesting unconventional route for the functionalization of a given carboxamide.[16] Recent elegant examples of transamidation reactions from the groups of Stahl[17] and Myers[18] showed the possibility of preparing secondary or tertiary amides under mild reaction conditions. Unfortunately, the existing methods to accomplish the desired amide exchange process involve either the use of an excess of expensive and waste-generating activation reagents (2–3 equivalents), or the reactions were reversible and gave mixtures of amides.

During our recent work on the catalytic amination of α-hydroxy amides,[19,20] serendipitously we observed the formation of amides.[21] While selective amination of the alcohol occurred in the presence of $[Ru_3(CO)_{12}]$/bidentate phosphine as the catalyst, the use of copper(II) complexes resulted in unexpected transamidation products (Scheme 2).



Scheme 2. Selective transamidation versus alcohol amination in α-hydroxycarboxamides.

To the best of our knowledge, copper-catalyzed transamidations have not yet been reported. Considering the economic attractiveness and excellent functional group tolerance of copper in homogenous catalysis, we became interested in developing a general transamidation methodology of nonactivated primary carboxamides with amines. Herein, we describe our results for the first time.

Our initial studies focused on developing a more efficient catalytic system for transamidations and we used the reaction of **1a** with **2a** as a model system (for structures see Table 1). At the start of our work the effect of representative precatalysts, as well as different temperatures and solvents were explored (see Table S1 in the Supporting Information). An optimal yield of **3a** was obtained at 140 °C by using 10 mol % of $Cu(OAc)_2$ as a catalyst and *t*-amyl alcohol as the solvent.

With an optimized catalytic system in hand, we then examined the generality of this copper-catalyzed transamidation protocol. As shown in Table 1, all the reactions proceeded smoothly and afforded the desired products in reasonable to excellent yields upon isolation. Electron-withdrawing and electron-donating substituents on the aryl ring of the anilines were tolerated with only little influence on the reactivity (Table 1, entries 1–3, 7–9, 11–14, and 16). We observed that alkyl amines (Table 1, entries 4–6, 17, and 18) as well as the hydrazine **2g** (Table 1, entry 10) exhibited excellent reactivity and yielded full conversion of benchmark substrates in only 5 hours. Notably, the transamidation reactions of α-hydroxy amides with aryl amines gave the corresponding products in good yields within 10 hours (70–82 %: Table 1, entries 7–14). The resulting products are synthetically interesting building blocks for the preparation

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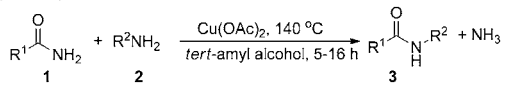
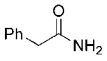
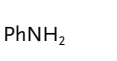
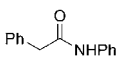
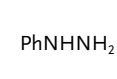
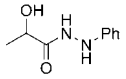
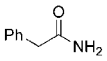
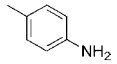
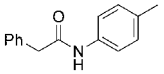
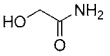
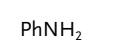
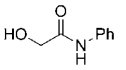
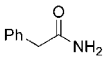
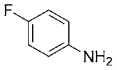
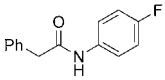
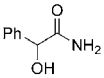
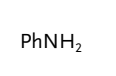
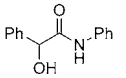
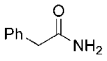
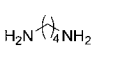
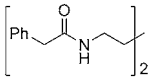
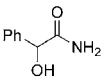
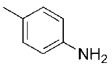
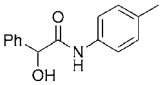
Table 1: Copper-catalyzed transamidation of primary amides with amines.[a]



