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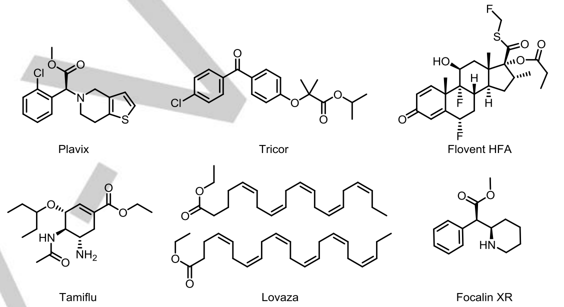
Copper-Catalyzed Alkoxycarbonylation of Alkanes with Alcohols

Yahui Li+,[a] Changsheng Wang+,[b] Fengxiang Zhu,[a] Zechao Wang,[a] Pierre H. Dixneuf,[b] and Xiao-Feng Wu*[a]

Abstract: Esters are important chemicals widely used in various areas and alkoxycarbonylation represents one of the most powerful tools for their synthesis. In this communication, we developed a novel copper-catalyzed carbonylative procedure for the synthesis of aliphatic esters from cycloalkanes and alcohols. Through direct activation of the $C_{(sp3)}$-H bond of alkanes and with alcohols as the nucleophiles, the desired esters were prepared in moderate to good yields. Paraformaldehyde can also be applied for *in situ* alcohol generation by radical trapping, and moderate yields of the corresponding esters can be produced. Notably, this is the first report on copper-catalyzed alkoxycarbonylation of alkanes.

Transition metal-catalyzed carbonylative transformation is already a powerful class of methodologies for the synthesis of carbonyl-containing chemicals, it extends the carbon chain while introduces a synthetically versatile carbonyl group.[1] However, by go through the literature, most of the known procedures are either requiring noble metal as the catalysts or using (pseudo)aryl halides and analogues as the starting materials. Due to the high price of noble metal catalysts and the tedious substrates pre-activation and preparation steps, alternative procedures are definitely under request. Recently, C(sp_3)-H activation and functionalization has attracted much attentions from our synthetic communities. Carbonylative activation of $C_{(sp3)}$-H bonds with the assistant of directing groups have been reported with palladium or ruthenium as the catalysts as well.[2,3] Additionally, among all the transition metal catalysts, copper salts hold many advantages including inexpensive and low toxicity.[4] The exploring of copper catalysts in carbonylative transformations is definitely attractive from the point of view of both academic and industrial applications.[5]

On the other hand, esters are naturally occurring and also important intermediates and building blocks in pharmaceutical and natural products.[6] Selected examples of bio-active esters are shown in Scheme 1.[7] Plavix is a thienopyridine-class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, cerebrovascular disease, and to prevent heart attack and stroke. Tricor is a drug for the fibrate class. Flovent HFA is used to treat asthma, allergic rhinitis, nasal polyps, various skin disorders and Crohn's disease and ulcerative colitis. Tamiflu is an antiviral medication used to treat influenza A and influenza B (flu), and to prevent flu after exposure. Under all these backgrounds, we wish to report here the first example on copper-catalyzed alkoxycarbonylation of alkanes with alcohols via C-H activation. Moderate to good yields of the desired esters can be obtained. Additionally, paraformaldehyde can also be applied for *in situ* alcohol generation by radical trapping, and give moderate yields of the corresponding esters.



Scheme 1. Selected examples of bio-active esters.

Initially, we chose cyclohexane and 1-octanol as the model substrates to establish this carbonylation procedure. Upon the variation of reaction conditions, different product yields could be obtained (Table 1). Among the different tested metal catalyst precursors (Table 1, entries 1-4), $CuCl_2$ showed the best results (85% NMR yield; 78% isolated yield; Table 1, entry 2). And decreased reaction efficiency was obtained with $CuBr(Me_2S)$ or $Cu(CH_3CN)_4BF_4$ as the catalyst (Table 1, entries 3 and 4). Only trace of the desired product can be obtained in the absence of catalyst system (Table 1, entry 1). The amount and usage of DTBP (di-*tert*-butyl peroxide) plays an important role in this reaction. When we decreased the use of DTBP from 1.5 equiv. to 1 equiv., only 58% of the desired product was obtained and no ester was produced with TBHP (*tert*-butyl hydroperoxide solution (70 wt. % in H_2O); Table 1, entries 5 and 6). To our delight, no obvious variation of yield was observed with decreased loading of catalyst and ligand (Table 1, entry 7). And the pressure of CO can also be decreased to 10 bar (Table 1, entry 8). However, the yield drops when further decreasing the pressure of CO (2 bar, 32% yield). Finally, two different ligands were studied in stand of 1,10-phenanthroline and lower reaction efficiency were obtained with 2,2'-bipyridine or PPh_3 as the ligand (Table 1, entries 9 and 10). Taking the outcome of substrates testing into consideration, we using 10 mol% of $CuCl_2$ and 1,10-phenanthroline together with DTBP (1.5 equiv.) under 20 bar CO for further studies.

