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Cu-Catalyzed C(sp^3)−H Bond Activation Reaction for Direct Preparation of Cycloallyl Esters from Cycloalkanes and Aromatic Aldehydes

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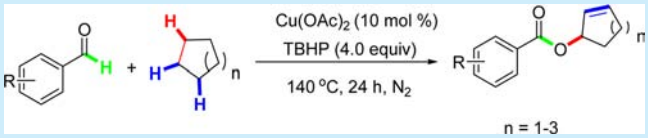
Supporting Information

ABSTRACT: Cu-catalyzed dehydrogenation−olefination and esterification of C(sp^3)−H bonds of cycloalkanes with TBHP as an oxidant has been developed. The reaction involves four C−H bond activations and gives cycloallyl ester products directly from cycloalkanes and aromatic aldehydes.



Catalytic dehydrogenation of alkanes to alkenes might have a great impact on the chemical industry in the following decades, due to the abundance of alkanes and increasing use of olefins as raw materials. In recent years, catalytic dehydrogenation of alkanes to alkenes has witnessed remarkable progress.[1,2] Among the known examples of catalytic dehydrogenation of cyclohexane described to date, the catalytic systems based on Ir,[3] Pt,[4] and Re[5] complexes are the most studied. Recently, Pérez and cowokers discovered that the dehydrogenation of cycloalkanes to cycloalkenes can be accomplished by the reaction between hydrocarbons and hydrogen peroxide with copper complexes as a catalyst.[6] Although the chemical yields of the these conversions into cycloalkenes were only 4%, the potential of copper-based catalysts could not be underappreciated as it is much more economical compared with the Ir, Pt, and Re derived catalysts. Therefore, Cu-catalyzed dehydrogenation−olefination of cycloalkanes is a research area of great scientific significance.

The formation of C−O bonds is a fundamental transformation in synthetic organic chemistry.[7] In particular, C−O construction through C−H activation is of great current interest. In the late 1950s, Kharasch and Sosnovsky reported the allylic oxidation of olefins using *tert*-butyl perbenzoate catalyzed by cuprous bromide.[8] Afterwards, a great deal of research effort has been invested to improve the efficiency of this copper-catalyzed allylic oxidation of olefins due to its potential utility in organic synthesis.[9]

More recently, the direct and catalytic transformation of C(sp^3)−H bonds to esters via C−H activation has attracted much scientific attention. In 2012, Patel's group developed a $Cu(OAc)_2$-catalyzed cross dehydrogenative coupling (CDC) reaction of aldehydes and alkyl benzenes using TBHP as the oxidant.[10a] This group also reported a metal-free CDC reaction for the synthesis of benzylic esters from alkyl benzenes.[10b] The Wan group[11] and Wang group[12] also have reported their important contribution to this field using Bu_4NI for the activation of the C(sp^3)−H bonds, adjacent to an oxygen atom, double bonds, or phenyl group, and subsequent coupling to form C−O bonds. However, direct functionalization of the nonactivated cycloalkanes has been virtually unexplored. Recently, the Liu group reported a copper-catalyzed cascade alkylarylation of alkenes with simple cycloalkanes.[13] Our group reported an Fe-catalyzed direct alkenylation of C(sp^3)−H bonds of cycloalkanes with DTBP as an oxidant.[14] Here, we would like to report our further significant progress in this area, the synthesis of cycloallyl esters directly from cycloalkanes through four C−H bond activations by copper catalysis.

Our initial investigation focused on examining the coupling reaction of benzaldehyde (**1**, 0.3 mmol) with CuI (0.03 mmol) using 4.0 equiv of *tert*-butyl hydroperoxide (TBHP, 1.2 mmol) as an oxidant in cyclohexane (2 mL) at 140 °C with stirring for 24 h under nitrogen, which provided cyclohex-2-en-1-yl benzoate **1a** in 23% yield (entry 1, Table 1). The byproduct of this reaction was found to be benzoic acid, isolated in 72% yield. We were quite encouraged by this initial result, as the overall process formally involved four C−H bond activations. Consequently further efforts were directed to improving the outcome of this novel C(sp^3)−H activation reaction. Other potential catalysts such as $Cu(OCCF_3)_2$, $CuCl_2$, $CuBr_2$, TBAI, and $Cu(OAc)_2$ were evaluated (entries 2−6). Among these $Cu(OAc)_2$ was found to be the most effective catalyst (entry 6). Using 1,10-phenanthroline (30 mol %) as the ligand or an increased loading of $Cu(OAc)_2$ up to 20 mol % gave no improvement of the target product (entries 7 and 8). TBHP as an oxidant was found to be superior over the other oxidants screened, such as di-*tert*-butyl peroxide (DTBP), benzoyl peroxide [$(PhCOO)_2$], and $K_2S_2O_8$ (entries 9−11). Decreasing or increasing the amounts of TBHP in the range between 2.0 to 6.0 equiv or differing the temperature from 120 to 150 °C, as