1 2 3

Entry	1	2	Yield [%][b]	Entry	1	2	Yield [%][b]
1				10[f]			
	1a	**2a**	**3a**: 78 (69)[c]		**1b**	**2g**	**3j**: 71
2				11[f]			
	1a	**2b**	**3b**: 92		**1c**	**2a**	**3k**: 70
3				12[f]			
	1a	**2c**	**3c**: 81		**1d**	**2a**	**3l**: 76
4[d]				13[f]			
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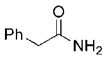
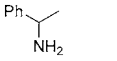
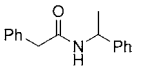
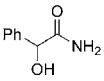
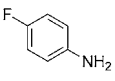
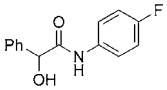
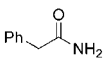
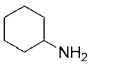
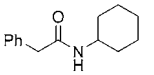
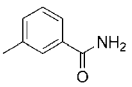
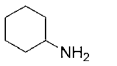
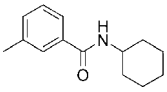
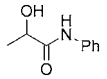
5[d]				14[f]			
	1a	**2e**	**3e**: 86		**1d**	**2c**	**3n**: 73
6[d]				15			
	1a	**2f**	**3f**: 90		**1e**	**2f**	**3o**: 30
7[f]		PhNH$_2$		16		PhNH$_2$	
	1b	**2a**	**3g**: 82		**1f**	**2a**	**3p**: 93
8[f]				17[d]			
	1b	**2b**	**3h**: 71		**1f**	**2h**	**3q**: 53
9[f]				18[g]			
	1b	**2c**	**3i**: 78		**1a**	**2i**	**3r**: 83

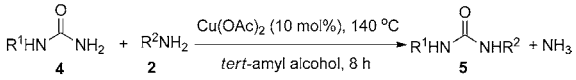
[a] Reaction conditions: Unless otherwise specified, all reactions were carried out under argon protection with **1** (1 mmol), **2** (1.3 mmol) and $Cu(OAc)_2$ (0.1 mmol) in *tert*-amyl alcohol (2 mL) at 140 °C for 16 h. [b] Yield of isoalted product. [c] Yield of product isolated from a 10 mmol scale experiment: **1a** (10 mmol, 1.35 g), **2a** (13 mmol, 1.21 g), $Cu(OAc)_2$ (1 mmol, 0.18 g), *tert*-amyl alcohol (3 mL). [d] Reactions time: 5 h. [e] **2d** (0.5 mmol). [f] Reaction time: 10 h. [g] Other tested linear secondary amines (i.e. dibenzylamine) showed lower reactivity.

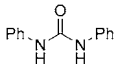
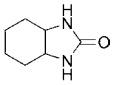
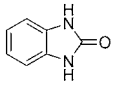
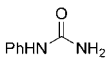
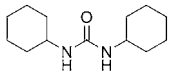
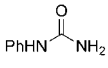
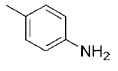
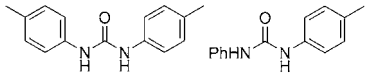
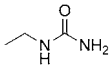
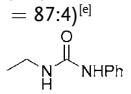
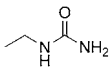
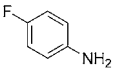
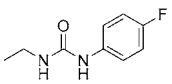
of α-amino acid derivatives through a direct alcohol amination strategy.[21] The modest reactivity of 3-methylbenzamide (**1e**; Table 1, entry 15) is consistent with the known stabilization of metal centers by arylamidate ligands, which should decrease the catalyst activity.[22]

Interestingly, the reaction between the primary amide **1a** and diamine **2d** gave the corresponding diamide **3d** in excellent yield (Table 1, entry 4). The amino-acid-derived amide **2h** can be employed to produce the dipeptide **3q** in reasonable yield (Table 1, entry 17). These results demonstrate the potential of our transamidation protocol for manufacturing polyamides or peptides by using appropriate substrates.

