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Oxidative Alkane C-H Alkoxycarbonylation

Lijun Lu,[a] Renyi Shi,[a] Luyao Liu,[a] Jingwen Yan,[a] Fangling Lu,[b] and Aiwen Lei*[a, b]

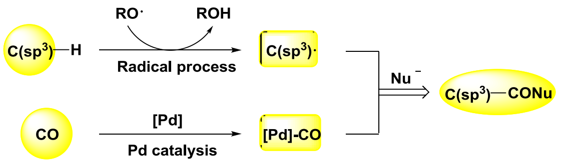
Abstract: Directly utilizing chemical feedstock to construct valuable compounds is an attractive prospect in organic synthesis. Significantly, the combination of C(sp^3)-H activation and oxidative carbonylation involving alkanes and CO gas is a promising and efficient method to synthesize carbonyl derivatives. However, due to the high C-H bond dissociation energy and low polarity of unactivated alkanes, the carbonylation of unactivated C(sp^3)-H bonds still remains a great challenge. In this work, we introduce a palladium-catalyzed radical oxidative alkoxycarbonylation of alkanes to prepare numerous alkyl carboxylates. Various alkanes and alcohols were compatible, generating the desired products in up to 94% yields. Remarkably, ethane, a constituent of natural gas, could be employed as a substrate under standard reaction conditions. Preliminary mechanistic studies revealed a probable palladium-catalyzed radical process.

Abundant, readily available from petroleum and natural gas, alkanes are main energy substances as well as important feedstock for the chemical industry. During the last decades, continuous efforts have been devoted to the conversion of alkanes.[1] On the other hand, as an important C1 source, CO has been widely applied in industry and academic research.[2] For example, Fischer-Tropsch synthesis and hydroformylation are mature in industry, and palladium-catalyzed carbonylation reaction represents one of the most powerful synthetic methods to obtain multifariously useful carbonyl derivatives such as acids, esters, amides, ketones, heterocycles, etc.[3] Hence, it is attractive to directly utilize easily available alkanes and CO to construct valuable compounds.

In recent years, C(sp^3)-H activation and functionalization has become a hot topic within the chemistry community.[4] For selected examples, Yu's ligand-controlled C(sp^3)-H arylation and olefination, Hartwig's borylation of alkanes and MacMillan's H-atom transfer process of C-H bonds are significant advancements in this area.[5] Meanwhile, oxidative carbonylation between C-H and X-H bonds has attracted more attention, which meets the principles of green chemistry and sustainable chemistry.[6] Therefore, C(sp^3)-H activation/oxidative carbonylation is a promising and efficient method to convert simple alkanes into their functionalized forms,[7] such as alkyl carboxylates and their derivatives.[8] These commodity chemicals are important building blocks of numerous natural products, pharmaceuticals and agrochemicals.[9]

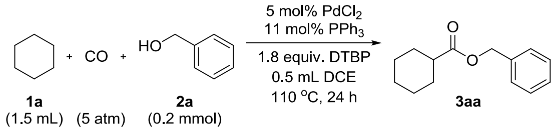
However, it is still a great challenge to achieve C(sp^3)-H functionalization. In general, the p*Ka* value of alkanes are more than 40 which is too high to undergo deprotonation with the aid of base, and C(sp^3)-H bonds of alkanes also have a high bond dissociation energy and a very low polarity.[10] It is difficult to achieve the C(sp^3)-H oxidative carbonylation of alkanes by the typical Pd-catalyzed C-H bond activation process until with the assistance of directing groups.

Alternatively, radical process has shown its potential in C-H bond functionalization, especially for C(sp^3)-H bonds in the past several decades. Numerous examples have been reported that the hydrogen atom from alkanes could be abstracted under simple and mild reaction conditions, among which Ryu and others have done pioneering works in radical carbonylation of alkanes.[11] Meanwhile, Pd catalysis has shown its power in the carbonylation transformations. Hence, oxidative C(sp^3)-H carbonylation might be achieved by combining Pd catalysis with radical process (Scheme 1). Herein we reported a novel palladium-catalyzed radical oxidative carbonylation of alkanes with alcohols to afford a series of alkyl carboxylates in one step.