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+ These authors contributed equally to this work.
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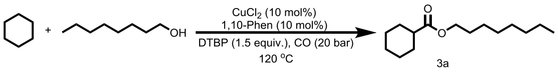
Table 1. Screening of the reaction conditions.[a]



3a

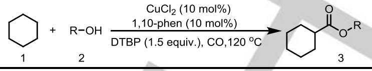
Entry	Variations from the standard conditions	Yield[b]
1	Without Catalyst and Ligand	Trace
2	-	85% 78%[c]
3	$CuBr(Me_2S)$	75 %
4	$Cu(CH_3CN)_4BF_4$	34%
5	1.0 equiv. DTBP	58%
6	TBHP instead of DTBP	Trace
7	5 mol% of $CuCl_2$ and 1,10-Phen	84%
8	10 bar instead of 20 bar	83%
9	2,2'-bipyridine instead of 1,10-Phen	64%
10	PPh_3 (20 mol%) instead of 1,10-Phen	46%

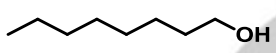
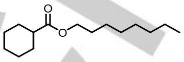
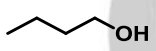
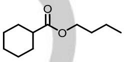
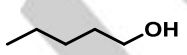
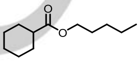
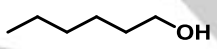
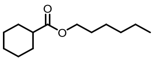
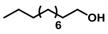
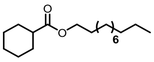
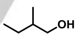
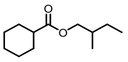
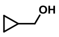
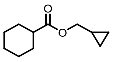
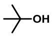
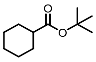
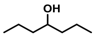
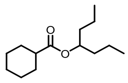
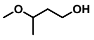
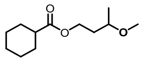
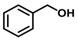
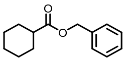
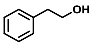
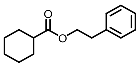
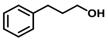
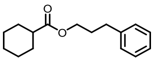
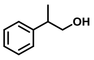
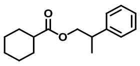
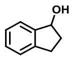
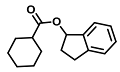
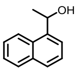
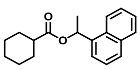
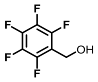
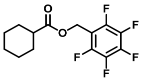
[a] 1-Octanol (0.5 mmol), catalyst (10 mol%), ligand (10 mol%), 0.75 mmol DTBP, 20 bar CO, cyclohexane (2 mL), 24 h. [b] NMR yields using mesitylene as the internal standard. [c] Isolated yield. DTBP: di-*tert*-butyl peroxide. TBHP: *tert*-butyl hydroperoxide solution (70 wt. % in H_2O).

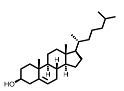
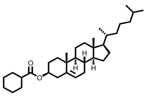
With the optimized reaction conditions in hand, we examined the scope of the reaction with a range of alcohols. As shown in Table 2, various alcohols were texted. We tested different aliphatic alcohols at the first stage. Moderate to good yields of the desired products can be produced in all the cases under standard conditions. Not only primary alcohols, but also secondary and tertiary alcohols are all applicable here and the reactions with *tert*-butanol and 4-heptanol gave good isolated yields of the products (Table 2, entries 8 and 9; 63% and 73% yields, respectively). To further explore the applicability of alcohols, phenyl substituted substrates were studied subsequently (Table 2, entries 11-17). The reactions of benzyl alcohol, phenethyl alcohol, 3-phenyl-1-propanol with cyclohexane gave the desired products in 81%, 87% and 86% yields respectively (Table 2, entries 11-13). To reveal the generality of this method, other kinds of alcohols were also tested. 2-Phenylpropan-1-ol gives a good result in 82% yield. Interestingly, when (perfluorophenyl) methanol was used in this reaction, excellent yield was obtained (Table 2, entry 17). Importantly, Cholesterol, an essential structural component of all animal cell membranes, can be reacted smoothly with cyclohexane and gave the desired product in 61 % isolated yield (Table 2, entry 18).

Furthermore, some alkane derivatives were tested and the results are listed in Table 3. Cyclopentane and cycloheptane worked well under the standard reaction conditions (Table 3, entries 1 and 2). Good yields of the corresponding esters were isolated (72% and 71%, respectively). Pentane and hexane were also tested under the same conditions, a mixture of different regioselective products were obtained (Table 3, entries 3 and 4).