In addition to transamidations of carboxamides, the related reaction of ureas constitutes a demanding goal. Hence, we started a set of investigations to also functionalize urea derivatives in a selective manner. Gratifyingly, the copper catalyst proved to be active for these transformations, too. All the reactions proceeded efficiently and furnished all types of substituted ureas in good to excellent yields (Table 2). The reaction between inexpensive urea and aniline resulted in diphenyl urea (**5a**) in 72% yield (Table 2, entry 1). Diamines such as cyclohexane-1,2-diamine (**2j**) and benzene-1,2-diamine (**2k**) were successfully converted into biologically interesting cyclic ureas[23] in high yields (Table 2, entries 2 and 3). Interestingly, the reaction of 1-phenylurea (**4b**) and

Table 2: Copper-catalyzed transamidation of ureas with amines.[a]

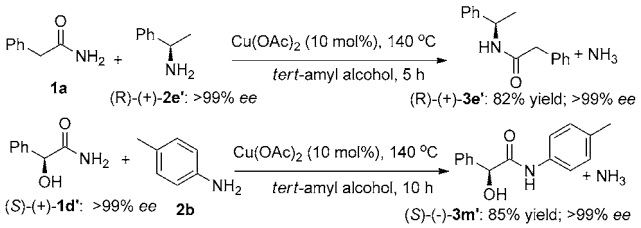


Entry	4	2	Yield [%][b]
1[c]			
	4a	**2a**	**5a**: 72
2			
	4a	**2j**	**5b**: 76
3			
	4a	**2k**	**5c**: 91
4			
	4b	**2f**[c]	**5d**: 83
5[d]			
	4b	**2b**	(**5a′**/**5a″** = 87:4)[e]
6			
	4c	**2a**	**5e**: 72
7			
	4c	**2c**	**5f**: 70

[a] Reaction conditions: Unless otherwise specified, all reactions were carried out under argon protection with **4** (1 mmol), **2** (1.3 mmol) and $Cu(OAc)_2$ (0.1 mmol) in *tert*-amyl alcohol (2 mL) at 140 °C for 8 h. [b] Yield of isolated product. [c] **2f** (2.4 mmol). [d] Mol ratio: **4b**/**2b** = 1:10. [e] Ratio was determined by GC and GC/MS analysis.

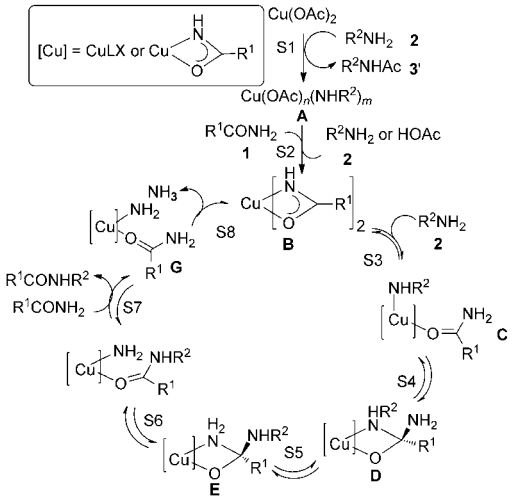
cyclohexylamine (**2f**) gave 1,3-dicyclohexylurea (**5d**) exclusively by replacing the aryl group with the cyclohexyl group (Table 2, entry 4). The exchange of two anilines having similar nucleophilicity (i.e., **2b** and **2a**) in ureas also took place and gave mixed products (see Scheme S1 in the Supporting Information). However, the reaction can be driven in the direction of forming 1,3-bis(*p*-tolyl)urea (**5a′**) by using an excess amount of amine **2b** (Table 2, entry 5). In contrast, reactions of 1-ethylurea (**4c**) with anilines **2a** and **2c** gave the unsymmetrical ureas **5e** (72%) and **5f** (70%), respectively, with retention of the ethyl group (Table 2, entries 6 and 7). These results indicate that this copper(II)-catalyzed transamidation of ureas undergoes a nucleophilic substitution mechanism, wherein the more nucleophilic amine substitutes the weaker one on the respective urea derivative. It should be noted that this urea transamidation protocol also provides new pathways to construct substituted heterocycles and peptides.

