Letter

Copper-Catalyzed Carbonylative Synthesis of Aliphatic Amides from Alkanes and Primary Amines via C(sp3)-H Bond Activation

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Copper-Catalyzed Carbonylative Synthesis of Aliphatic Amides from Alkanes and Primary Amines *via* $C_{(sp3)}$-H Bond Activation

Yahui Li,[a] Fengxiang Zhu,[a] Zechao Wang,[a] and Xiao-Feng Wu*[a,b]

a. Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)

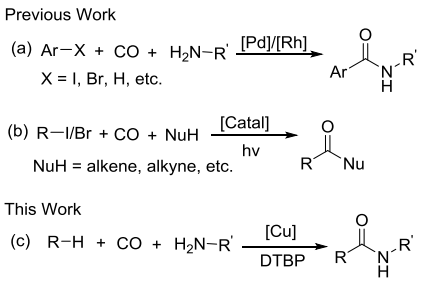
b. Department of Chemistry, Zhejiang Sci-Tech University, Xiasha Campus, Hangzhou 310018, People's Republic of China

ABSTRACT: Amides are important intermediates and building blocks in organic synthesis. Among the known preparation procedures, aminocarbonylation is an interesting and powerful tool. However, most of the studies were focused on noble metal-catalyzed synthesis of aromatic amides. Herein, we describe an attractive copper-catalyzed synthesis of aliphatic amides from alkanes and amines. A variety of amides were prepared in good yields by carbonylation of the $C_{(sp3)}$-H bond of alkanes with different amines. Good functional groups tolerance can be observed.

KEYWORDS: copper catalyst • amides synthesis • carbonylation • amines • alkanes

Amides are important chemicals that prevalent in pharmaceuticals, natural products, and many functional materials.[1] Hence, the development of efficient and selective procedure for new amide bonds construction is a long-standing task for organic chemists.[2] Among the known methodologies, aminocarbonylation is a straightforward process for the synthesis of amide moieties.[3] Depending on the amides needed, by choosing proper amines and reaction partners, CO as one of the cheapest and most abundant C1 source can be easily installed into the amide products. However, by go through literature, main of the reported aminocarbonylation procedures are based on using $C_{(sp2)}$-X (X = I, Br, H, etc.) as the starting materials. With noble metal complex as the catalyst, aromatic amides (benzamides) can be selectively produced (Scheme 1, eq. a).[4] In comparison, studies on carbonylative transformation of $C_{(sp3)}$-X bonds are already become limited which can produce important aliphatic carbonyl containing compounds (Scheme 1, eq. b). The developed methods also require noble catalyst and/or UV irradiation under high CO pressure (50-80 bar).[5] Not surprisely, report on aminocarbonylation of $C_{(sp3)}$-X (X = I, Br, H, etc.) bonds is even more rare,[6] which can be explained by the following four reasons: 1) the increased difficulty of oxidative addition of $C_{(sp3)}$-X (X = I. Br. Cl) bond toward metal center; 2) easier β-hydrogen elimination of the intermediate complex; 3) easy and fast nucleophilic substitution reaction of $C_{(sp3)}$-X (X = I. Br. Cl) and amines with amines as the reaction partner and also as the base; 4) the easier oxidation of amines under oxidative conditions. Hence, aminocarbonylation of $C_{(sp3)}$-X bonds is remaining challenge.

On the other hand, copper salts have advantages include non-expensive and low toxicity which have been extensively applied as catalysts and additives in organic synthesis.[7] In some topics, such as oxidation reactions, the catalysis behavior of copper catalyst is comparable or even better then palladium catalysts.[8] However, in the area of carbonylative coupling transformations, copper catalyst is still in its infancy while palladium catalysts are already matured. The few reports on copper-catalyzed carbonylative coupling reactions are limited with aryl iodides or diaryliodonium salts as the substrates.[9] And we recently extended to carbonylative coupling of cycloalkanes with amides which is stable under oxidative conditions.[10] As our continuing interests on developing new carbonylative coupling reactions and also been attracted by copper catalysts, we wish to report here an interesting procedure on copper-catalyzed aminocarbonylation of alkanes. With amines as the reaction partners and copper as the catalyst, the $C_{(sp3)}$-H bond of simple alkanes were selectively carbonylated and give the corresponding aliphatic amides in good yields (Scheme 1, eq. c).

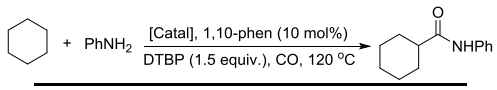


Scheme 1. General carbonylative coupling reactions.