Scheme 1. Combination of Pd Catalysis and Radical Process.

Table 1. Optimization of Reaction Conditions for the Palladium-catalyzed Radical Oxidative Carbonylation of Cyclohexane with Benzyl Alcohol.[a]



Entry	Variations from the standard conditions	Yield [%][b]
1	Without $PdCl_2$	17
2	-	84 (79)
3	1 mol% $PdCl_2$ instead of 5 mol% $PdCl_2$	54
4	$Pd(OAc)_2$ instead of $PdCl_2$	67
5	1.0 equiv. DTBP instead of 1.8 equiv. DTBP	54
6	TBHP instead of DTBP	4
7	Without DCE	41
8	MeCN instead of DCE	68
9	Without PPh_3	24
10	1 atm CO instead of 5 atm CO	75
11	90 °C instead of 110 °C	76

[a] Reaction conditions: **1a** (1.5 mL), **2a** (0.20 mmol), CO (5 atm), $PdCl_2$ (5 mol% based on **2a**), PPh_3 (11 mol% based on **2a**), DTBP (1.8 equiv. based on **2a**), DCE (0.5 mL), 110 °C, 24 h. [b] Yields were determined by GC analysis, calibrated using biphenyl as the internal standard (isolated yield in parentheses).

Initially, we explored the process with cyclohexane (**1a**) and benzyl alcohol (**2a**) as substrates (Table 1). With the combination of 5 mol% $PdCl_2$ as catalyst, 11 mol% PPh_3 as ligand and DTBP (di-tert-butyl peroxide) as oxidant, 84% yield of

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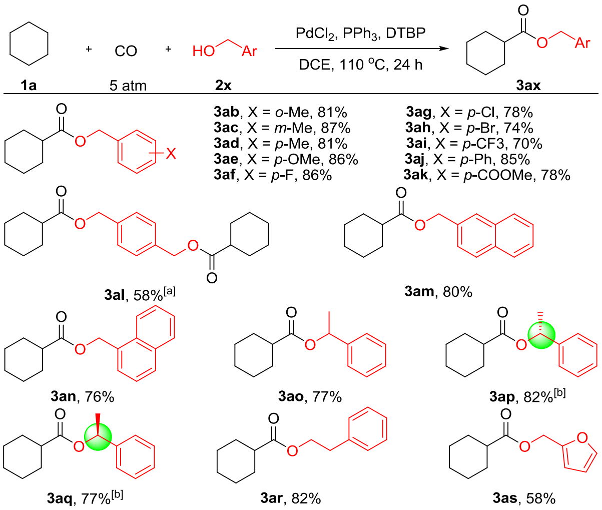
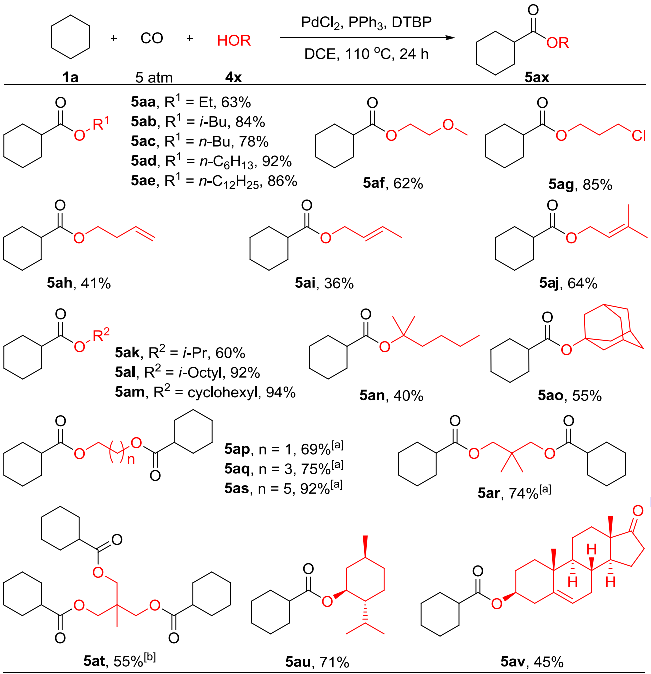
the desired product could be obtained in DCE (entry 2). To our surprise, 17% yield of **3aa** was obtained without Pd catalyst (entry 1). With $Pd(OAc)_2$ the yield was slightly decreased (entry 4). When decreasing the Pd catalyst loading to 1 mol%, there was an obvious drop in yield (entry 3). DTBP plays an important role in this reaction. We observed a drop in yield when we used less equivalent of DTBP or used TBHP instead of DTBP as oxidant (entries 5, 6). Under neat condition or using MeCN as solvent resulted in less yields (entries 7, 8), and the reaction could not proceed well without PPh_3 (entry 9). The pressure of CO and the temperature seemed to have less influence for this transformation, for 75% yield of **3aa** could be obtained even when using non-pressurized CO (entries 10, 11).