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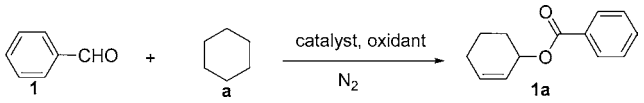
Table 1. Optimization of the Reaction Conditions[a]



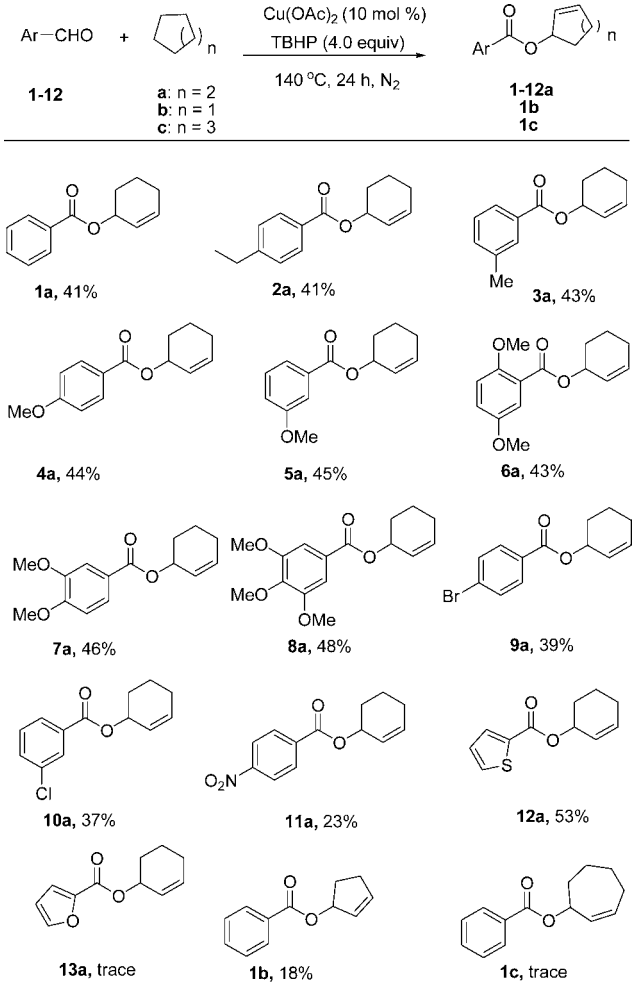
entry	catalyst (mol %)	oxidant (equiv)	temp (°C)	yield (%)[b]
1	CuI (10)	TBHP (4)	140	23
2	$Cu(OCCF_3)_2$ (10)	TBHP (4)	140	0
3	$CuCl_2$ (10)	TBHP (4)	140	5
4	$CuBr_2$ (10)	TBHP (4)	140	8
5	TBAI (20)	TBHP (4)	140	32
6	$Cu(OAc)_2$ (10)	TBHP (4)	140	41
7	$Cu(OAc)_2$ (10)	TBHP (4)	140	39[c]
8	$Cu(OAc)_2$ (20)	TBHP (4)	140	41
9[d]	$Cu(OAc)_2$ (10)	DTBP (4)	140	28
10	$Cu(OAc)_2$ (10)	TBPB (4)	140	38
11	$Cu(OAc)_2$ (10)	$K_2S_2O_8$ (4)	140	0
12	$Cu(OAc)_2$ (10)	TBHP (6)	140	40
13	$Cu(OAc)_2$ (10)	TBHP (2)	140	28
14	$Cu(OAc)_2$ (10)	TBHP (4)	120	19
15	$Cu(OAc)_2$ (10)	TBHP (4)	150	39
16	$Cu(OAc)_2$ (10)	TBHP (4)	140	40[d]
17	–	TBHP (4)	140	0
18	$Cu(OAc)_2$ (10)	–	140	0
19	$Cu(OAc)_2$ (10)	TBHP (4)	140	20[e]

[a]Conditions: **1** (0.3 mmol), **a** (2 mL), catalyst, oxidant, 140 °C, 24 h. [b]Isolated yields based on **1**. [c]Using 1,10-phenanthroline (30 mol %) as the ligand. [d]48 h. [e]Without protection of nitrogen.

well extending the reaction time to 48 h, did not lead to any noticeable increase in the yield of the desired product (entries 12−16). Control experiments carried out in the absence of either $Cu(OAc)_2$ or TBHP failed to give the target product (entries 17 and 18) strongly suggesting the requirement of both the metal catalyst and oxidant. A lower chemical yield was obtained when the reaction was performed without protection of the nitrogen (entry 19).

