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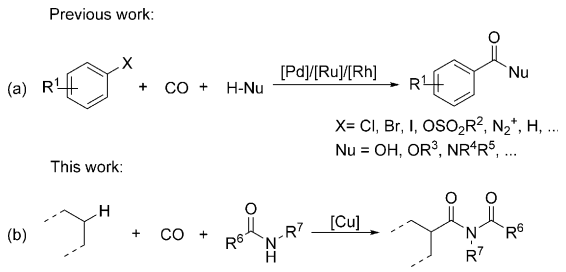
Copper-Catalyzed Carbonylative Coupling of Cycloalkanes and Amides

*Yahui Li, Kaiwu Dong, Fengxiang Zhu, Zechao Wang, and Xiao-Feng Wu**

Abstract: *Carbonylation reactions are a most powerful method for the synthesis of carbonyl-containing compounds. However, most known carbonylation procedures still require noble-metal catalysts and the use of activated compounds and good nucleophiles as substrates. Herein, we developed a copper-catalyzed carbonylative transformation of cycloalkanes and amides. Imides were prepared in good yields by carbonylation of a C(sp^3)–H bond of the cycloalkane with the amides acting as weak nucleophiles. Notably, this is the first report of copper-catalyzed carbonylative C–H activation.*

Transition-metal-catalyzed carbonylative reactions are powerful methods for the synthesis of carbonyl-containing compounds.[1] Through carbonylation, the carbon chain of a parent molecule can be easily elongated with carbon monoxide (CO) as one of the cheapest and most abundant C1 building blocks. However, most of the known procedures require either noble-metal catalysts, activated substrates, and/or sufficiently reactive nucleophiles (Scheme 1a). More specifically, catalysts based on palladium, ruthenium, and rhodium are frequently explored. Aryl halides and analogues thereof are commonly applied reactants whereas alcohols, amines, and organometallic reagents are usually employed as the nucleophiles. Hence, these methods suffer from some common limitations, such as expensive catalysts and tedious substrate preparation.

Various carbonylative C–H activation reactions of arenes that benefit from the assistance of directing groups have been reported.[2] In the presence of a noble-metal catalyst and a suitable oxidant, the C(sp^2)–H bonds of arenes were carbonylated and gave the desired products in good yields. A few rare examples of the directing-group-assisted carbonylation of C(sp^3)–H bonds with palladium or ruthenium catalysts have been reported[3] whereas directing-group-free variants are without precedence.[4] On the other hand, the free radical carbonylation of (cyclo)alkanes in the presence of radical initiators has been well established.[1f–i]



Scheme 1. Carbonylation reactions.

Among all transitional-metal catalysts, copper salts are particularly inexpensive and benefit from their low toxicity.[5] The use of copper catalysts in carbonylative transformations is thus attractive for both academic and industrial purposes. However, to our surprise, only few examples of copper-catalyzed carbonylative coupling reactions with aryl iodides or diaryliodonium salts have been reported.[6]

On the other hand, amides occur frequently in nature, and they are also important intermediates and building blocks in organic synthesis.[7] Based on the diversity of available amides, the development of new reactions that employ amides as reactants is a worthwhile pursuit. However, compared with alcohols and amines, the low nucleophilicity of amides has hindered their application in carbonylative coupling reactions.[8] On the other hand, owing to the comparatively high stability of amides towards oxidants, suitable conditions for the use of amides as coupling partners should be easily found.

With all of these considerations in mind, we herein report the first copper-catalyzed carbonylative C–H activation of cycloalkanes. With amides as the reaction partners, the C(sp^3)–H bond of simple cycloalkanes were carbonylated to finally provide the corresponding imides in good yields (Scheme 1b).

Initially, we chose cyclohexane (both as reagent and solvent) and *N*-methylacetamide as the model substrates to establish this carbonylation reaction (Table 1). Among various metal catalyst precursors (entries 1–10), CuBr(Me_2S) gave the best result (80% GC yield, product isolated in 75% yield; entry 6). Notably, the decreased reaction efficiency with $Pd(OAc)_2$, $PdCl_2$, $Mn_2(CO)_{10}$, and $Co(acac)_2$ excludes the possibility that such metal impurities in the copper salt play a role in the overall reaction (entries 7–10).