Initially, we chosen cyclohexane and aniline as the model substrates in the presence of 20 bar of CO and the effects of copper catalysts were tested (Table 1, entries 1-9). Under our former reaction conditions, only 19% of the desired *N*-phenylcyclohexanecarboxamide can be produced (Table 1, entry 1). Nitrobenzene, nitrosobenzene, azobenzene and other non-charactable could be detected with the full conversion of aniline. Nevertheless, these results proven our hypothesis and encouraged us to move forward. In the other tested copper salts, improved yields can be achieved in general and the best selectivity can be obtained with CuF_2 as the catalyst (Table 1, entry 8). Excitingly, 67% of *N*-phenylcyclohexanecarboxamide was isolated and with good reproducibility. In the case with $Pd(OAc)_2$ as the catalyst,

only trance of the desired amide can be detected together with the aniline oxidation by-products (Table 1, entry 10). Additionally, in the absence of a copper catalyst or ligand, no desired product can be observed. Screening of other nitrogen ligands (pyridine, bipyridine, TMEDA, DMEDA, DMPA, L-proline) revealed that 1,10-phenanthroline hydrate is the most effective ligand for delivering the desired amide product. Then we tested the influences of reaction temperature, additives and CO pressure on this aminocarbonylation reaction (Table 1, entries 11-15). Dramatic yields decreasing were observed when K_2CO_3 or AcOH was added into the reaction mixture (Table 1, entries 12 and 13; 26% and 23% yields respectively). Interestingly, moderate yields can still be obtained under lower CO pressure (10 bar; Table 1, entry 11), lower temperature (100 °C; Table 1, entry 14) and lower catalyst loading (5 mol%; Table 1, entry 15). It's meaningful to mention that full conversion of aniline could be observed in all the reactions performed.

Table 1. Cu-catalyzed amide synthesis: Optimization reaction conditions.[a]

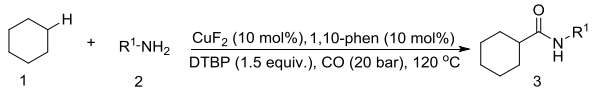


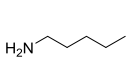
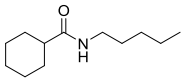
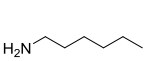
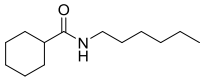
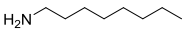
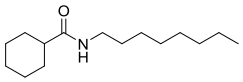
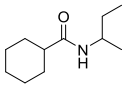
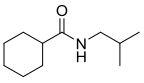
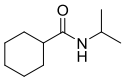
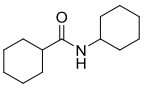
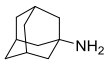
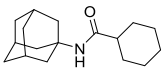
Entry	Catalyst	Yield[b]
1	$CuBr(Me_2S)$	19%
2	$Cu(acac)_2$	42%
3	$CuBr_2$	36%
4	$Cu(CH_3CN)_4PF_6$	48%
5	$Cu(CF_3CO_2)_2$	18%
6	CuI	27%
7	CuCl	42%
8	CuF_2	67%[c]
9	$Cu(OTf)_2$	24%
10	$Pd(OAc)_2$	trace
11[d]	CuF_2	48%
12[e]	CuF_2	26%
13[f]	CuF_2	23%
14[g]	CuF_2	54%
15[h]	CuF_2	65%

[a] Aniline (0.5 mmol), catalyst (10 mol%), ligand (10 mol%), DTBP (0.75 mmol; 1.5 equiv.), CO (50 bar), cyclohexane (1.5 mL), 24 h. [b] GC yields with hexadecane as the internal standard. [c] Isolated yields. [d] CO (10 bar). [e] K_2CO_3 (1 equiv.). [f] CH_3CO_2H (1 equiv.). [g] 100 °C. [h] Catalyst (5 mol%), ligand (5 mol%).1,10-Phen = 1,10-phenanthroline hydrate.

With the optimized reaction conditions in hand, we examined the scope of the reaction with a range of amines. As shown in Table 2, various aliphatic amines were successfully applied. Good yields of the desired amides can be produced by reacting pentylamine, hexylamine and octylamine with cyclohexane (Table 2, entries 1-3). Branched amines can be applied as reaction partners as well and give the corresponding aliphatic amides in good to excellent yields (Table 2, entries 4-8). Cyclohexylamine and amantadine can provide the desired amides in 65-68% yields (Table 2, entries 7-8).

