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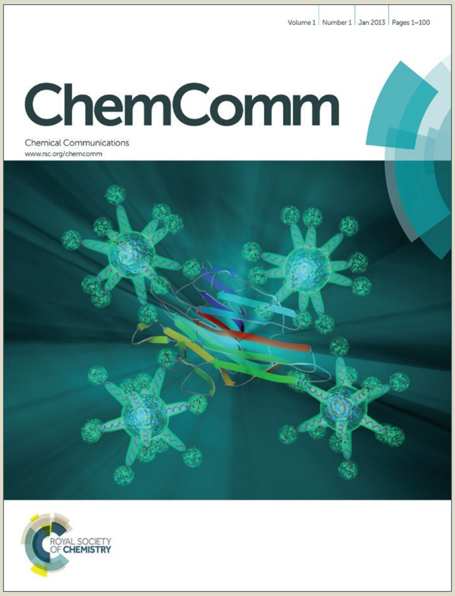

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Copper-Catalyzed Oxidative Coupling of Acids with Alkanes Involving Dehydrogenation: Facile Access to Allylic Esters and Alkylalkenes

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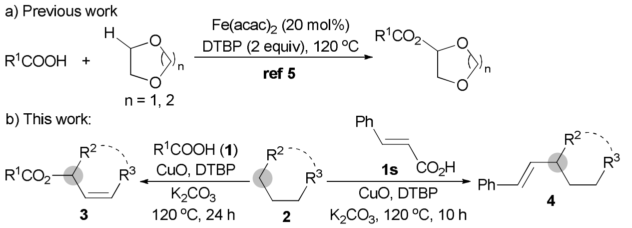
We here describe a new copper-catalyzed oxidative coupling of acids with alkanes for the selective synthesis of allylic esters and alkylalkenes. This method achieves multiple dehydrogenation and esterification, representing a new unactivated C(sp^3)–H oxidative esterification of acids with common alkanes.

Esters are versatile building blocks with wide applications in synthesis,[1] as well as are importantly ubiquitous cores in many natural products, pharmaceutical molecules and fine chemicals.[1,2] As a result, much attention has been longstanding attracted for the development of the practical and efficient strategies for ester synthesis.[1,3-5] The classic methods for the synthesis of esters mainly include the reaction of acids and their derivatives (acyl chlorides and anhydrides) with alcohols.[1] However, these methods suffer from several disadvantages, including limited substrate scope, harsh reaction conditions (eg. high temperatures and/or strong acids), large amounts of unwanted by-products and the requirement of additional purification steps. Thus, new efficient strategies for assembling various functionalized esters would be desirable and mandatory.

The C-H oxidative functionalization has become an important and highly atom-economic method for the formation of various chemical bonds.[6] In this field, two new C-H oxidation strategies for ester synthesis using alkanes as the starting materials have been reported:[3-5] one is the direct oxidative C-H activation/esterification of acids with alkanes,[3] and the other involves the tandem C-H oxidation/ esterification between acid precursors (aldehydes, arylmethanes, alkenes or alkynes) and alkanes.[4,5] However, these transformations are restricted to the requirement of the directing[3] or nono-directing[5b-d] activation groups in alkanes, limited substrate scope or/and expensive catalysts. In addition, only a paper has been described by Han and co-workers on the oxidative esterification of acids with the unactivated C(sp^3)–H bonds in ethers using Fe catalysts and di-*tert*-butyl peroxide (DTBP) oxidant (Scheme 1a).[5a] To our knowledge, the oxidative esterification of acids with the unactivated C(sp^3)–H bonds of common alkanes has not been reported.[4o] Herein, we report a new Cu-catalzyed oxidative coupling of acids with common alkanes for the synthesis of allylic esters[7] using DTBP as oxidant and a catalytic amount of K_2CO_3 as promoter (Scheme 1b), which is successfully realized through the C-H oxidative esterification and dehydrogenation cascade.[4m-o,8] Gratifyingly, this Cu/DTBP system can be applicable to the decarboxylative coupling of cinnamic acid with alkanes for accessing alkylalkenes.[9]



Scheme 1 Oxidative Coupling of Acids with Alkanes.