Next, various ligands were studied (entries 11–20). **L2**, **L6**, and **L7** achieved similar results to 1,10-phenanthroline hydrate (entries 12, 16, and 17) whereas other ligands were less effective. Subsequently, the CO pressure was varied. To our surprise, the yield of **3a** improved with a decrease in the CO pressure (entries 21 and 22). Other additives, such as I_2 and KI, were also tested, but led to decreased reaction efficiency (entries 23 and 24). Furthermore, in the absence of catalyst or ligand, only trace amounts of the desired product were observed (entries 25 and 26). Overall, it was found that

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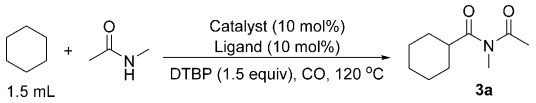
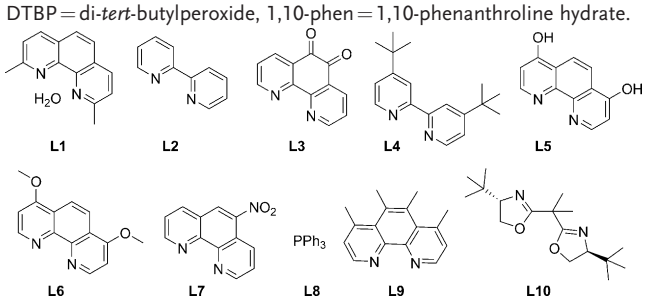
Table 1: Catalyst screen.[a]



Entry	Catalyst	Ligand	Yield[b]
1	CuI	1,10-phen	40%
2	$Cu(CH_3CN)_4BF_4$	1,10-phen	22%
3	$Cu(CH_3CN)_4SO_3CF_3$	1,10-phen	15%
4	$Cu(CH_3CN)_4PF_6$	1,10-phen	23%
5	$Cu(CF_3CO_2)_2$	1,10-phen	17%
6	$CuBr(Me_2S)$	1,10-phen	80% (75%)[c]
7	$PdCl_2$	1,10-phen	34%
8	$Pd(OAc)_2$	1,10-phen	trace
9	$Mn_2(CO)_{10}$	1,10-phen	0%
10	$Co(acac)_2$	1,10-phen	6%
11	$CuBr(Me_2S)$	**L1**	54%
12	$CuBr(Me_2S)$	**L2**	74%
13	$CuBr(Me_2S)$	**L3**	62%
14	$CuBr(Me_2S)$	**L4**	45%
15	$CuBr(Me_2S)$	**L5**	33%
16	$CuBr(Me_2S)$	**L6**	72%
17	$CuBr(Me_2S)$	**L7**	71%
18	$CuBr(Me_2S)$	**L8**	29%
19	$CuBr(Me_2S)$	**L9**	64%
20	$CuBr(Me_2S)$	**L10**	27%
21[d]	$CuBr(Me_2S)$	1,10-phen	88% (84%)
22[e]	$CuBr(Me_2S)$	1,10-phen	89% (88%)
23[f]	$CuBr(Me_2S)$	1,10-phen	13%
24[g]	$CuBr(Me_2S)$	1,10-phen	74%
25	–	1,10-phen	0%
26	$CuBr(Me_2S)$	–	trace

[a] Reaction conditions: *N*-Methylacetamide (0.5 mmol), catalyst (10 mol%), ligand (10 mol%), DTBP (0.75 mmol), CO (50 bar), cyclohexane (1.5 mL), 24 h. [b] Determined by GC analysis. [c] Yields of isolated products given in parentheses. [d] Catalyst (5 mol%), ligand (5 mol%), CO (30 bar). [e] Catalyst (5 mol%), ligand (5 mol%), CO (20 bar). [f] I_2 (10 mol%). [g] KI (10 mol%). acac = acetylacetonate, DTBP = di-*tert*-butylperoxide, 1,10-phen = 1,10-phenanthroline hydrate.

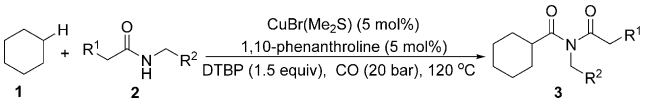


the use of 5 mol% of $CuBr(Me_2S)$ and 1,10-phen together with DTBP (1.5 equiv) under CO atmosphere (20 bar) gave **3a** in 89% yield (determined by GC analysis; entry 22).

With the optimized reaction conditions in hand, we examined the scope of the reaction with a range of amides. As shown in Table 2, the desired imides were formed in good yield when *N*-ethylacetamide or *N*-butylpropionamide was used in combination with cyclohexane (yield of isolated **3b** and **3c**: 69% and 74%, respectively). Long-chain imides were also formed in good to excellent yields (such as **3e**, **3f**, **3g**, and **3h**).