Table 2. Cu-catalyzed carbonylative synthesis of aliphatic amides.[a]

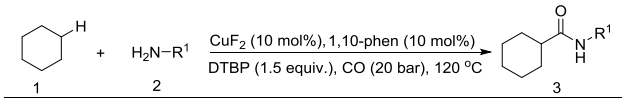


Entry	2	Product	Yield[b]
1	 2a	 3a	80%
2	 2b	 3b	80%
3	 2c	 3c	78%
4	 2d	 3d	72%
5	 2e	 3e	86%
6	 2f	 3f	91%
7	 2g	 3g	68%
8	 2h	 3h	65%

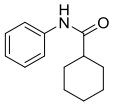
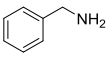
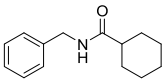
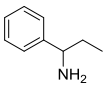
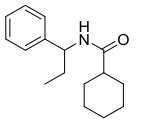
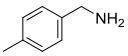
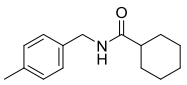
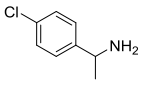
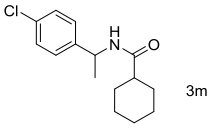
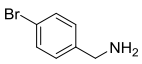
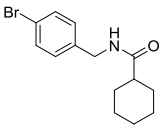
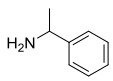
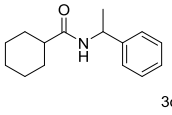
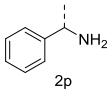
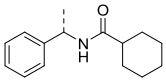
[a] 2 (0.5 mmol), CuF_2 (10 mol%), 1,10-phen (10 mol%), DTBP (0.75 mmol), CO (20 bar), cyclohexane (1.5 mL), 120 °C, 24 h. [b] Isolated yields.

To reveal the generality of this method, aniline and benzylic amines were also tested (Table 3), these substrates are more intended to be oxidized compared with aliphatic amines tested. To our delight, aniline was smoothly transformed into the desired amide in 67% yield (Table 3, entry 1). Various benzyl amines can be reacted as well and give the corresponding amides in moderate to good yields (Table 3, entries 2-8). For example, (4-bromophenyl)-methanamine and 1-(4-chlorophenyl)ethan-1-amine can successfully give the wanted products which are ready for further modification *via* cross-coupling reactions. Notably, enantioenriched substrate can be applied as well and keep excellent chirality in the final product (Table 3, entry 8).

Table 3. Cu-catalyzed synthesis of amides from aromatic and benzyl amines.[a]



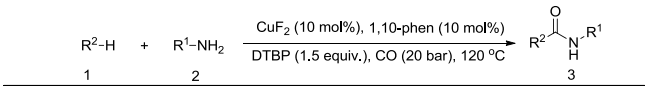
1 2 3

Entry	2	3	Yield[b]
1	 2i	 3i	67%
2	 2j	 3j	76%
3	 2k	 3k	51%
4	 2l	 3l	53%
5	 2m	 3m	53%
6	 2n	 3n	53%
7	 2o	 3o	54%
8	 2p	 3p	56%, (97% ee)

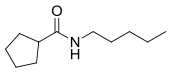
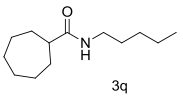
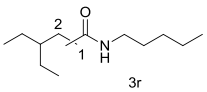
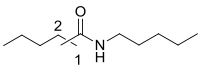
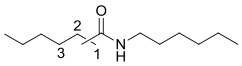
[a] 2 (0.5 mmol), CuF_2 (10 mol%), 1,10-phen (10 mol%), DTBP (0.75 mmol), CO (20 bar), cyclohexane (1.5 mL), 120 °C, 24 h. [b] Isolated yields.

Additionally, alkane derivatives were tested under our standard reaction conditions (Table 4). Cyclopentane and cycloheptane worked well under our reaction conditions and give the corresponding amides in 57-66% yields (Table 4, entries 1-2). Non-cyclic alkanes were applied as well, and moderate selectivity can be obtained in general. The reaction of 3-ethylpentane occurred preferentially at secondary and primary C-H bonds over the tertiary C-H bond (Table 4, entry 3). In the case of using pentane and hexane as the reactants and solvents, moderate to good yields of the corresponding amides can be isolated with moderate selectivity (Table 4, entries 4-5). Remarkably, around 5% of the C3 product of pentane can be detected in the crude NMR. Due to the low amount, we did not isolate it.