Our initial investigation began with the oxidative coupling of 4-methoxybenzoic acid (**1a**) with cyclohexane (**2a**) to optimize the reaction conditions (Table 1). In the presence of $Cu(NO_3)_2$ and DTBP, acid **1a** successfully coupled with cyclohexane (**2a**) through the multiple dehydrogenation process, furnishing the desired cyclohex-2-en-1-yl 4-methoxybenzoate (**3aa**) in 38% yield (entry 1). Gratifyingly, a series of bases, namely K_2CO_3, Ag_2CO_3, NaOAc and Et_3N, were found to improve the reaction (entries 2-6), and 20 mol% K_2CO_3 gave the best results. The reason may be that bases can stabilize the radical intermediate.[10] Among the reaction temperature examined, it turned out that 120 °C was preferred in terms of yields (entry 2 vs. entries 7 and 8). In light of these results, a number of other Cu catalysts, including $CuCl_2$, $Cu(OAc)_2$, CuO and Cu_2O, were investigated(entries 9-12). The results demonstrated that all the Cu catalysts effected the reaction, and CuO displayed the highest catalytic activity (entry 11 vs. entries 9,10 and 12). It should be noted that Cu_2O was also an efficient catalyst for the reaction (entry 12). When varying the amounts of DTBP, we found that the reaction with four equivalents of DTBP offered the best results (entry 11 vs. entries 13 and 14). However, in the absence of DTBP, the reaction did not result in the formation of detectable amounts of **3aa** (entry 15). Finally, there other oxidants, such as *tert*-butyl hydroperoxide (TBHP), dicumyl peroxide (DCP) and $K_2S_2O_8$, were evaluated (entries 16-18). The yield in the presence of TBHP (entry 16) or DCP (entry 17) was inferior to that of DTBP (entry 11), but the coupling was completely suppressed by using $K_2S_2O_8$ (entry 18).

After establishing the optimal reaction conditions, we next probe the scope of this oxidative coupling protocol with a range of alkanes (Scheme 2) and acids (Table 2). Initially, a variety of alkanes, including cycloalkanes **2b-d** and linear alkanes **2e-g** were employed to couple with 4-methoxybenzoic acid (**1a**) in the presence of CuO, DTBP and K_2CO_3, and the

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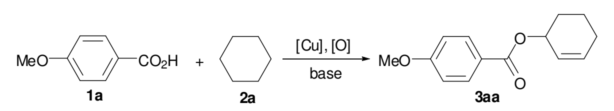
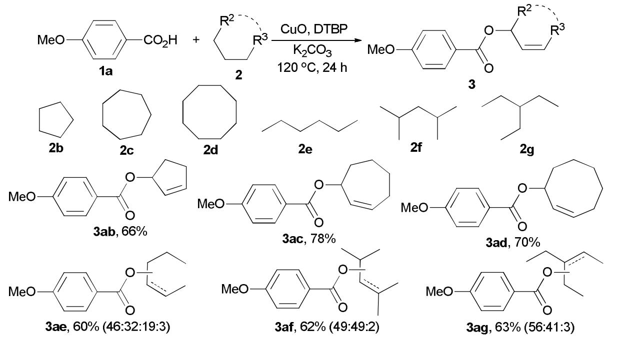
Table 1 Screening for Optimal Reaction Conditions[a]