Encouraged by the results in Table 1, we next explored the substrate scope of this palladium-catalyzed radical oxidative alkoxycarbonylation reaction. Firstly, various benzyl alcohols were tested (Scheme 2). *Ortho*, *meta* and *para*-position methyl benzyl alcohols all afforded high yields (**3ab**-**3ad**). Benzyl alcohol with electron-donating groups such as methoxyl group was effective under the standard conditions (**3ae**). Electron-withdrawing substituents, such as *p*-CF_3, and *p*-COOMe also gave the desired products in satisfactory yields (**3ai**, **3ak**). Delightfully, 1,4-benzenedimethanol could give the diester in 58% yield (**3al**). Halide groups such as F, Cl and Br were well tolerated (**3af**-**3ah**). Furthermore, 4-biphenylmethanol, 1-naphthalenemethanol and 2-naphthalenemethanol could be transformed into the corresponding esters smoothly (**3aj**, **3am**, **3an**). Not only primary alcohols, but also secondary alcohols were suitable substrates for this reaction (**3ao**-**3aq**). Moreover, chiral alcohols underwent this reaction with full retention. Other aromatic alcohols such as 2-phenylethanol and furfuryl alcohol gave the esters in 82% and 58% yields, respectively (**3ar**, **3as**).



Scheme 2. Substrate Scope of Aromatic Alcohols. Reaction conditions: **1a** (1.5 mL), **2x** (0.20 mmol), CO (5 atm), $PdCl_2$ (5 mol% based on **2x**), PPh_3 (11 mol% based on **2x**), DTBP (1.8 equiv. based on **2x**), DCE (0.5 mL), 110 °C, 24 h. Yield of isolated product. [a] **2l** (0.10 mmol), $PdCl_2$ (10 mol% based on **2l**), PPh_3 (22 mol% based on **2l**), DTBP (3.6 equiv. based on **2l**). [b] Enantiomeric excess = 100%.

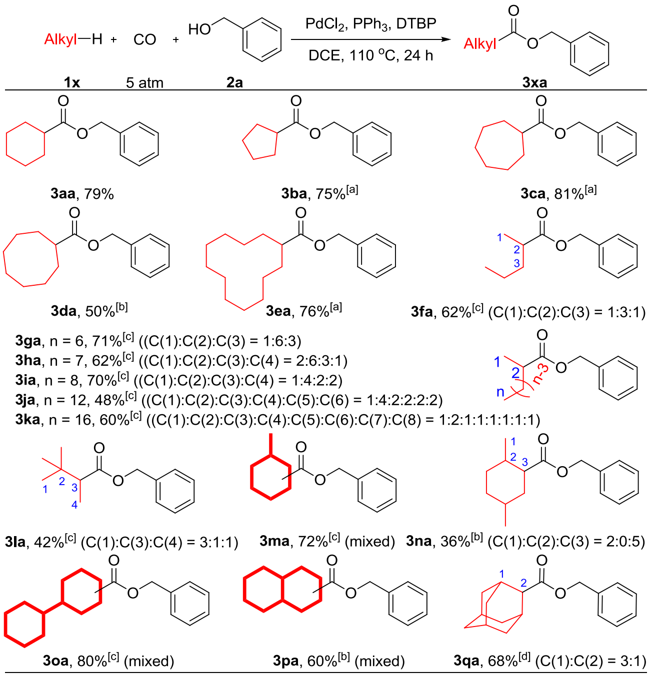
Moving on to aliphatic alcohols (Scheme 3), we were pleased to find that, ethanol, isobutanol, 1-butanol, 1-hexanol and 1-dodecanol all afforded the corresponding products in good to excellent yields (**5aa**-**5ae**). In addition, a variety of functional groups such as alkoxy, chloro and alkenyl were tolerated in this transformation (**5af**-**5aj**). To further explore the applicability of alcohols, various secondary alcohols were also investigated. Reactions of isopropanol, 2-octyl alcohol and cyclohexanol proceeded well to afford the desired esters in excellent yields (**5ak**-**5am**). However, tertiary alcohols such as 2-methyl-2-hexanol and 1-adamantanol could only give moderate yields (**5an**, **5ao**). In comparison to 1,4-benzenedimethanol, diols such as ethanediol, 1,4-butanediol, neopentyl glycol and 1,6-hexanediol showed better reaction efficiency (**5ap**-**5as**). Surprisingly, trimethylolethane was also compatible (**5at**). Importantly, natural products such as L-menthol and dehydroepiandrosterone (DHEA), widely exist in plants and animals, can be reacted smoothly with **1a** to provide the oxidative carbonylation products (**5au**, **5av**).