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

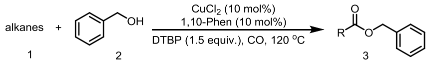


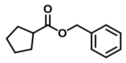
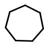
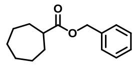
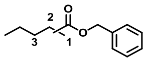
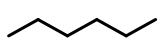
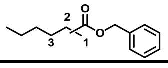
Entry	Alcohol	Product	Yield [%]
1			78
2			54
3			74
4			65
5			91
6			81
7			87
8			63
9			73
10			77
11			81
12			87
13			86
14			82
15			65
16			64
17			92

18			61

[a] Alcohol (0.5 mmol), $CuCl_2$ (10 mol%), 1,10-phen (10 mol%), DTBP (0.75 mmol), CO (20 bar), cyclohexane (2 mL), 120 °C, 24 h. [b] Isolated yields.

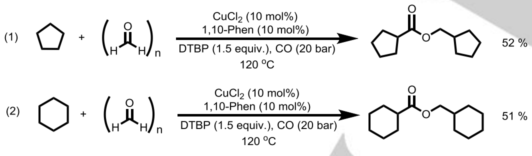
Table 3. Cu-catalyzed alkoxycarbonylation of alkanes.[a]



Entry	Alkane	Product	Yield [%]
1			72
2			71
3			59[c]
4			56[d]

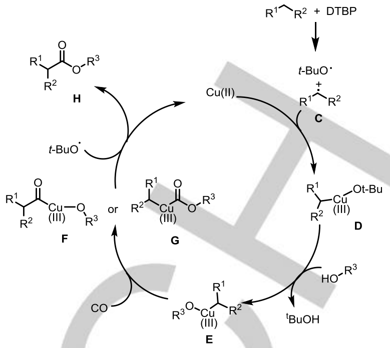
[a] Benzyl alcohol (0.5 mmol), $CuCl_2$ (10 mol%), 1,10-phen (10 mol%), 0.75 mmol DTBP, 20 bar CO, alkane (2 mL), 120 °C, 24 h. [b] Isolated yields. [c] The ratio was determined by ^{1}H NMR (C1:C2:C3 =1.15: 2.92: 1). [d] Mixture.

To further explore the applicability of this reaction in aliphatic esters synthesis, we used paraformaldehyde for *in situ* alcohol generation by radical trapping and got the desired products in 52 % and 51 % respectively (Scheme 2).[8] In these cases, no addition of alcohol is required.



Scheme 2. Using paraformaldehyde for in situ generation of alcohols.

Based on our results, a possible reaction mechanism is 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 D. Than complex D reacts with alcohols to produce Cu(III) intermediate E. Followed by CO insertion forms the intermediate F or G, which then give the final carbonylation product after reductive elimination. The meanwhile formed Cu(I) reacted with radical and regenerate the active Cu(II) species for the next catalytic cycle. The radical nature of this reaction was proven by experiments with TEMPO. The reaction was totally inhibited by the addition of 2 or 4 equivalents of TEMPO to the standard conditions.



Scheme 3. Proposed reaction mechanism.

In conclusion, a novel copper-catalyzed alkoxycarbonylation of alkanes with alcohols has been developed. With copper salt as the catalyst, various esters were prepared in moderate to good yields via $C_{(sp3)}$-H bond activation of alkanes. Paraformaldehyde can also be applied for *in situ* alcohol generation by radical trapping, and moderate yields of the corresponding esters can be produced. Notably, this is the first report on copper-catalyzed alkoxycarbonylation of alkanes.

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General procedure A: A 4 mL screw-cap vial was charged with $CuCl_2$ (6.7 mg, 10 mol%), 1,10-phenanthroline hydrate (9 mg, 10 mol%) 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 (2 mL), DTBP (0.75 mmol), alcohols (0.5 mmol) were injected by syringe, the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 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 = 100:1).

General procedure B: A 4 mL screw-cap vial was charged with $CuCl_2$ (6.7 mg, 10 mol%), 1,10-phenanthroline hydrate (9 mg, 10 mol%), paraformaldehyde (15 mg, 0.5 mmol) 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 (2 mL) and DTBP (0.75 mmol) were injected by syringe, the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 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 ^{o}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 = 100:1).

Keywords: copper catalyst • alcohols • carbonylation • esters • alkanes

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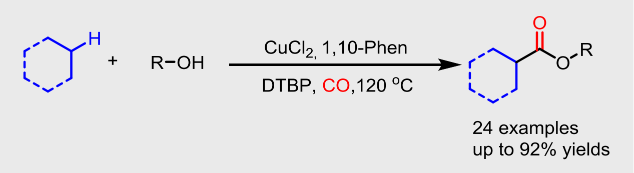

A novel copper-catalyzed carbonylative transformation of alkanes and alcohols has been developed. Esters were prepared in good yields by carbonylation of the $C_{(sp3)}$-H bond of alkanes with alcohols as the nucleophiles. Notably, this is the first report on copper-catalyzed carbonylative C-H activation between alkanes and alcohols.

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