Table 4. Cu-catalyzed synthesis of amides from alkanes.[a]

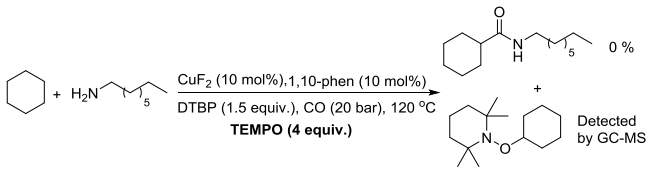


1 2 3

Entry	1	3	Yield[b]
1	 2b	 3p	66%
2	 2c	 3q	57%
3	 2d	 3r	52% (2:1=1.75:1)
4	2e	 3s	59% (2:1=2.75:1)
5	2f	 3t	60% (3:2:1=2.5:3:1)

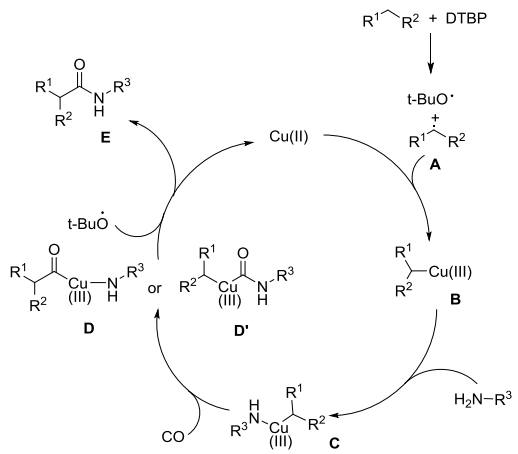
[a] 2 (0.5 mmol), CuF_2 (10 mol%), 1,10-phen (10 mol%), DTBP (0.75 mmol), CO (20 bar), alkane (1.5 mL), 120 °C, 24 h. [b] Isolated yields.

In order to get insight into the reaction mechanism, an experiment with TEMPO was carried out and shown in Scheme 2. When 4 equivalents of TEMPO were added to the standard reaction mixture, no desired amide product can be obtained. And a product from the reaction between cyclohexane and TEMPO was found in GC-MS analysis.



Scheme 2. Control experiment.

Based on our results, a possible reaction mechanism is been proposed (Scheme 3). The reaction started with a copper(II)-catalyzed or thermal hemolytic cleavage of a peroxide to generate the *tert*-butoxy radical, which reacts with cyclohexane and sequential oxidation of the copper(II) species to give the Cu(III)-cyclohexane species **B**. Then complex **B** go X ligand exchange with amine to produce Cu(III) intermediate **C** with alkyl and amine X ligands. Subsequent CO coordination and insertion forms the intermediate **D** or **D'**, which then afford the final aminocarbonylation product **E** after reductive elimination and along with a Cu (I) intermediate which can be oxidized by *t*BuO radical into the active Cu (II) species for the next catalytic cycle.



Scheme 3. Proposed reaction mechanism.

In conclusion, a novel copper-catalyzed aminocarbonylation reaction of alkanes with amines has been developed. With copper salt as the catalyst, various aliphatic amides were prepared in good yields by carbonylative activation of the $C_{(sp3)}$-H bond of alkanes. Notably, this is the first report on copper-catalyzed aminocarbonylation reaction for aliphatic amides synthesis.

ASSOCIATED CONTENT

Supporting Information: General procedure, NMR data and spectrum are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

E-mail: Xiao-Feng.Wu@catalysis.de

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General procedure:

A 4 mL screw-cap vial was charged with CuF_2 (5.05 mg, 10 mol%), 1,10-phenanthroline hydrate (9.9 mg, 10 mol%), aniline (0.5 mmol), cyclohexane (1.5 mL) and an oven-dried stirring bar. The vial was closed by Teflon septum and phenolic cap and connected with atmosphere with a needle. After cyclohexane (1.5 mL), DTBP (0.75 mmol) were injected by syringe, the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (500 mL) under argon atmosphere. At room temperature, the autoclave is flushed with carbon monoxide for three times and 20 bar of carbon monoxide was charged. The autoclave was placed on a heating plate equipped with magnetic stirring and an aluminum block. The reaction is allowed to be heated under 120 °C for 24 hours. Afterwards, the autoclave is cooled to room temperature and the pressure was carefully released. After removal of solvent under reduced pressure, pure product was obtained by column chromatography on silica gel (eluent: pentane/ethyl acetate = 10:1).