Scheme 3. Substrate Scope of Aliphatic Alcohols. Reaction conditions: **1a** (1.5 mL), **4x** (0.20 mmol), CO (5 atm), $PdCl_2$ (5 mol% based on **4x**), PPh_3 (11 mol% based on **4x**), DTBP (1.8 equiv. based on **4x**), DCE (0.5 mL), 110 °C, 24 h. Yield of isolated product. [a] **4x** (0.10 mmol), $PdCl_2$ (10 mol% based on **4x**), PPh_3 (22 mol% based on **4x**), DTBP (3.6 equiv. based on **4x**). [b] **4t** (0.06 mmol), $PdCl_2$ (15 mol% based on **4t**), PPh_3 (33 mol% based on **4t**), DTBP (5.4 equiv. based on **4t**).

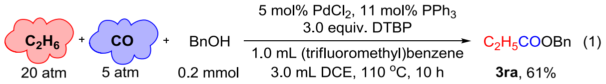
Furthermore, numerous alkanes were tested (Scheme 4). In the case of cycloalkanes, such as cyclopentane, cyclohexane, cycloheptane, cyclooctane and cyclododecane, becase all the reacting sites are equivalent, the reaction proceeded smoothly to afford single products (**3aa**-**3ea**). Other alkanes with nonequivalent reacting sites offered mixed products (See Supporting Information). Above all, linear alkanes from C5 to C16 were compatible (**3fa**-**3ka**). In addition, branched alkane, 2, 2-dimethylbutane gave the mixed products in 42% yield (**3la**). Cyclohexane with alkyl substituent such as methylcyclohexane, 1, 4-dimethylcyclohexane, bi(cyclohexane) and decahydronaphthalene could be transformed into the corresponding products in moderate to high mixed yields (**3ma**-

3pa). Additionally, solid adamantane gave a good mixed yield (**3qa**).