Interestingly, the reaction of the primary amide **1a** with enantiopure amine (*R*)-(+)-**2e′** or the reaction between enantiopure amide (*S*)-(+)-**1d′** and aniline **2b** produced enantiopure carboxamides (*R*)-(+)-**3e′** and (*S*)-(−)-**3m′**, respectively, in good yields with retention of the chiral configuration (Scheme 3). These results show that the copper(II)-catalyzed transamidation protocol is also applicable for the preparation of chiral amides from chiral substrates.



Scheme 3. Copper(II)-catalyzed synthesis of a chiral amides.

The reaction mechanism has not yet been elucidated, but on the basis of the previously reported mechanistic studies of amine exchange processes conducted with amidate complexes by Stahl and co-workers,[17b,d] we assume the following mechanism (Scheme 4): Initially, formation of an active mono- or bisamidate copper complex **B** takes place by



Scheme 4. Possible mechanism for the copper(II)-catalyzed transamidation of primary carboxamides.

substitution of the acetate ligand. Indeed, the expected product **3′** (step S1) can be detected in the reaction mixture by means of GC/MS. The resulting amido ligand in complex **A** can abstract a proton from the coordinated amide ligand to give the catalytically active species **B** (step S2). After coordination of an amine and proton transfer, the intermediate **C** (step S3) is formed. Then, nucleophilic attack of the amido ligand onto the carboxamide results in the formation of the tetrahedral intermediate **D** (step S4), which can either revert to **C** or isomerize to **E** through coordination of the second nitrogen atom to the copper(II) center (step S5). Cleavage of **E** (step S6) and exchange of neutral carboxamide ligand gives **G** and the transamidation product (steps S6 and S7). Finally, proton transfer from the amide to the amido ligand (step S8) completes the amine exchange process along

with regeneration of copper(II) catalyst **B** and liberation of ammonia. Notably, the release of ammonia also shifts the equilibrium to the desired product. As one of the referees pointed out,[24] the transamidation of ureas might proceed via an isocyanate intermediate.[25] We cannot rule out this possibility, which could also count for the fact that the transamidation of second ureas is easier than that of secondary amides (see Scheme S1 in the Supporting Information).

In summary, we have developed a straightforward copper-catalyzed transamidation methodology for the first time. Primary carboxamides and ureas can be selectively transaminated in an efficient manner. Compared to previously known transamidation catalysts, $Cu(OAc)_2$ is comparably inexpensive and can be conveniently used without special precautions. A wide range of functionalized products including amides, ureas, and chiral amides can be effectively produced from available primary carboxamides and amines in good to excellent yields. We are convinced that this procedure is and will be of significant value for the synthesis of a variety of amides, peptides, polyamides, heterocycles, etc., which are of significant importance for organic chemistry.

Experimental Section

Typical procedure for the preparation of **3a**: $Cu(OAc)_2$ (18 mg, 0.1 mmol), 2-phenylacetamide **1a** (135 mg, 1 mmol), aniline **2a** (121 mg, 1.3 mmol), and *tert*-amyl alcohol (2 mL) were added successively to a Schlenk tube (25 mL) equipped with a magnetic stirrer bar. The Schlenk tube was then closed and the resulting mixture was stirred at 140 °C for 14 h under an argon atmosphere. The accumulated ammonia gas in the pressure tube was then released under argon protection, and the reaction mixture was stirred at 140 °C for another 2 h. After cooling down to room temperature, the reaction solvent was removed under vacuum. The residue was directly purified by flash chromatography on silica gel eluting with heptane/ethanol (25:1) to give *N*,2-diphenylacetamide (**3a**) as a white solid (165 mg, 78 %).

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