Different cyclic amides were also tested (Table 3). Azepan-2-one (**2j**) and azocan-2-one (**2k**) gave the corresponding products in very good yields (**3j** and **3k**, 91% and 85%, respectively). Interestingly, these products belong to a family of proinflammatory mediators that promote the recruitment and activation of leukocytes (e.g., monocytes, lymphocytes, and granulocytes). The reactions between phenyl-substituted amides (**2l**, **2m**, and **2n**) and cyclohexane gave the desired products in yields of 85%, 86%, and 69%, respectively. Whereas *N*-methylbenzamide gave the desired coupling product in 61% yield, with *N*-phenylacetamide and *N*-phenylformamide, only the corresponding amides were obtained rather than the desired imides. This may due to the low stability of the imides, which decompose immediately to give these amides. Furthermore, benzamide and acetamide, as exemplary primary amides, were reacted with cyclohexane under the standard reaction conditions, but the desired imides were not detected.

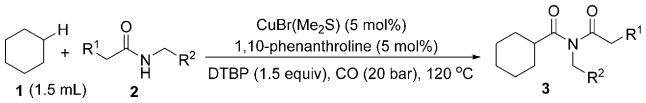
Table 2: Copper-catalyzed carbonylative imide synthesis.[a]



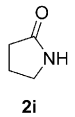
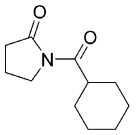
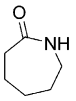
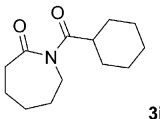
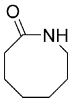
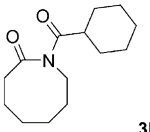
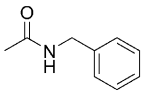
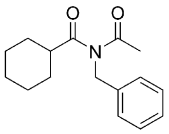
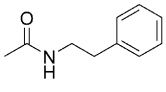
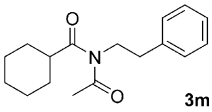
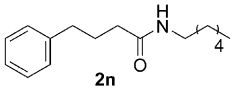
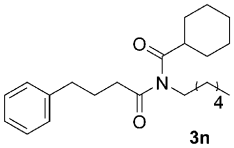
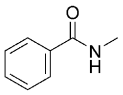
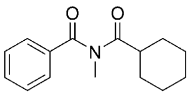
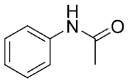
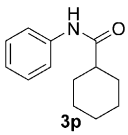
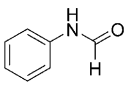
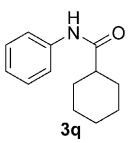
Entry	2	Product	Yield[b]
1	**2a**	**3a**	88%
2	**2b**	**3b**	69%
3	**2c**	**3c**	74%
4	**2d**	**3d**	67%
5	**2e**	**3e**	88%
6	**2f**	**3f**	81%
7	**2g**	**3g**	62%
8	**2h**	**3h**	68%

[a] **2** (0.5 mmol), $CuBr(Me_2S)$ (5 mol%), 1,10-phen (5 mol%), DTBP (0.75 mmol), CO (20 bar), cyclohexane (1.5 mL), 24 h. [b] Yields of isolated products.

Table 3: Copper-catalyzed carbonylation with lactams and amides.[a]



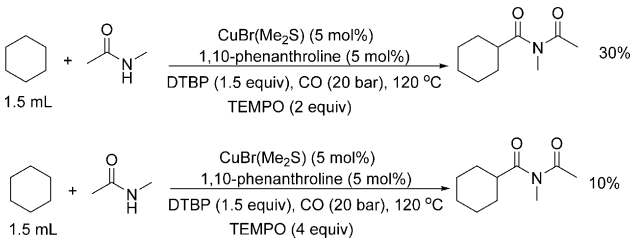
1 (1.5 mL) 2 3

Entry	2	3	Yield[b]
1	 2i	 3i	67%
2	 2j	 3j	91%
3	 2k	 3k	85%
4	 2l	 3l	85%
5	 2m	 3m	86%
6	 2n	 3n	69%
7	 2o	 3o	61%
8	 2p	 3p	67%
9	 2q	 3q	62%

[a] **2** (0.5 mmol), $CuBr(Me_2S)$ (5 mol%), 1,10-phen (5 mol%), DTBP (0.75 mmol), CO (20 bar), cyclohexane (1.5 mL), 24 h. [b] Yields of isolated products.

Furthermore, several cycloalkane derivatives were tested (Table 4). Cyclopentane, cycloheptane, and cyclooctane worked well under the standard reaction conditions (entries 1–3), and the corresponding imides were isolated in moderate to good yields (**3q**, **3r**, and **3s**). With adamantane as the reactant, the desired imide was formed in 31% when (trifluoromethyl)benzene was used as the solvent (entry 4). The use of pentane under the standard reaction conditions resulted in a mixture of two products.