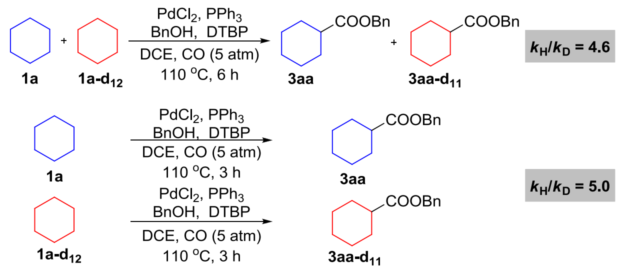


Scheme 4. Substrate Scope of Alkanes. Reaction conditions: **1x** (1.5 mL), **2a** (0.20 mmol), CO (5 atm), $PdCl_2$ (5 mol% based on **2a**), PPh_3 (11 mol% based on **2a**), DTBP (1.8 equiv. based on **2a**), DCE (0.5 mL), 110 °C, 24 h. Yield of isolated product. [a] 5 mol% Xantphos instead of 11 mol% PPh_3, 6.0 equiv. DTBP instead of 1.8 equiv. DTBP. [b] 10 mol% $PdCl_2$ instead of 5 mol% $PdCl_2$, 10 mol% Xantphos instead of 11 mol% PPh_3, 6.0 equiv. DTBP instead of 1.8 equiv. DTBP. [c] 10 mol% $PdCl_2$ instead of 5 mol% $PdCl_2$, 22 mol% PPh_3 instead of 11 mol% PPh_3, 4.0 equiv. DTBP instead of 1.8 equiv. DTBP. [d] **1q** (1.00 mmol), **2a** (0.20 mmol), CO (5 atm), $PdCl_2$ (10 mol% based on **2a**), PPh_3 (22 mol% based on **2a**), DTBP (4.0 equiv. based on **2a**), (Trifluoromethyl)benzene (0.5 mL), DCE (1.5 mL), 110 °C, 24 h.

It is especially noteworthy that gaseous ethane could be used as alkane source in this reaction, affording 61% yield of benzyl propionate under 5 atm of CO (Eq. (1) **3ra**).



In order to gain brief insights into the mechanism of the reaction, several experiments were conducted under the standard reaction conditions. The competition experiment of the mixture of cyclohexane and cyclohexane-d_{12} was performed affording the desired products in a 4.6:1.0 ratio. The reaction progress of the carbonylation of cyclohexane and cyclohexane-d_{12} were also monitored (Scheme 5, see Supporting Information). A significant kinetic isotopic effect (k_H/k_D = 5.0) can be observed, which indicated that C-H bond activation might be involved in the rate-determining step.



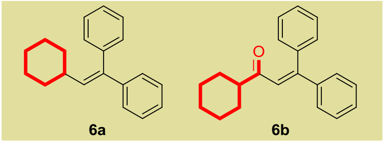
Scheme 5. Kinetic Isotope Effect Experiments.

On the other hand, radical-trapping experiments were conducted. When TEMPO was used as the radical-trapping reagent, no desired product **3aa** could be detected (Eq. (2)). With the treatment of 1,1-diphenylethene, the desired product **3aa** was obtained in only 31% yield while the coupling products of 1,1-diphenylethene with cyclohexane (**6a**) and cyclohexanecarboxaldehyde (**6b**) were obtained in 35% and 13% yield, respectively (Eq. (3)). **6a** and **6b** were also detected in the absence of Pd catalyst (Eq. (4)). These results indicated that cyclohexyl radical and cyclohexylformyl radical are probably involved in this transformation.

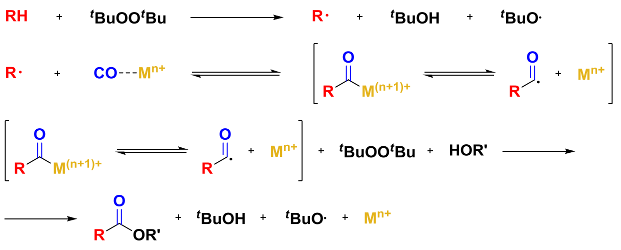
$$\underset{1.5\text{ mL}}{\mathbf{1a}} + \underset{5\text{ atm}}{\mathrm{CO}} + \underset{0.2\text{ mmol}}{\mathbf{2a}} \xrightarrow[\mathbf{2.0\ equiv.\ TEMPO}\text{, }110\,^{\circ}\text{C, 24 h}]{\text{5 mol \%}PdCl_2\text{, 11 mol\% }PPh_3\text{, 1.8 equiv. DTBP, 0.5 mL DCE}} \underset{\text{n. d.}}{\mathbf{3aa}} \quad (2)$$

$$\underset{1.5\text{ mL}}{\mathbf{1a}} + \underset{5\text{ atm}}{\mathrm{CO}} + \underset{0.2\text{ mmol}}{\mathbf{2a}} \xrightarrow[\mathbf{2.0\ equiv.\ 1,1\text{-}diphenylethene}\text{, }110\,^{\circ}\text{C, 24 h}]{\text{5 mol\% }PdCl_2\text{, 11 mol\% }PPh_3\text{, 1.8 equiv. DTBP, 0.5 mL DCE}} \underset{31\%}{\mathbf{3aa}} + \underset{35\%}{\mathbf{6a}} + \underset{13\%}{\mathbf{6b}} \quad (3)$$