Under the optimized reaction conditions, the substrate scope was studied. As can be seen from Scheme 1, benzaldehyde with the electron-donating groups on the phenyl ring, such as methyl, ethyl, and methoxy groups, reacted smoothly with cyclohexane and gave the corresponding products (**2a**−**8a**) in 41−49% yields. Meanwhile, benzaldehyde with electron-withdrawing groups, such as Br, Cl, and NO_2 groups, also reacted with cyclohexane giving rise to the products **9a**−**11a** in 39%, 37%, and 23% yields, respectively. Thus, the electron-donating groups on the phenyl rings clearly favored the reaction as compared to the electron-withdrawing groups resulting in lower yields. Furthermore, the steric effects of the aromatic substitution had a rather insignificant impact on the yields (**6a** and **7a**). In addition, heterocyclic aromatic aldehydes, such as 2-thenaldehyde, were also tested in this reaction, and the desired products **12a** were obtained in the noticeably highest yield (53%), probably because 2-thenaldehyde can be considered as an electron-rich substrate. However, almost no desired product was obtained when furaldehyde was used as the substrate (**13a**). This may be due to the fact that the electron-donating ability of the furyl group is weaker than that of the thienyl group. To test the generality of this reaction in terms of the cycloalkane part, other derivatives, such as cyclopentane and cycloheptane, were reacted under the optimal reaction conditions. Cyclopentane, which has greater ring tension than cyclohexane, reacted with benzaldehyde giving rise

Scheme 1. Cu-Catalyzed Dehydrogenation−Olefination and Esterification of Cycloalkanes[a]



[a]Reaction conditions: aromatic aldehydes (0.3 mmol), cycloalkanes (2 mL), $Cu(OAc)_2$ (10 mol %), TBHP (4.0 equiv), 140 °C, 24 h, N_2.

to the corresponding product **1b** in 18% yield. However, cycloheptane reacted with benzaldehyde affording cyclohept-2-en-1-yl benzoate **1c** in <5% yield. This outcome was similar to the previous report on the iron-catalyzed allylic arylation of olefins via C(sp^3)−H activation.[15] Then, an example of substituted cycloalkane, methylcyclohexane, was tried for this reaction, which unfortunately gave a complex mixture of products (see Supporting Information). Finally, a linear alkane, hexane, was examined as a substrate. The reaction proceeded to form the desired cycloallyl esters in an overall 26% yield. However, the product contains several isomers which cannot be isolated in a chemically pure state (see Supporting Information).

Several key control experiments were performed to probe the reaction mechanism (Scheme 2). We found that the addition of radical scavengers, such as azobis(isobutyronitrile) (AIBN) or TEMPO (Scheme 2a), completely inhibited the reaction, and almost no desired products were obtained. Instead, the adduct from TEMPO with an acyl radical was found (see Supporting Information). This result indicated that the current transformation might proceed via formation of radical species. Next, instead of benzaldehyde, benzoic acid was used to react with cyclohexane under the optimal reaction conditions. Again,

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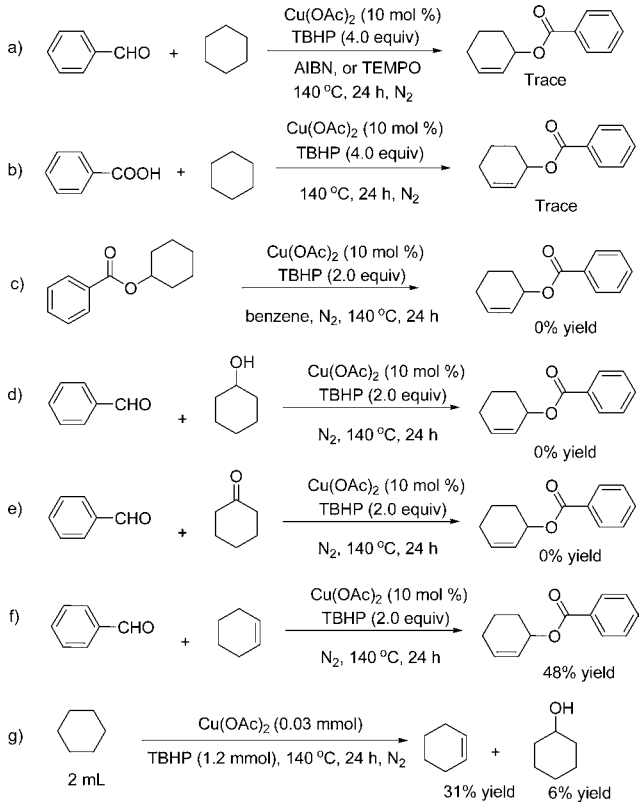
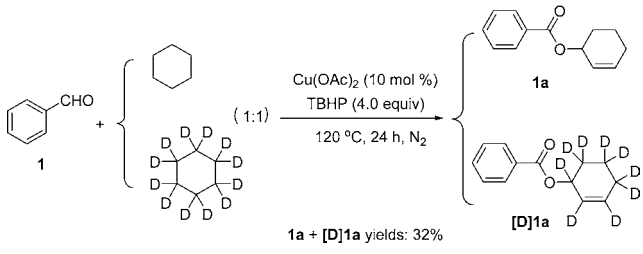
Scheme 2. Investigation of the Reaction Mechanism