Entry	[Cu]	[O] (equiv)	Base (mol%)	T (°C)	Yield (%)[b]
1	$Cu(NO_3)_2$	DTBP (4)	—	120	38
2	$Cu(NO_3)_2$	DTBP (4)	K_2CO_3 (20)	120	68
3	$Cu(NO_3)_2$	DTBP (4)	K_2CO_3 (50)	120	53
4	$Cu(NO_3)_2$	DTBP (4)	Ag_2CO_3 (20)	120	57
5	$Cu(NO_3)_2$	DTBP (4)	NaOAc (20)	120	60
6	$Cu(NO_3)_2$	DTBP (4)	Et_3N (20)	120	59
7	$Cu(NO_3)_2$	DTBP (4)	K_2CO_3 (20)	100	15
8	$Cu(NO_3)_2$	DTBP (4)	K_2CO_3 (20)	130	65
9	$CuCl_2$	DTBP (4)	K_2CO_3 (20)	120	66
10	$Cu(OAc)_2$	DTBP (4)	K_2CO_3 (20)	120	18
11	CuO	DTBP (4)	K_2CO_3 (20)	120	79
12	Cu_2O	DTBP (4)	K_2CO_3 (20)	120	75
13	CuO	DTBP (3)	K_2CO_3 (20)	120	57
14	CuO	DTBP (5)	K_2CO_3 (20)	120	78
15	CuO	—	K_2CO_3 (20)	120	0
16	CuO	TBHP (4)	K_2CO_3 (20)	120	24
17	CuO	DCP (4)	K_2CO_3 (20)	120	57
18	CuO	$K_2S_2O_8$ (4)	K_2CO_3 (20)	120	trace

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (1 mL), [M] (10 mol%), [O], and base in argon for 24 h. [b] Isolated yield.

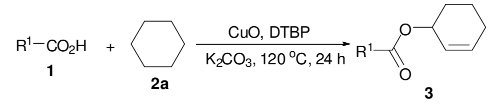
results are summarized in Scheme 2. To our delight, the optimal conditions were compatible with cycloalkanes **2b-d**, giving the corresponding allylic esters **3ab-ad** in good yields. Using linear alkanes **2e-g** to react with acid **1a** delivered a mixture of regioselective isomers **3ae-ag**. For example, the reaction of hexane (**2e**) gave four isomers **3ae** with the ratio of 46:32:19:3.

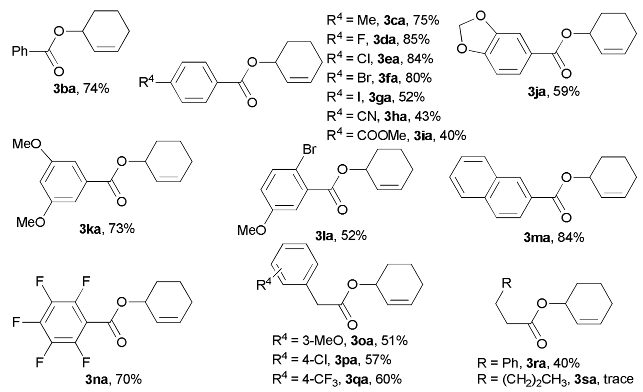


Scheme 2 Variation of Alkanes (**2**). Reaction conditions: **1a** (0.3 mmol), **2** (1 mL), CuO (10 mol%), DTBP (4 equiv), and K_2CO_3 (20 mol%) at 120 °C in argon for 24 h. The regioselectivity ratio is given in the parenthesis.

As show in Table 2, the optimal conditions were applicable to a wide range of acids, namely aryl acids **1b-n**, benzyl acids **1o-q** and alkyl acid **1r** (**3ba-pa**). Gratifyingly, several substituents, such as Me, MeO, F, Cl, Br, I, CN and CO_2Me, on the aromatic ring were well-tolerated, and their reactivity decreased from electron-donating to electron-withdrawing substitution (**3ca-na**). In the presence of cyclohexane (**2a**), CuO, DTBP and K_2CO_3, benzoic acid (**1b**) was a suitable substrate to assemble **3ba** in 74% yield. Me-substituted acid **1c** offered **3ca** in 75% yield, whereas CN-substituted acid **1h** and CO_2Me-susbtituted acid **1i** had lower reactivity leading to **3ha** and **3ia** in 43% and 40% yields, respectively. Interestingly, halide substituents (I, Br, Cl, and F) were consistent with these oxidative coupling conditions (**3da-ga** and **3la**), thereby serving as handles for further synthetic manipulations. For acids **1j-l** with two substituents, esters **3ja-la** were also formed in moderate to good yields. It is noteworthy that 1-naphthoic acid (**1m**) and pentafluorobenzoic acid (**1n**) are viable for the construction of **3ma** and **3na** in high yields. Subsequently, a variety of alkyl acids **1o-r** were tested under the optimal conditions: they were suitable substrates, albeit with lower yields (**3oa-ra**). However, hexanoic acid (**1s**) showed lower reactivity (**3sa**).