$$\underset{1.5\text{ mL}}{\mathbf{1a}} + \underset{5\text{ atm}}{\mathrm{CO}} + \underset{0.2\text{ mmol}}{\mathbf{2a}} \xrightarrow[\mathbf{2.0\ equiv.\ 1,1\text{-}diphenylethene}\text{, }110\,^{\circ}\text{C, 24 h}]{\text{no }PdCl_2\text{, 11 mol \%}PPh_3\text{, 1.8 equiv. DTBP, 0.5 mL DCE}} \underset{\text{n. d.}}{\mathbf{3aa}} + \underset{15\%}{\mathbf{6a}} + \underset{6\%}{\mathbf{6b}} \quad (4)$$



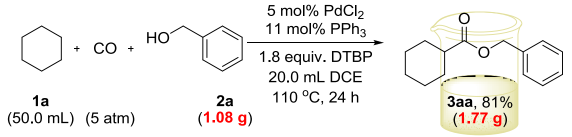
Although the mechanistic details of this transformation remain unclear at the moment, we proposed a plausible mechanism on the basis of the results obtained (Scheme 6). Firstly, DTBP abstracts hydrogen atom from the alkane to afford the alkyl radical. Then, CO coordinated with metal could be attacked by the alkyl radical to form acyl metal species which can be transformed into acyl radical. At last, acyl metal species can be reacted with DTBP and benzyl alcohol to generate the desired product.



Ligand was omitted for clarity

Scheme 6. Proposed Reaction Mechanism.

Notably, this reaction could be performed on gram scale (Eq. (5)). Treatment 1.08 g of **2a** in 50.0 mL of **1a** furnished 1.77 g of **3aa** in 81% yield.



(5)

In conclusion, the present study provides a promising and efficient method to construct alkyl carboxylates by directly utilizing the commonly available alkanes and CO. This process has an excellent substrate suitability, which can demonstrates potential applications in the area of agricultures and pharmaceutical chemistry. Ongoing work seeks to gain a detailed mechanistic understanding of this reaction, and applications of this process in other reactions are currently in progress.

Experimental Section

General procedure for palladium-catalyzed radical oxidative alkoxycarbonylation of cyclohexane: In an oven-dried teflon tube equipped with a stir-bar, $PdCl_2$ (1.8 mg, 5 mol% based on benzyl alcohol), PPh_3 (5.8 mg, 11 mol% based on benzyl alcohol) were combined. Then cyclohexane (1.5 mL) and DCE (0.5 mL) were added to the teflon tube via a syringe. After that, benzyl alcohol (0.2 mmol), DTBP (65 µL, 0.36 mmol) were added to the teflon tube. At last, place the teflon tube in an autoclave, then the autoclave was purged for three times and charged with CO at 5 atm. The reaction mixture was stirred at 110 °C for 24 hours and then cooled to room temperature. Next CO was carefully released. The corresponding reaction mixture was purified by flash column chromatography on a silica gel to give the desired product using hexane and ethyl acetate (12:1).

Acknowledgements

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Keywords: C-H activation • palladium-catalyzed • radical • carbonylation • alkane

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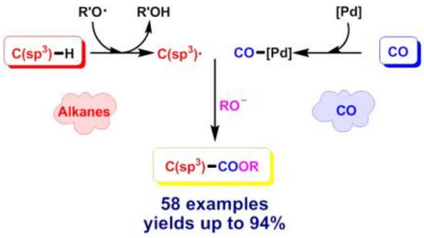

A novel palladium-catalyzed radical oxidative alkoxycarbonylation of alkanes has been developed. Various alkanes and alcohols were compatible, generating the desired products in up to 94% yields. In this transformation, Pd catalysis and radical process were combined smoothly, which solves the problems of high-pressure CO and activation of C(sp^3)-H bonds.

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