almost no desired product was obtained in this case (Scheme 2b). We assumed that the cyclohexyl benzoate, cyclohexanol, cyclohexanone, or cyclohexene could be intermediates in the catalytic cycle. However, when cyclohexyl benzoate reacted with $Cu(OAc)_2$ using 2.0 equiv of TBHP at 140 °C with stirring for 24 h under nitrogen, the desired product was not obtained (Scheme 2c). The reactions of benzaldehyde and cyclohexanol (Scheme 2d) or cyclohexanone (Scheme 2e) under the same conditions did not produce the desired product either. Finally, the reaction of benzaldehyde with cyclohexene (Scheme 2f), conducted under the standard conditions, gave rise to the desired product in 48% yield. When the reaction was carried out in the absence of benzaldehyde, cyclohexene and cyclohexanol were detected in the reaction mixture by ^1H NMR in a ratio of 5:1 (31% and 6% yields respectively, Scheme 2g). This positive result strongly suggested that the catalytic cycle might proceed via cyclohexene as the intermediate.

An intermolecular competing kinetic isotope effect (KIE) experiment was also carried out (Scheme 3). As a result, a significant KIE was observed with the $k_H/k_D = 0.84/0.16 = 5.25$ (see Supporting Information). These results indicated that the

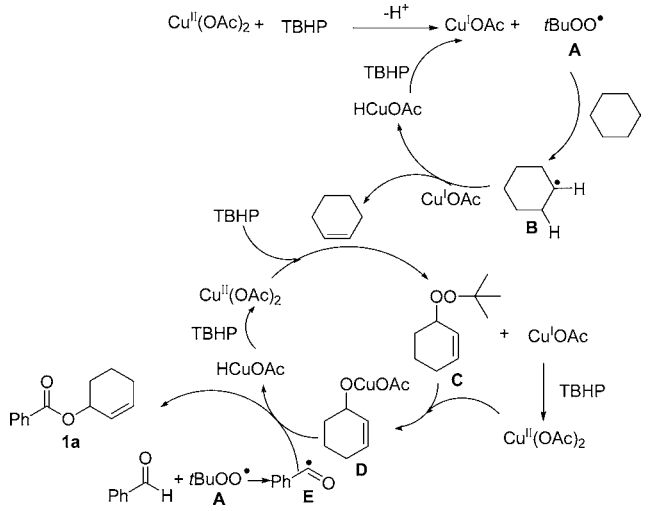
Scheme 3. KIE Experiment



sp^3 C−H bond cleavage should be involved in the rate-determining step of this procedure.

On the basis of these results as well as the literature data,[10−12] we propose a plausible mechanism including dehydrogenation of cycloalkanes to cycloolefins followed by a cross-coupling process, as illustrated in Scheme 4. Initially, the

Scheme 4. Possible Mechanism



Cu(II) reacts with TBHP forming the *tert*-butylperoxy radical **A**, Cu(I), and H^+ according to the mechanism suggested by Sasson and co-workers.[16] The cyclohexane radical **B** is generated by the reaction between **A** and cyclohexane, which undergoes dehydrogenation to cyclohexene, according to the process described by Pérez and co-workers.[6] Cyclohexene reacts with Cu(II) and TBHP forming intermediate **C**, which reacts with Cu(II) to give the intermediate **D**. The reaction of **D** with acyl radical **E**, generated from the hydrogen atom abstraction of benzaldehyde by a *tert*-butoxy radical,[17] gives final product **1a** along with HCuOAc for the next reaction cycle.[10a]

In conclusion, this work describes the first example of the Cu-catalyzed dehydrogenation-olefination and esterification of the $C(sp^3)$−H bond of cycloalkanes with aromatic aldehydes in the presence of TBHP as the oxidant. This reaction involves four formal C−H bond activations. An appreciable range of aromatic aldehydes can be used in this reaction with cycloalkanes allowing a direct preparation of the corresponding cycloallyl esters in 18−53% yields. Based on the extensive experimental data, we propose a plausible mechanism, which includes dehydrogenation−olefination of cycloalkanes followed by a cross dehydrogenative coupling reaction. Further studies to refine the mechanism and to expand the synthetic scope of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data for compounds **1a**−**12a** and **1b** and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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