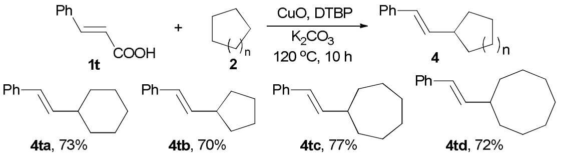
Table 2 Variation of Acids (**1**)[a]





[a] Reaction conditions: **1** (0.3 mmol), **2a** (1 mL), CuO (10 mol%), DTBP (4 equiv), and K_2CO_3 (20 mol%) at 120 °C in argon for 24 h.

We also applied the optimal conditions in the coupling of cinnamic acid (**1t**) with alkanes **2** (Scheme 3). However, the coupling delivered the decarboxylative coupled products **4ta-td**,[9] not the expected allylic esters **3**, in good yields.



Scheme 3 Coupling of Cinnamic Acid (**1s**) with Alkanes (**2**).

To understand the mechanism, some control experiments were carried out (Scheme 4). The reaction of acid **1a** with cyclohexene (**5a**) successfully constructed ester **3aa** in 81% yield (Eq 1). However, substrate **6a** could not be converted into ester **3aa** (Eq 2). The results suggest that the reaction may proceed via the formation of alkene. Notably, radical inhibitors, TEMPO, hydroquinone or BHT, completely suppressed the reaction, and offered product **7a** (Eq 3), implying that the coupling includes a radical process.

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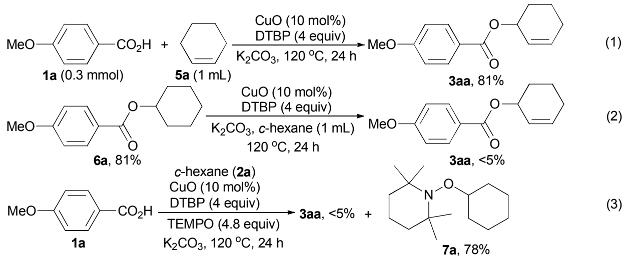
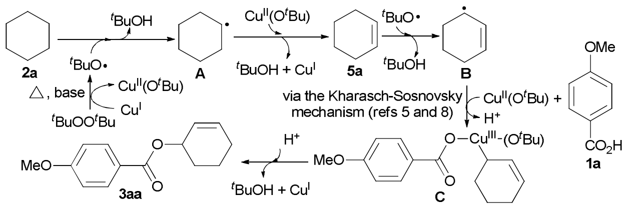


Scheme 4 Control Experiments.

The possible mechanism outlined in Scheme 5 was proposed.[4-9] Abstraction of the hydrogen atom of cyclohexane (**1a**) by ^{t}BuOO·,[4-9] which is generated from DTBP under heating with the aid of the active Cu^I species[4-9] and base,[10] occurs to afford alkyl radical **A** and Cu^{II}(O^{t}Bu), followed by dehydrogenation of intermediate **A** with Cu^{II}(O^{t}Bu) gives intermediate **5a** and regenerates the active Cu^I species. Intermediate **5a** undergoes the reported Kharasch-Sosnovsky mechanism[5,8] to offer the desired product **3aa**.



Scheme 5 Possible Mechanism.

In summary, we have developed a new oxidative dehydrogenation strategy for the selective synthesis of allylic esters by copper-catalyzed oxidative coupling of acids with alkanes using DTBP as oxidant. Moreover, this Cu and DTBP system were applicable to the decarboxylative coupling of cinnamic acid with cycloalkanes leading to alkylalkenes. Further studies on applications of this oxidative coupling method in synthesis are currently underway in our laboratory.

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