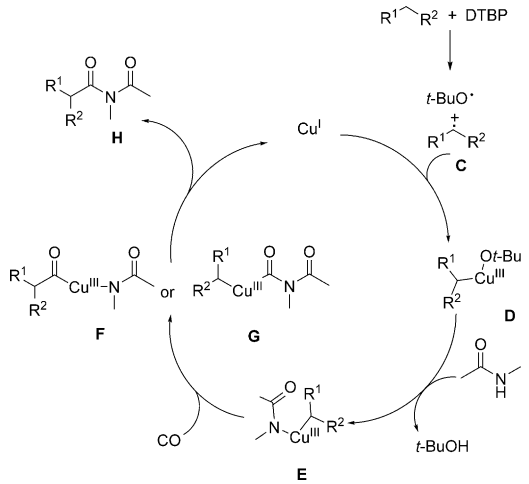
To gain insight into the reaction mechanism, we conducted some control experiments (Scheme 2). When 2 equiv of TEMPO were added to the standard reaction conditions, the desired product was only formed in 30% yield (determined by GC). The yield further decreased to 10% in the presence of 4 equiv of TEMPO.



Scheme 2. Control experiments.

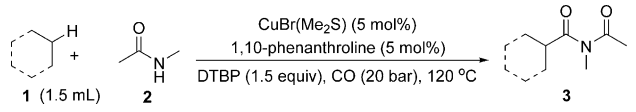
Based on our results, a possible reaction mechanism is proposed (Scheme 3). The reaction is initiated by the copper(I)-catalyzed or thermal homolytic cleavage of the peroxide to generate a *tert*-butoxy radical, which reacts with cyclohexane; sequential oxidation of the copper(I) species gives the Cu^{III}–cyclohexane intermediate **D**. Then, complex **D** reacts with the amide to yield Cu^{III} intermediate **E**. Subsequent CO insertion forms intermediate **F** or **G**, which then affords the final carbonylation product after reductive elimination while the active Cu^{I} species is regenerated for the next catalytic cycle.

In conclusion, we have developed a copper-catalyzed carbonylation reaction of cycloalkanes with amides as the nucleophiles. Various imides were prepared in good yields by carbonylation of a $C(sp^3)$–H bond of the cycloalkane.

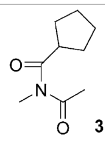
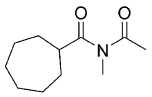
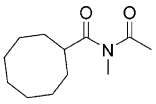
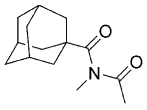


Scheme 3. Proposed reaction mechanism.

Table 4: Copper-catalyzed synthesis of imides with various alkanes.[a]



1 (1.5 mL) 2 3

Entry	1	3	Yield[b]
1	 2b	 3q	70%
2	 2c	 3r	77%
3	 2d	 3s	57%
4	 2e	 3t	31%[c]

[a] **2** (0.5 mmol), $CuBr(Me_2S)$ (5 mol%), 1,10-phen (5 mol%), DTBP (0.75 mmol), CO (20 bar), alkane (1.5 mL), 24 h. [b] Yields of isolated products. [c] $PhCF_3$ (1.5 mL), adamantane (0.5 mmol), $CuBr(Me_2S)$ (5 mol%), 1,10-phen (5 mol%), DTBP (0.75 mmol), CO (20 bar), 24 h.

Notably, this is the first report of copper-catalyzed carbonylative C–H activation.

Experimental Section

General procedure: A 4 mL screw-cap vial was charged with $CuBr(Me_2S)$ (5.1 mg, 5 mol%), 1,10-phenanthroline hydrate (5 mg, 5 mol%), cyclohexane (1.5 mL), and an oven-dried stir bar. The vial was closed with a Teflon septum and cap and connected to the atmosphere via a needle. After cyclohexane (1.5 mL) and DTBP (0.75 mmol) had been added with a syringe, the vial was moved to an alloy plate and put into a Paar 4560 series autoclave (500 mL) under argon atmosphere. At room temperature, the autoclave was flushed with CO three times and then subjected to 20 bar of CO. The autoclave was placed on a heating plate equipped with a magnetic stirrer and an aluminum block. The reaction mixture was heated to 120°C for 24 h. Afterwards, the autoclave was cooled to room temperature, and the pressure was carefully released. After solvent removal under reduced pressure, the product was isolated by column chromatography on silica gel (pentane/ethyl acetate = 20:1).

Acknowledgements

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Keywords: amides · carbonylation · copper catalysis · cycloalkanes · imides

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