REFERENCES

[1] (a) *Novel Synthetic Chemistry of Ureas and Amides* (Hutchby, M.), Springer, **2013**. (b) Mintzer, M. A.; Simanek, E. E. *Chem. Rev*. **2009**, *109*, 259-302.

[2] (a) Carey, J. S.; Laffan, D.; Thomson, C.; M. Williams, T. *Org. Biomol. Chem*. **2006**, *4*, 2337-2347. (b) Cupido, T.; Tulla-Puche, J.; Spengler, J.; Albericio, F. *Curr. Opin. Drug Discovery Dev*. **2007**, *10*, 768-783.

[3] (a) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed*. **2009**, *48*, 4114-4133. (b) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, *7*, 591-599.

[4] For selected reports on aminocarbonylation for benzamides synthesis, see: (a) Schoenberg, A.; Heck, R. F. *J. Org. Chem*. **1974**, *39*, 3327-3331. (b) Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett*. **2002**, *4*, 2849-2851. (c) Cunico, R. F.; Maity, B. C. *Org. Lett*. **2002**, *4*, 4357-4359. (d) Yamazaki, K.; Kondo, Y. *J. Comb. Chem*. **2004**, *6*, 121-125. (e) Schnyder, A.; Indolese, A. F. *J. Org. Chem*. **2002**, *67*, 594-597. (f) Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835-2838. (g) Ueda, K.; Sato, Y.; Mori, M. *J. Am. Chem. Soc*. **2000**, *122*, 10722-10723. (h) Liang, Z.; Zhang, J.; Liu, Z.; Wang, K.; Zhang, Y. *Tetrahedron* **2013**, *69*, 6519-6526. (i) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342-14343. (j) Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci*. **2011**, *2*, 312-315.

[5] For leading reviews on radical carbonylation, see: (a) Schiesser, C. H.; Wille, U.; Matsubara, H.; Ryu, I. *Acc. Chem. Res.* **2007**, *40*, 303-313. (b) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563-1574. (c) Ryu, I.; Sonoda, N. *Angew. Chem. Int. Ed.* **1996**, *35*, 1050-1066. (d) Ryu, I. *Chem. Rec.* **2002**, *2*, 249-258. for reports on carbonylation of cycloalkanes with alkenes, see: (e) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1869-1872. (f) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. *Chem. Sci.* **2014**, *5*, 2893-2898.

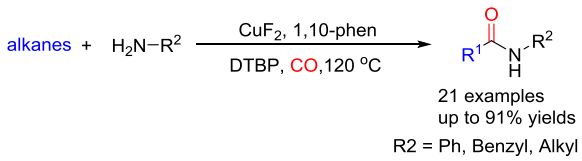
[6] (a) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378-17380. (b) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc*. **2014**, *136*, 5267-5270. (c) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129-133. (d) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070-8073. (e) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, *6*, 4610-4614. For reports on carbonylation of $C_{(sp3)}$-H bond of benzylic substrates, see: (f) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902-9905. (g) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, *15*, 3370-3373. (h) Liu, H.; Laurenczy, G.; Yan, N.; Dyson, P. J. *Chem. Commun*. **2014**, *50*, 341-343. For a general review on $C_{(sp3)}$-X bond carbonylations, see: (i) Wu, L.; Fang, X.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X.-F. *ACS Catal*. **2014**, *4*, 2977-2989.

[7] Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev*. **2013**, *113*, 6234-6458.

[8] McCann, S. D.; Stahl, S. S. *Acc. Chem. Res.* **2015**, *48*, 1756–1766.

[9] (a) Liu, J. M.; Zhang, R. Z.; Wang, S. F.; Sun, W.; Xia, C. G. *Org. Lett*. **2009**, *11*, 1321-1324. (b) Tambade, P.; Patil, Y.; Nandurkar, N.; Bhanage, B. *Synlett*, **2008**, 886-888. (c) Kang, S.-K.; Yamaguchi, T.; Kim, T.-H.; Ho, P.-S. *J. Org. Chem.* **1996**, *61*, 9082-9083. (d) Romano, U.; Tesel, R.; Rebora, P.; Mauri, M. *Ind. Eng. Chem. Prod. Res. Dev*. **1980**, *19*, 396-403.

[10] Li, Y.; Dong, K.; Zhu, F.; Wang, Z.; Wu, X.-F. *Angew. Chem. Int. Ed*. **2016**, *55*, 7227-7230.



21 examples
up to 91% yields
R2 = Ph, Benzyl, Alkyl